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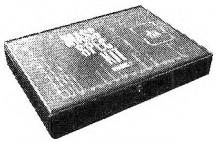

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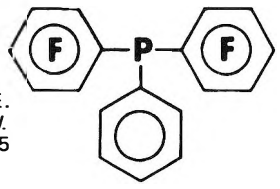

James W. Eichelberger, L.E. Harris, W.L. Budde, *Anal. Chem.* Vol. 47, No. 7, 995

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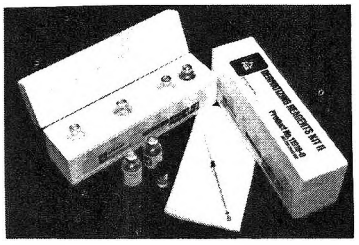

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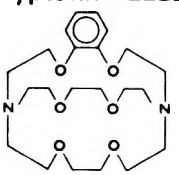

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AUTHOR INDEX

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NOVEMBER 12, 1976

Directed Metalation Reactions. 6.[1a] Competition of Substituents for Ortho Direction of Metalation in Substituted Anisoles

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Received October 31, 1974

Directed lithiation of benzenes containing the substituent groups $-NMe_2$, $-CH_2NMe_2$, $-CH_2CH_2NMe_2$, -CONHMe, -OMe, $-SO_2NMe_2$, $-SO_2NHMe$, $-CF_3$, and -F are well known. This investigation summarizes metalation of a series of para-substituted anisoles whereby the competative directed metalation ability of the methoxy group vs. the eight other cited substituents was measured. Certain of the ortho and meta isomers of these compounds were also examined. In all instances a regiospecific metalation resulted such that the following ranking of directory substituents can be offered: $-SO_2NMe_2$, $-SO_2NHMe$, -CONHMe, $-CH_2NMe_2$ > -OMe > $-CH_2CH_2NMe_2$, $-NME_2$, $-CF_3$, -F. In order to assess the effect of a para situated methoxy substituent upon benzyl proton acidity and benzoyl carbonyl electrophilicity, *p*-methoxy-*N*,*N*-dimethylbenzamide and the monomethyl derivative of *p*-methoxyphenylacetamide were treated with *n*-butyllithium. An ability of the methoxy substituent of some of these anisoles to cause exclusion of certain side reactions with *n*-butyllithium in these systems such as elimination of phenethylamines, nucleophilic substitution at the carbonyl in dimethylbenzamides, benzyne formation in fluorobenzenes, and benzylic hydrogen abstraction in phenylacetamide derivatives was discovered. Finally, an examination of the effect of tetramethylethylenediamine (TMEDA) upon the rate and orientation of metalation in the series of substituted anisoles was undertaken. Although this reagent had been found to be useful in controlling the rate and selectivity in a number of "random" metalations, its usefulness in "directed" metalation reactions had not previously been systematically explored.

The ability of certain substituents on aromatic systems to direct metalation at a position ortho to the substituent (ortho-directed metalation) has been observed[2] to be typical in a number of metalation reactions involving organolithium reagents. This phenomenon is of synthetic interest since such a procedure enables one to produce ortho disubstituted products virtually uncontaminated by meta or para isomers.

For the benzene aromatic system, the following substituent groups have been reported to direct the lithium atom to the ortho position upon metalation with *n*-butyllithium: $-NMe_2$,[3] $-CH_2NMe_2$,[4] $-CH_2CH_2NMe_2$,[5] -OMe,[6] -CONHR,[7] $-SO_2NHR$,[8] $-SO_2NR_2$,[9] $-CF_3$,[10,11] and -F.[12] Pertinent data concerning the metalation of these substituted benzenes[13] are presented in Table I. Since a number of biological compounds contain aromatic systems with a methoxy or hydroxy substituent along with various amine, carboxamide, and sulfonamide substituents,[14] a knowledge of the relative ortho-directing abilities of the various substituents toward metalation would be of great utility in planning the synthesis of such compounds.

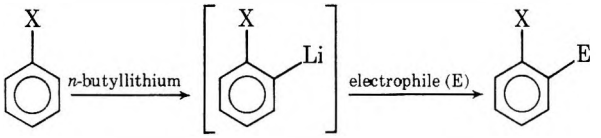
In three instances, data have appeared in the literature for para-substituted anisoles from which the relative directing ability of the methoxy group vs. a few other groups can be assessed. Klein and Hauser[15] found that metalation of *p*-methoxy-*N*,*N*-dimethylbenzylamine (**4**) gave exclusive 70% metalation ortho to the dimethylaminomethyl group based upon the yield of benzophenone adduct. Metalation of the corresponding meta-substituted isomer gave, exclusively, 75% metalation at the position ortho to both substituents, indicating that steric effects apparently were negligible in this case. Narasimhan and Bhide[16] later examined the metalation of *p*-, *m*-, and o-methoxy-*N*,*N*-dimethylbenzylamine (**4**, **5**, and **6**) as a synthetic route to methoxy isoquinolines and found that, in agreement with the results of Hauser and co-workers, metalation of the para and meta isomers (**4** and **5**) occurred at the position ortho to the amine side chain, and at the position mutually ortho to both substituents, respectively. Metalation of the ortho isomer (**6**) led to the observation that ". . . the reaction took a complex course and no useful result was obtained".

Narasimhan and Bhide[16] also examined the metalation of the *o*-, *m*-, and *p*-methoxy-*N*-methylbenzamides as a possible route to methoxy isocoumarins and found that metalation of the para and meta isomers (**10** and **11**) occurred in good yields at the position ortho to the amide substituent, and at the position mutually ortho to both substituents, respectively. Once again, however, ". . . complications were encountered . . ." with the ortho isomer.

Metalation of *p*-fluoroanisole with *n*-butyllithium[17] gave upon carbonation 2-methoxy-5-fluorobenzoic acid in 13% yield whereas metalation with methyllithium[18] gave a 17% yield of the same acid.

Although the relative directing ability of the methoxy group

Table I. Metalation of Monosubstituted Benzenes with *n*-Butyllithium



Registry no.	X	E	*n*-BuLi/ substrate	Solvent	Metalation period, h	Temp, °C	% yield	Ref
121-69-7	$-NMe_2$	Ph_2CO	1.0	Hexane	12	68	56	3
103-83-3	$-CH_2NMe_2$	Ph_2CO	2.0	Ether/hexane	18	25	84	4
1126-71-2	$-CH_2CH_2NMe_2$	Ph_2CO	1.2	Ether/hexane	11	25	7[a]	5
100-66-3	$-OMe$	CO_2	1.0	Ether/hexane	21	35	65	6, 11
613-93-4	$-CONHMe$	Ph_2CO	2.5[b]	THF/hexane	0.25	65	81	7
5183-78-8	$-SO_2NHMe$	Ph_2CO	2.5[b]	THF/hexane	0.25	0	82	8
14417-01-7	$-SO_2NMe_2$	Ph_2CO	1.2	THF/hexane	0.25	0	82	9
98-08-8	$-CF_3$	CO_2	1.5	Ether	6	35	48[c]	10
462-06-6	$-F$	CO_2	1.0	THF	7	−50	60	12

[a] Apparently reaction proceeded to give mostly styrene via elimination. [b] A molar ratio of 2 butyllithium to 1 substrate needed owing to formation of dilithio intermediate. [c] Also gave approximately 8% of meta acid as product.

vs. three other directing substituents could be qualitatively determined from the literature in a limited number of cases, it appeared worthwhile to examine the entire series of eight substituents vs. the methoxy substituent and, to some extent, assess the relative importance of coordination and electronic effects on the directing ability of the various substituents. In addition, examination of the ortho and meta isomers was deemed of interest because of the potential utility of this method as a route to a series of relatively inaccessible 1,2,3-trisubstituted benzenes.

The addition of TMEDA to the reaction mixture has exerted a profound influence upon the rate of metalation of benzene[19] and toluene[20] substrates. The effect of TMEDA upon the rate and site of metalation in some systems involving a heteroatom has been noted in a preliminary communication.[21] Increased rates of ortho metalation were observed for dimethylbenzylamine, dimethylaniline, and anisole. In addition the site of metalation for *p*-methoxy-*N,N*-dimethylbenzylamine was altered from the usual site ortho to the amine side chain to the site ortho to the methoxy substituent by the addition of 1 equiv of TMEDA to the metalation reaction mixture.

A method for controlling the site of metalation at either the 2 or 8 position of 1-methoxynaphthalene by use of *n*-butyllithium/TMEDA has recently been described.[22] It was found that metalation of 1-methoxynaphthalene with *n*-butyllithium in ether/hexane gave upon carbonation a 28% yield of carboxylic acid products consisting of 73% 2 metalation and 27% 8 metalation. Under the same reaction conditions except that 1 equiv of TMEDA was present a product composition of 99.3% 2 metalation and 0.3% 8 metalation was obtained. The yield of 1-methoxy-2-naphthalenecarboxylic acid was increased to 60%. Similarly, increased rate as well as increased selectivity has been noted[23a] upon using *n*-butyllithium/TMEDA in the metalation of *o*- and *p*-*N,N*-dimethyltoluidines.

We would now like to report a comprehensive study of the ortho-directing ability of the methoxy substituent relative to other ortho-directing substituents in metalation reactions with *n*-butyllithium. Also discussed is the effect of TMEDA on the rate and course of the directed metalation reaction.

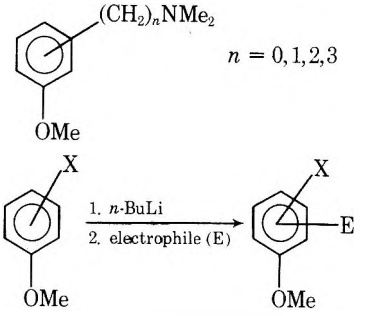
Results and Discussion

Since there are eight ortho-directing groups besides the methoxy group ($-NMe_2$, $-CH_2NMe_2$, $-CH_2CH_2NMe_2$, $-CONHR$, SO_2NHR, SO_2NR_2, $-CF_3$, and $-F$) a simple calculation shows that 24 substituted anisoles exist if all para, meta, and ortho isomers are considered. However, certain of the meta and ortho compounds were accessible only through rather complicated synthetic routes and in most of these cases it was felt that examination of these compounds would lend little to the study. In all, 16 of the isomers including all the para isomers and representative meta and ortho compounds were prepared: *p*-, *m*-, and o-methoxy-*N,N*-dimethylaniline (**1, 2,** and **3,** respectively), *p*-, *m*-, and *o*-methoxy-*N,N*-dimethylbenzylamine (**4, 5,** and **6,** respectively), *p*- and o-methoxy-*N,N*-dimethylphenethylamine (**7** and **8,** respectively), *p*-, *m*-, and *o*-methoxy-*N*-methylbenzamide (**10, 11,** and **12,** respectively), *p*-methoxy-*N*-methylbenzenesulfonamide (**15**), *p*-methoxy-*N,N*-dimethylbenzenesulfonamide (**16**), *p*-methoxybenzotrifluoride (**17**), and *p*- and *o*-fluoroanisole (**18** and **19,** respectively). These compounds were obtained by either the synthetic procedure or from the commercial source given in the Experimental Section. In addition 3-(*p*-methoxyphenyl)-*N,N*-dimethylpropylamine (**9**), *p*-methoxy-*N,N*-dimethylbenzamide (**13**), and *p*-methoxyphenyl-*N*-methylacetamide (**14**) were prepared. All compounds were metalated with *n*-butyllithium using 1 equiv of *n*-butyllithium except for the methoxy-*N*-methylbenzamides (**10, 11, 12**), *p*-methoxy-*N*-methylbenzenesulfonamide (**15**), and phenylacetamide (**14**). In these systems 2 equiv of *n*-butyllithium was used, since the first equivalent was completely consumed in the abstraction of the amide proton. When conditions favoring metalation ortho to group one and those conditions favoring metalation ortho to group two of the disubstituted benzene were considerably different, the disubstituted benzene was metalated under both sets of conditions. However, as indicated in Tables II–IV, no appreciable change in orientation was brought about by this particular variance in the reaction conditions.

An examination of the effect of tetramethylethylenediamine upon the metalation reaction was accomplished by the addition of 1 equiv (with respect to the molar quantity of *n*-butyllithium or substrate) of this reagent to the reaction mixture. The *n*-butyllithium/TMEDA complex was first formed by dissolving TMEDA in the solvent and treating with *n*-butyllithium. Metalation was accomplished by adding the substrate to the *n*-butyllithium/TMEDA complex solution. In the equations which follow, yields in parentheses are those using TMEDA.[23b]

Aminoanisoles [Substituents $(CH_2)_nNMe_2$, n = 0, 1, 2, 3]. $-NMe_2$. Metalation of *N,N*-dimethyl-*p*-anisidine (**1**) with *n*-butyllithium indicated that metalation proceeded in 71% yield at the position ortho to the methoxy group, judging from the condensation product with benzophenone. The site of metalation was determined by NMR analysis of the D_2O hydrolysis product. Although the NMR spectrum of anisidine **1** did not exhibit an AA′BB′ spectrum for the aromatic pro-

Table II. Metalation Data for Aminoanisoles (1–9)



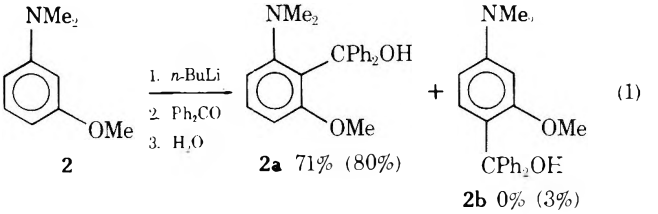
Compd	X	Metalation conditions			Electrophile	% product ortho to	
		Agent[a]	Time, h	Temp, °C		Methoxy	X substituent
1	p-NMe_2	A	12	35	Ph_2CO	71	
1	p-NMe_2	A	12	35	D_2O	85	
1	p-NMe_2	A	21	35	D_2O	85	
1	p-NMe_2	B	0.25	35	D_2O	22	
1	p-NMe_2	B	5	35	D_2O	45	
1	p-NMe_2	B	12	35	D_2O	78	
2	m-NMe_2	A	12	35	Ph_2CO	71[b]	
2	m-NMe_2	B	12	35	Ph_2CO	80[b]	3[c]
3	o-NMe_2	A	12	35	Ph_2CO	56	
3	o-NMe_2	B	12	35	Ph_2CO	49	
4	p-CH_2NMe_2	A	24	27	Ph_2CO		80
4	p-CH_2NMe_2	A	24	27	D_2O		70
4	p-CH_2NMe_2	B	2	27	Ph_2CO	55	7
4	p-CH_2NMe_2	B	5	27	D_2O	48	18
4	p-CH_2NMe_2	B	0.25	27	D_2O	37	18
4	p-CH_2NMe_2	B	24	27	D_2O	16	5
5	m-CH_2NMe_2	A	2	27	Ph_2CO	79[b]	
5	m-CH_2NMe_2	B	0.5	27	Ph_2CO	62[b]	
5	m-CH_2NMe_2	B	5	27	Ph_2CO	54[b]	
6	o-CH_2NMe_2	A	24	27	Ph_2CO	30–35	4–10[c]
6	o-CH_2NMe_2	A	2	27	Ph_2CO	58	<5[c]
6	o-CH_2NMe_2	B	5	27	Ph_2CO	38	8[c]
7	p-$CH_2CH_2NMe_2$	A	32	27	Ph_2CO	60	
7	p-$CH_2CH_2NMe_2$	A	28	27	D_2O	72	
7	p-$CH_2CH_2NMe_2$	B	2	27	D_2O	55	
7	p-$CH_2CH_2NMe_2$	B	24	27	D_2O	23	
8	o-$CH_2CH_2NMe_2$	A	28	27	Ph_2CO	*d*	
8	o-$CH_2CH_2NMe_2$	A	2	27	Ph_2CO	*d*	
8	o-$CH_2CH_2NMe_2$	B	4	27	Ph_2CO	*d*	
9	p-$CH_2CH_2CH_2NMe_2$	A	24	27	Ph_2CO	71	
9	p-$CH_2CH_2CH_2NMe_2$	A	2	27	D_2O	26	
9	p-$CH_2CH_2CH_2NMe_2$	A	24	27	D_2O	70	
9	p-$CH_2CH_2CH_2NMe_2$	B	0.25	27	D_2O	56	
9	p-$CH_2CH_2CH_2NMe_2$	B	5	27	D_2O	64	

[a] Metalation agents: A, 1.0 equiv *n*-BuLi/equiv substrate; ether–hexane solvent; B, 1.0 equiv *n*-BuLi + 1.0 equiv TMEDA/equiv substrate; ether–hexane solvent. [b] Metalation occurred at position between two substituents. [c] These yields determined by NMR data; product not isolated. [d] Compound **6** apparently underwent elimination to give *o*-methoxystyrene.

tons, the quaternary methiodide salt of *p*-anisidine showed such a spectrum in the τ 2.50 region. Hydrolysis of the lithio intermediate of *N,N*-dimethyl-*p*-anisidine (1) with D_2O and subsequent treatment with methyl iodide gave a deuterated methiodide of compound 1 having 2.00 protons downfield and 1.15 protons in the upfield portion of the AA′BB′ system. The downfield portion of the spectrum was assigned to the protons ortho to the quaternary amine substituent due to its deshielding effect. This result corresponded to an 85% yield of metalation at the position ortho to the methoxy substituent.

The addition of TMEDA to the metalation mixture had no effect upon the site of metalation and very little effect upon the yield of ortho metalation as yields of 22, 45, and 78% metalation ortho to the methoxy substituent were realized after metalation periods of 0.25, 5, and 12 h, respectively. These yields were determined by the extent of NMR signal attenuation after deuterolysis of the lithio intermediate as described above. Products resulting from metalation at the position ortho to the dimethylamine substituent were not detected in any of the experiments performed.

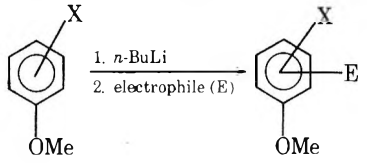
Metalation of *N,N*-dimethyl-*m*-anisidine (2) gave the anticipated result of metalation at the site mutually ortho to both substituents (eq 1). Condensation of the lithio intermediate of anisidine **2** with benzophenone gave as the sole product a 71% yield of 2-diphenylhydroxymethyl-*N,N*-dimethyl-*m*-anisidine (**2a**).



2 **2a** 71% (80%) **2b** 0% (3%)

Determination of the orientation of substituents in benzophenone condensation products such as **2a** resulting from

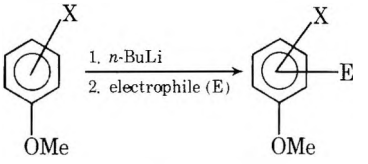
Table III. Metalation Data for Carboxamidoanisoles (10–14) and Sulfonamidoanisoles (15, 16)



Compd	Substituent X	Metalation conditions			Electrophile	% product ortho to X substituent
		Agent[a]	Time, h	Temp, °C		
10	*p*-CONHMe	A	0.25	65	Ph_2CO	47
10	*p*-CONHMe	A	0.25	65	D_2O	40
10	*p*-CONHMe	A	24	65	D_2O	50
10	*p*-CONHMe	B	5	65	D_2O	60
11	*m*-CONHMe	A	0.25	65	Ph_2CO	48[b]
11	*m*-CONHMe	B	1	65	Ph_2CO	65[b]
12	*o*-CONHMe	A	5	65	Ph_2CO	46
12	*o*-CONHMe	B	0.25	65	Ph_2CO	23
12	o-CONHMe	B	1	65	Ph_2CO	53
13	*p*-$CONMe_2$	C	0.25	35	Ph_2CO	c
14	*p*-$CH_2CONHMe$	A	0.5	27	D_2O	*d*
14	*p*-$CH_2CONHMe$	A	24	27	D_2O	*d*
15	*p*-SO_2NHMe	A	0.5	0–5	Ph_2CO	77
15	*p*-SO_2NHMe	A	0.5	0–5	D_2O	80
15	*p*-SO_2NHMe	B[e]	0.5	0–5	Ph_2CO	50
15	*p*-SO_2NHMe	B[e]	0.5	0–5	D_2O	65
16	*p*-SO_2NMe_2	D	0.5	0–5	Ph_2CO	62
16	*p*-SO_2NMe_2	D	0.5	0–5	D_2O	74
16	*p*-SO_2NMe_2	E	1.0	27	D_2O	*f*

[a] Metalation agents: A, 2.0 equiv *n*-BuLi/equiv substrate, since first equivalent of base required to abstract amide proton; THF–hexane solvent; B, 2.0 equiv *n*-BuLi + 2.0 equiv TMEDA/equiv substrate; THF–hexane solvent; C, 1.0 equiv *n*-BuLi/equiv substrate; ether–hexane solvent; D, 1.0 equiv *n*-BuLi/equiv substrate; THF–hexane solvent; E, 1.0 equiv *n*-BuLi + 1.0 equiv TMEDA/equiv substrate; ether–hexane solvent. [b] Metalation occurred at position between two substituents and product isolated was the lactone which obviously arose from the appropriate ortho carbinolamide. [c] Compound 13 apparently underwent nucleophilic displacement of amide carbonyl to give 78% yield of *p*-methoxyvalerophenone. No ring metalation products were detected. [d] Compound 14 gave metalation exclusively at the benzyl and amide position. No ring metalation was detected. [e] Solvent employed for metalation using TMEDA was ether–hexane rather than THF–hexane. Metalations using TMEDA in THF–hexane gave no metalated products. [f] Under these conditions compound 16 apparently underwent nucleophilic attack at the sulfonamide linkage. No ring metalation products were detected.

Table IV. Metalation Data for Trifluoromethyl- and Fluoroanisoles (17–19)



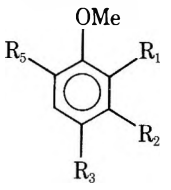
Compd	Substituent X	Metalation conditions			Electrophile	% product ortho to methoxy
		Agent[a]	Time, h	Temp, °C		
17	*p*-CF_3	A	6	35	Ph_2CO	79
17	*p*-CF_3	A	6	35	D_2O	92
17	*p*-CF_3	A	21	35	D_2O	90
17	*p*-CF_3	B	4	35	D_2O	90
18	*p*-F	A	7	−50	CO_2	*b*
18	*p*-F	C	5	27	CO_2	32
18	*p*-F	B	5	27	CO_2	c
19	o-F	C	5	27	CO_2	*d*
19	o-F	B	2	27	CO_2	*e*

[a] Metalation agents: A, 1.0 equiv *n*-BuLi/equiv substrate; ether–hexane solvent; B, 1.0 equiv *n*-BuLi + 1.0 equiv TMEDA/equiv substrate; ether–hexane solvent; C, 1.0 equiv *n*-BuLi/equiv substrate; THF–hexane solvent. [b] Only starting fluoroanisole was recovered. No metalation products were observed. [c] No metalation products were obtained. Reaction product carried phenolic odor. [d] Base-soluble material contained 36% yield of o-fluorophenol apparently via nucleophilic attack at the methoxy group. Starting fluoroanisole recovered in 32% yield. [e] Base-soluble material contained 27% yield of *o*-fluorophenol. Starting fluoroanisole recovered in 44% yield.

directed lithiation of the various anisoles was based largely on anisotropic effects exerted by the diphenylcarbinol substituent upon the protons of ortho-situated substituents.[24] An upfield shift of at least 10 Hz was deemed sufficient to identify the substituent(s) ortho to the diphenylcarbinol moiety (Table V).

Metalation of anisidine **2** using *n*-butyllithium/TMEDA followed by condensation with benzophenone produced a crude product which appeared to be a mixture of two isomers in a ratio of approximately 20:1. The NMR absorptions of the more abundant isomer were identical with those of the 1,2,3-oriented carbinolamine **2a**. Based on data recorded in

Table V. Proton Anisotropic Shifts (Relative to Monosubstituted Anisole) Due to Introduction of Diphenylcarbinol Substituent. Metalation Site Determination[a]



Compd	Proton anisotropic shifts for –OMe	–NMe_2	CH_2NMe_2[b]	Inferred position of $–CPh_2OH$
2a	+28.5	+22.0 (R_2)		R_1
2b	0	+35.0 (R_2)		R_5
3a	+34.0	+13.5 (R_1)		R_5
4a	+8.5		+24.5 (R_3)	R_2
4b	+14.0		+7.5 (R_3)	R_1
6a	+39.0		+1.0 (R_1)	R_5
6b	+9.0		+14.5 (R_1)	R_2

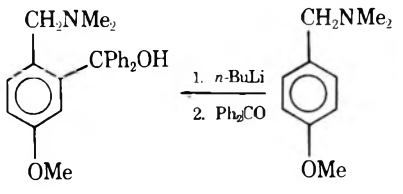
[a] All spectra obtained in $CDCl_3$; for a further explanation of this technique see ref 24. [b] Anisotropic shifts reported for methylene protons.

Table V isomer **2b** was identified as the 1,3,4 isomer. The products **2a** and **2b** were obtained in 80 and 3% yields, respectively.

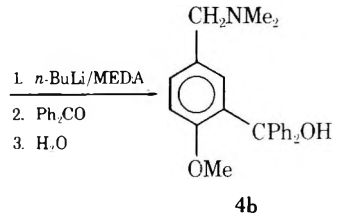
Metalation of *N,N*-dimethyl-*o*-anisidine (**3**) with *n*-butyllithium followed by condensation with benzophenone gave a crude product which was shown by its NMR spectrum to contain only one of two possible isomers. The product, obtained in 56% yield, was identified as 3-diphenylhydroxymethyl-*N,N*-dimethyl-*o*-anisidine (**3a**) on the basis of its NMR data (Table V).

Metalation of anisidine **3** using *n*-butyllithium/TMEDA produced a crude product after condensation with benzophenone that was shown by NMR analysis to contain only isomer **3a.** The use of TMEDA did not appear to have any significant effect upon the yield of **3a** as 49% of this product was obtained.

–CH_2NMe_2. Results from the metalation of *p*-methoxy-*N,N*-dimethylbenzylamine (**4**) indicated agreement with previous work[15,16] in that good yields of metalation exclusively at the position ortho to the amine side chain were obtained. Condensation of the lithio intermediate with benzophenone afforded an 80% yield of the benzophenone adduct (**4a**) (eq 2). The site of metalation in compound **4** has been verified in this study by application of our anisotropy technique (Table V)[24] and by hydrolyzing the lithio intermediate with D_2O followed by analysis of the NMR spectrum of the deuterated product. The NMR spectrum of amine **4** gave a well-resolved



4a **4**



(2)

4b

AA′BB′ system in the τ 3.0 region for which the upfield proton signal was assigned to the protons ortho to the methoxy group. These assignments were based on a comparison with the NMR spectrum of *p*-methylanisole in which the upfield signal was assigned[25] to the protons ortho to the methoxy group. The deuterated product obtained via metalation of amine **4** followed by hydrolysis with D_2O showed attenuation of the downfield proton signal and broadening of the upfield signal indicating deuterium incorporation ortho to the amine side chain. Integration of relative signal intensities indicated deuterium incorporation of about 70% of one deuterium.

In addition to the above results it was discovered that the site of ring metalation in *p*-methoxy-*N,N*-dimethylbenzylamine (**4**) can actually be reversed through the use of tetramethylethylenediamine (TMEDA). Metalation of amine **4** for 5 h with the addition of 1 equiv of TMEDA gave 55% metalation at the position ortho to the methoxy group based on NMR integration of the D_2O hydrolysis product. A small amount of deuterium incorporation at the position ortho to the amine side chain was also indicated.

Metalation of amine **4** with the *n*-butyllithium/TMEDA complex for 2 h followed by condensation with benzophenone gave products **4b** and **4a** in 55 and 7% yields, respectively (eq 2). This preferential metalation ortho to the methoxy group in the presence of TMEDA may reflect some manifestation of lower order coordination in this system when compared to *n*-butyllithium/ether or it simply may reflect metalation at the most acidic site of the substrate.

Identification of isomer **4b** was based upon spectral and analytical data. The NMR data shown in Table XI (see paragraph at end of paper regarding supplementary material) indicated that the diphenylcarbinol substituent was situated at a ring position different than that of isomer **4a.** The relative integration of the $–OCH_3$ and $–CH_2–$ protons of **4a** and **4b** were identical, indicating that metalation had not occurred at these positions. The anisotropic data shown in Table V were consistent with a compound having the diphenylcarbinol substituent situated at the position ortho to the methoxy substituent.

Results obtained in the metalation of *m*-methoxy-*N,N*-dimethylbenzylamine (**5**) likewise indicated agreement with previous work[15,16] in that good yields of metalation exclusively at the position mutually ortho to both the methoxy and the amine side chain were obtained. Condensation of the lithio intermediate with benzophenone gave the corresponding, 1,2,3-trisubstituted benzene product (**5a**) in 79% yield. This result indicated that the transition state involved in stabilizing metalation at the position ortho to the dimethylaminomethyl side chain apparently was not sterically hindered by the presence of the methoxy group. In fact the methoxy group apparently contributed to the stability of the intermediate to some extent; otherwise metalation would have proceeded at the position ortho to the amine side chain but para to the methoxy group. This result was somewhat surprising in view of a previous examination of the steric and conformational aspects of alkyl aryl ether metalations[26] which had indicated that an increase in the steric bulk of the alkyl group resulted in a decrease in the overall rate of metalation.

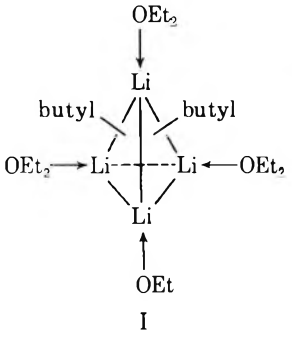
As recorded in Table II, metalation of amine **5** in the presence of TMEDA had no effect upon the site of metalation. Apparently the combined ortho-directing effects of 2 coordination by the dimethylaminomethyl substituent and inductive electron withdrawal by the methoxy substituent served to stabilize metalation at the position mutually ortho to both substituents to such an extent that an orientation reversal was not observed when the reaction was carried out in the presence of TMEDA.

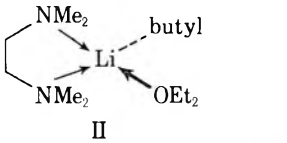
Previous attempts to metalate *o*-methoxy-*N,N*-dimethylbenzylamine (**6**) were reported to be unsuccessful.[16]

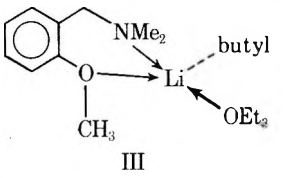
In this study amine **6** was observed to undergo metalation in good yield, primarily at the position ortho to the methoxy group, although small amounts of metalation were observed at the position ortho to the dimethylaminomethyl substituent (Table II).

Metalation of amine **6** for 24 h and condensation of the lithio intermediate with benzophenone gave a 30–35% yield of 3-diphenylhydroxymethyl-2-methoxy-*N*,*N*-dimethylbenzylamine (**6a**) and a 4–10% yield of another isomer, presumably the corresponding 6 isomer **6b**. Isomer **6b** was not separated and characterized but was noted in the NMR spectrum of the reaction product; its structure is inferred from the data in Table V. Metalation of amine **6** for a period of 2 h gave 58% of **6a** and 5% of **6b**.

It is interesting to speculate as to the cause of domination of the methoxy group over the dimethylaminomethyl substituent in its ability to direct ortho metalation in amine **6**. It has been suggested that *n*-butyllithium in ether exists as a tetramer[27] as in structure I (*n*-butyl chains are also bonded







to the away faces of the pyramid). *n*-Butyllithium in an ether solution of TMEDA exists as a 1:1 complex that is monomeric,[2b] perhaps similar to structure II. Amine **6** is also capable of forming a 1:1 bidentate complex with *n*-butyllithium as illustrated in structure III. Models show that the O–N distance in amine **6** is essentially identical with the N–N distance in TMEDA. Para and meta amines **4** and **5** were incapable of such bidentate coordination; thus tetrameric *n*-butyllithium apparently effected metalation ortho to the dimethylaminomethyl substituent. Metalation of amines **4** and **5** by monomeric *n*-butyllithium generated in the presence of bidentate TMEDA occurred ortho to the methoxy group. In the case of methoxyamine **6** the possibility exists of the formation of monomeric *n*-butyllithium via complexation by the bidentate methoxyamine (III). As a result, metalation with or without TMEDA was observed to occur ortho to the methoxy group, the predicted site for metalation by monomeric *n*-butyllithium. This more basic, lower order coordinated metalating reagent may simply effect metalation at the most acidic site in the molecule, presumably in each case that ortho to the methoxy group.

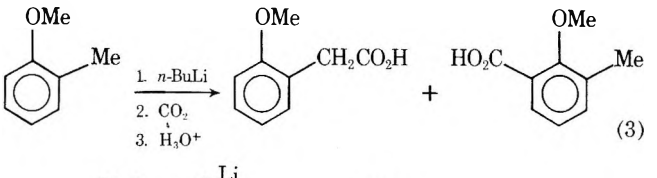
The identification of amine **6a** was determined from a number of observations. The benzophenone condensation product exhibited an NMR spectrum for which data shown in Table V are consistent with the situation of the diphenylcarbinol substituent ortho to the methoxy group. An ir spectrum of the benzophenone condensation product of the lithio intermediate of amine **6** exhibited a sharp O–H stretching frequency indicative of a "free" hydroxyl group experiencing little hydrogen bonding. If the diphenylcarbinol substituent had been situated ortho to the dimethylaminomethyl group an ideal intramolecular hydrogen bonding situation would exist and a broad hydroxyl absorption should have been observed.

The methiodide salt of carbinolamine **6a** was formed and subjected to a temperature of 200 °C. Under these conditions the methiodide salts of corresponding isomers **4a** and **5a** cyclized to give the cyclic ethers.[15] The methiodide salt of carbinolamine **6a** gave no detectable cyclic ether under these conditions suggesting metalation at a site other than that ortho to the dimethylaminomethyl group.

–$CH_2CH_2NMe_2$. The dimethylaminoethyl substituent has recently been demonstrated to be a good ortho-directing substituent as excellent yields of 2 metalation in *N*,*N*-dimethylaminoethylferrocene were obtained.[28] The benzene analogue, *N*,*N*-dimethyl-β-phenethylamine, has been shown[5] to give small amounts of ortho metalation but the primary course of reaction with *n*-butyllithium was the elimination of the elements of dimethylamine to give a styrene residue. Apparently the acidity of the benzyl proton was sufficiently greater than that of the ortho proton that metalation occurred at the benzyl site to give a lithio intermediate capable of facile elimination of the dimethylamide anion.

It was hypothesized that a methoxy group situated at the para position of *N*,*N*-dimethylphenethylamine might sufficiently decrease the acidity of the benzyl proton to permit ortho metalation to compete effectively with the elimination reaction. Metalation of *p*-methoxy-*N*,*N*-dimethylphenethylamine (**7**) with *n*-butyllithium in ether-hexane for 32 h gave 60% metalation exclusively ortho to the *methoxy* group, judging from the benzophenone condensation product. Hydrolysis of the metalation mixture with D_2O gave recovered amine **7** having 1.28 protons remaining (72% metalation) at the position ortho to the methoxy substituent. The NMR spectrum of amine **7** gave a well-resolved AA′BB′ system in the τ 3.1 region. In accord with the proton assignments of *p*-methylanisole,[25] which gives a similar AA′BB′ system, the upfield proton resonance was assigned to the protons situated ortho to the methoxy substituent. This metalation result was of interest because it reflected the superior ability of the dimethylaminomethyl substituent over the dimethylaminoethyl substituent to direct metalation to the ortho position. No vinyl products were found, a situation which was also true for *N*,*N*-dimethylaminoethylferrocene.[28]

Earlier results had indicated that the methoxy substituent situated at the para position on a benzene ring played an important role in decreasing the acidity of benzyl protons to such an extent that ring metalation could be effected. Results from the metalation of *o*-methylanisole[29] indicated that an ortho-situated methoxy group may have an entirely different effect upon benzyl anion formation (eq 3). Metalation of o-methylanisole followed by carbonation reportedly gave equal amounts (although in low yield) of side-chain and ring metalated products. Although the authors did not elaborate upon the reasons for stabilization of the benzyl anion, it seemed plausible to consider stabilization via a five-membered coordinate ring as shown in structure IV. Stabilization simply by inductive electron withdrawal by oxygen (structure IVa) could also stabilize the benzyl anion.



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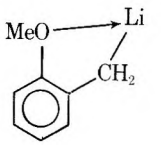
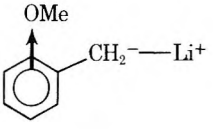


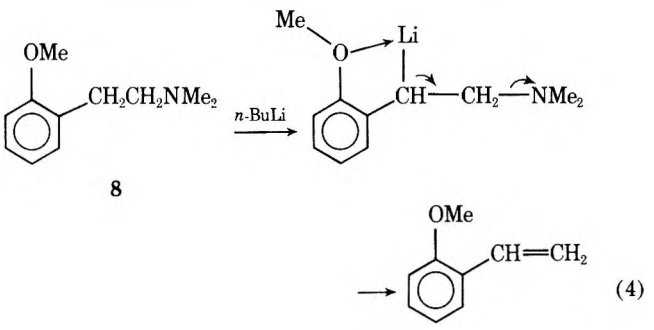
IV



IVa

Attempts to metalate *o*-methoxy-*N*,*N*-dimethylphenethylamine (**8**) gave no detectable ortho-metalation product. Compound **8** apparently underwent elimination to give a methoxystyrene residue as evidenced by ir data (band at 6.2

μ) and NMR data (absence of $-NMe_2$ methyls and presence of vinyl proton absorptions). Presumably the *o*-methoxy substituent facilitated formation of the benzyl anion intermediate which could easily collapse to olefin with elimination of the dimethylamide anion (eq 4). Metalation of amine **8** with

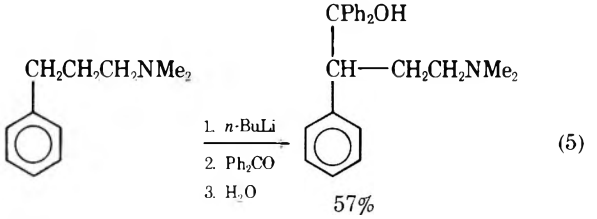


8

(4)

n-butyllithium/TMEDA likewise gave no ortho metalation, judging from the absence of any diphenylcarbinol product after treatment of the reaction mixture with benzophenone.

$-CH_2CH_2CH_2NMe$. The role of the methoxy group in decreasing the acidity of benzyl protons was further illustrated in the case of 3-(*p*-methoxyphenyl)-*N,N*-dimethylpropylamine. Metalation of 3-phenyl-*N,N*-dimethylpropylamine and condensation of the lithio intermediate with benzophenone has been reported to give the metalation product resulting from metalation exclusively at the benzyl position[30] (eq 5).



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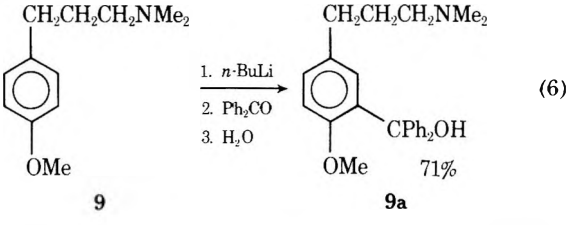


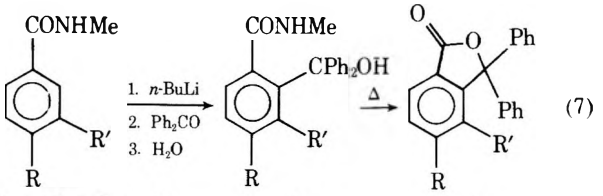
9 **9a**

(6)

Metalation of 3-(*p*-methoxyphenyl)-*N,N*-dimethylpropylamine (**9**) followed by condensation with benzophenone gave a 71% yield of carbinolamine **9a** having the diphenylcarbinol substituent situated on the ring ortho to the methoxy group (eq 6). No other isomeric products were detected. Proof of structure for the benzophenone condensation product **9a** was based on NMR and analytical data recorded in Tables X and XI (see paragraph at end of paper regarding supplementary material). The site of metalation was determined by hydrolysis of the metalation mixture with D_2O and analysis of the AA'BB' system as was done previously for amines **4** and **7**.

The use of TMEDA appeared to have no effect upon the orientation of metalation for phenethylamine **7** and phenylpropylamine **9**. As shown in Table II a significant increase in the rate of metalation of these amines was observed although extended metalation periods using TMEDA actually tended to decrease the yield of metalation of amine **1**. Optimum periods for metalation of amines of this type with TMEDA appeared to be 2–4 h.

Amide Anisoles (Substituents $-CONHMe$, $-CONMe_2$, $-CH_2CONHMe$). $-CONHMe$. Results from the metalation of *p*-methoxy-*N*-methylbenzamide (**10**) indicated partial agreement with previous work,[16] in that metalation was found to proceed in good yield exclusively at the position ortho to the carboxamide substituent. Under the experimental conditions employed (*n*-butyllithium in refluxing ether followed by condensation with benzophenone at room temperature) the carbinolamide **10a** (mp 198 °C dec to expel a basic gas) was isolated as the sole product in 47% yield. Earlier reports[16] identified the corresponding lactone **10b** as the reaction product. However, upon heating carbinolamide **10a** near 200 °C essentially quantitative conversion to the lactone **10b** was observed (eq 7).



10, R = OMe; R′ = H **10a** **10b**
11, R = H; R′ = OMe **11a** **11b**

(7)

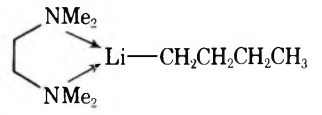
The ring proton NMR spectrum of amide **10** exhibited a well-resolved AA'BB' spectrum in which the upfield resonance was assigned to the protons ortho to the methoxy group. The data for D_2O incorporation listed in Table III were obtained from the NMR integration of the D_2O hydrolysis products. Metalation of amide **10** using *n*-butyllithium/TMEDA produced a slight increase in the amount of metalation ortho to the carboxamide substituent (60% metalation after 5 h).

Reexamination of the metalation of *m*-methoxy-*N*-methylbenzamide (**11**) indicated agreement with a previous study[16] in that a good yield of metalation exclusively at the position mutually ortho to both substituents was observed. Condensation of the lithio intermediate of amide **11** with benzophenone afforded the corresponding lactone **11b** (48% yield) which, in view of the result for amide **10**, certainly arose from the corresponding carbinolamide **11a**. None of the isomeric carbinolamide resulting from metalation at either of the other two possible metalation sites was observed.

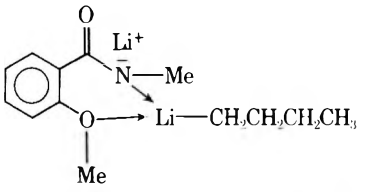
It is interesting to note that although identical conditions were employed for both amides **10** and **11**, amide **10** gave the carbinolamide product **10a** while amide **11** gave the lactone product (**11b**). The difference in product appears to be another manifestation of the effect of a para-situated methoxy group. Apparently, the resonance effects of the methoxy group situated para to the carboxamide substituent decreased the electrophilicity of the carbonyl group and therefore discouraged cyclization which would have involved nucleophilic substitution at the carbonyl. The methoxy substituent situated meta to the carbonyl could not donate deactivating negative charge to the carbonyl and therefore cyclization via nucleophilic substitution occurred at room temperature.

Metalation of amide **11** with *n*-butyllithium/TMEDA resulted in a substantial increase in yield of metalation as a 65% yield of lactone **11b** was obtained. No isomeric products resulting from metalation at either of the two possible metalation sites were observed.

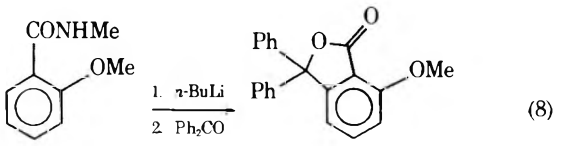
It was reported in an earlier study[16] that metalation of *o*-methoxy-*N*-methylbenzamide (**12**) gave extremely poor yields of metalation ortho to the carboxamide substituent. Although the authors did not indicate the solvent employed for this experiment, it was presumed that THF was used since the metalation of *N*-methylbenzamide was carried out in THF. Our attempts to metalate amide **12** in THF met with no success. However, attempts to metalate amide **12** in ether gave a fair yield (46% lactone **12b**) which certainly arose via metalation ortho to the carboxamide substituent (eq 8). Metalation of amide **12** using *n*-butyllithium/TMEDA gave a slight increase in yield (53%) of the lactone product **12b**.



V



VI



12 12b 48% (65%) (8)

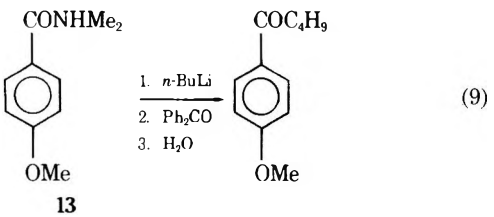
The fact that metalation of amide **12** proceeded only in ether solvent, whereas that of isomeric amides **10** and **11** proceeded in both ether and THF, would prompt one to speculate that the ortho situation of the methoxy and carboxamide substituents may have been responsible for this phenomenon. In the case of *o*-methoxy-*N,N*-dimethylbenzylamine (**6**) it was proposed that a complex could be formed with *n*-butyllithium in a manner similar to that with TMEDA and therefore monomeric *n*-butyllithium was responsible for the observed metalation ortho to the methoxy substituent.

Rausch and Ciappenelli have shown[31] that attempts to effect metalation using TMEDA in THF have been unsuccessful. Although THF often enhances the yield of metalation as compared to ether solvent, certain organolithium reagents are reportedly[32] relatively unstable in the presence of THF.

Perhaps complexation of the type shown by structure VI is responsible for generation of monomeric butyllithium in these solvent systems, as is the case when *n*-butyllithium is complexed with TMEDA (structure V). Since metalation in THF by monomeric butyllithium complexed with TMEDA is known to be unsuccessful, failure of metalation attempts in THF using monomeric butyllithium generated by complexation with amide **12** might be anticipated.

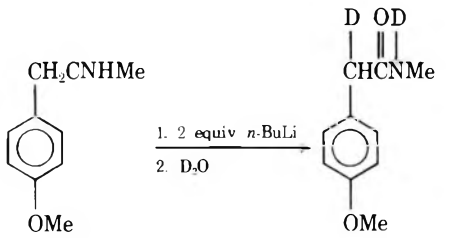
–CONMe$_2$ and –CH$_2$CONHMe. The electron-donating effects of the methoxy substituent situated at the para position of certain substituted benzenes was shown earlier in this study to decrease the acidity of benzyl protons and decrease the electrophilicity of the carbonyl group. These results prompted an examination of the metalation of *p*-methoxy-*N,N*-dimethylbenzamide (**13**) and *p*-methoxyphenyl-*N*-methylacetamide (**14**).

N,N-Dimethylbenzamide had been shown[7] to undergo substitution with *n*-butyllithium to form valerophenone. It was anticipated that the *p*-methoxy substituent would decrease the electrophilicity of the carbonyl sufficiently to allow the directed ring metalation as an alternative course of reaction. However, excellent yields of *p*-methoxyvalerophenone were obtained upon treatment of amide **13** with *n*-butyllithium (eq 9). Apparently the electron-donating effect of the para-situated methoxy substituent is not sufficient to discourage substitution at the amide carbonyl. No products resulting from ring metalation were observed.



13 (9)

In order to more accurately assess the effect of the para methoxy group upon benzyl proton acidity, the metalation of *p*-methoxyphenyl-*N*-methylacetamide (**14**) was examined. As might be expected, metalation of *N*-methylphenylacetamide with 2 equiv of *n*-butyllithium gave essentially quantitative metalation at the benzyl and amide proton sites. It was anticipated that the *p*-methoxy substituent would sufficiently decrease the benzyl proton acidity to allow ring metalation either ortho to the amide or methoxy substituent in amide **14**. However, the effect of the para-situated methoxy substituent was not sufficient to effect this result as near-quantitative metalation at the benzyl and amide protons of amide **14** was observed judging from NMR integration of the D$_2$O hydrolysis products (eq 10).



14 (10)

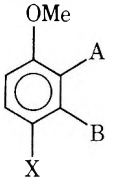
Although the results obtained for *p*-methoxy-*N,N*-dimethylphenethylamine (**7**), 3-(*p*-methoxy)-*N,N*-dimethylpropylamine (**9**), and methoxy-*N*-methylbenzamides **10**, **11**, and **12** indicated that the para-situated methoxy substituent is capable of altering the usual course of metalation in certain cases, apparently such influence is not sufficient to allow the predominance of ring metalation over alternate reaction routes for compounds **13** and **14**.

Sulfonamide Anisoles (Substituents –SO$_2$NHMe, –SO$_2$NMe$_2$). –SO$_2$NHMe. As shown in Table III, metalation of *p*-methoxy-*N*-methylbenzenesulfonamide (**15**) with *n*-butyllithium indicated that the methylsulfonamide group predominated over the methoxy substituent in ortho-directing ability to afford good yields of 4-methoxy-2-diphenylhydroxymethyl-*N*-methylbenzenesulfonamide (**15a**). Carbinolsulfonamide **15a** was not cyclized; rather identification of the site of metalation was based on hydrolysis of the lithio intermediate of sulfonamide **15** with D$_2$O and subsequent NMR integration of the deuterated product. Sulfonamide **15** exhibited an NMR spectrum having a well-resolved AA′BB′ pattern representing the aromatic protons in the τ 2.64 region. Based on the spectra of known compounds, the downfield resonance was assigned to the protons ortho to the sulfonamide substituent. Hydrolysis of the lithio intermediate of sulfonamide **15** gave a deuterated product having 1.20 protons downfield and 2.00 protons upfield in the AA′BB′ system.

Metalation of amide **15** using *n*-butyllithium/TMEDA brought about no change of orientation of metalation, although a slightly lower yield of carbinolsulfonamide **15a** was realized, possibly the result of the use of ether as solvent rather than THF.

–SO$_2$NMe$_2$. As shown in Table III, metalation of *p*-methoxy-*N,N*-dimethylbenzenesulfonamide (**16**) with *n*-butyllithium indicated that the dimethylsulfonamide substituent was a better ortho-directing substituent than the methoxy substituent. Proof of the site of metalation was based on NMR integration of the deuterated product obtained from hydrolysis of the lithio intermediate of sulfonamide **16** with D$_2$O. Sulfonamide **16** exhibited an NMR spectrum having a well-resolved AA′BB′ pattern in the τ 2.68 region representing the aromatic protons assignments for which were analogous to those of sulfonamide **15**.

Table VI. Competitive Metalation of Para-Substituted Anisoles



X	% metalation[a] Position A	Position B
$-CH_2NMe_2$	0 (55)	80 (7)
$-CONHMe$	0 (0)	50 (60)
$-SO_2NHMe$	0 (0)	80 (65)
$-SO_2NMe_2$	0 (0)	74 (0)
$-CH_2CH_2NMe_2$	72 (55)	0 (0)
$-CF_3$	92 (90)	0 (0)
$-NMe_2$	85 (78)	0 (0)
$-F$	32 (0)	0 (0)

[a] Yields for metalation using TMEDA are given in parentheses. Maximum yields from D_2O hydrolysis or benzophenone condensation are cited.

Attempts to metalate sulfonamide **16** with *n*-butyllithium/TMEDA were unsuccessful. Spectroscopic examination indicated that the *n*-butyl anion may have effected substitution at the sulfonamide linkage to give a sulfone derivative as evidenced by the presence of a nine-proton multiplet in the alkyl region of the NMR spectrum. This result was consistent with the observation that *N,N*-dimethylbenzamide was more susceptible to nucleophilic substitution at the carbonyl than was *N*-methylbenzamide.[7]

Fluorinated Anisoles (Substituents $-CF_3$, $-F$). $-CF_3$. Results obtained in the metalation of *p*-methoxybenzotrifluoride (**17**) indicated that the methoxy substituent was a better ortho director than was the trifluoromethyl substituent. The site of metalation was determined by NMR analysis of the deuterated product obtained by hydrolysis of the lithiointermediate of *p*-methoxybenzotrifluoride (**17**) with D_2O. Compound **17** exhibited a well-resolved AA'BB' spectrum in the τ 2.80 region representing the aromatic protons for which the downfield resonance was assigned to the protons ortho to the trifluoromethyl substituent. Judging from the data (Table IV), TMEDA apparently had little effect upon the course of metalation for compound **17**.

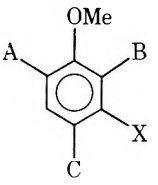
–F. Metalation of *p*-fluoroanisole (**18**) with *n*-butyllithium in THF at ambient temperature afforded 5-fluoro-2-methoxybenzoic acid (32%) upon carbonation with dry ice. *p*-Fluoroanisole was recovered in 42% yield and the crude product possessed a slight phenolic odor indicative of a small amount of decomposition to a phenolic product, perhaps *p*-fluorophenol. A previous study[17] had reported a 13% yield of 5-fluoro-2-methoxybenzoic acid via metalation with *n*-butyllithium.

It is interesting to note that the metalation of fluorobenzene itself was carried out at low temperatures (−50 °C) since benzyne formation to yield triphenylene occurs at room temperature.[17] However, attempts to metalate *p*-fluoroanisole at −50 °C were unsuccessful and only starting material was recovered.

Metalation of *p*-fluoroanisole using *n*-butyllithium/TMEDA followed by carbonation with dry ice gave no acid product except valeric acid. It is suggested that decomposition of the *p*-fluoroanisole to the corresponding phenol may account for a portion of the loss of starting material. Although this product was not isolated, the reaction product carried a strong phenolic odor.

Metalation of *o*-fluoroanisole (**19**) with *n*-butyllithium gave no ring metalation under the conditions employed. This result

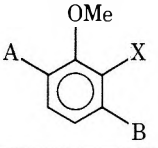
Table VII. Competitive Metalation of Meta-Substituted Anisoles



X	% metalation[a] Position B	Position C
$-CH_2NMe_2$	79 (62)	
$-CONHMe$	48 (65)	
$-NMe_2$	71 (80)	0 (3)

[a] Yields for metalation using TMEDA are given in parentheses. Maximum yields from D_2O hydrolysis or benzophenone condensation are cited.

Table VIII. Competitive Metalation of Ortho-Substituted Anisoles

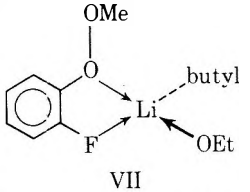


X	% metalation[a] Position A	Position B
$-CH_2NMe_2$	58 (38)	5 (8)
$-CH_2CH_2NMe_2$		
$-CONHMe$		46 (53)
$-NMe_2$	56 (49)	
$-F$		

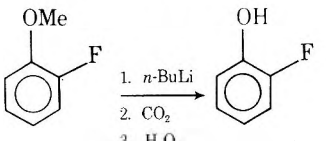
[a] Yields for metalation using TMEDA are given in parentheses. Maximum yields from D_2O hydrolysis or benzophenone condensation are cited.

was not surprising since our argument of bidentate chelation of certain ortho-substituted anisoles with *n*-butyllithium to form the monomeric complex could be extended to *o*-fluoroanisole (structure VII). Earlier it was noted that attempts to metalate *p*-fluoroanisole with *n*-butyllithium/TMEDA gave no ring metalation but instead some phenolic product was formed.

Metalation of *o*-fluoroanisole gave a product identified by ir spectroscopy as *o*-fluorophenol in 36% yield along with 33% recovery of *o*-fluoroanisole (eq 11). Attempted metalation of



VII



19 **19a** 36% (27%) (11)

o-fluoroanisole with *n*-butyllithium/TMEDA gave a 27% yield of *o*-fluorophenol along with 44% recovery of starting material. No ring metalation products were detected in any of the experiments performed.

Conclusions

Tables VI–VIII provide a summary of metalation results

Table IX. Preparation of Substituted Anisoles[a]

Compd	X	% yield	Mp or bp, °C (mm)	Lit. mp or bp, °C (mm)	Ref
1	p-(NMe_2)	29	mp 45–47	mp 48–49	33, 40
2	m-(NMe_2)	20	bp 119–123 (17)	bp 237 (760)	33, 44
3	o-(NMe_2)	22	bp 86–90 (16)	bp 113 (18)	33
4	p-(CH_2NMe_2)	74	bp 88–90 (3.5)	bp 73–77 (2.0)	34, 36
5	m-(CH_2NMe_2)	80	bp 76–78 (3)	bp 101–102 (9.5)	35, 41
6	o-(CH_2NMe_2)	70	bp 82–84 (4)	bp 113 (20)	35, 42
7	p-($CH_2CH_2NMe_2$)	75	bp 50–52 (1.0)	bp 108 (11)	34
8	o-($CH_2CH_2NMe_2$)	40	bp 101–105 (3)		36
9	p-($CH_2CH_2CH_2NMe_2$)	80	bp 115–117 (4)		30
10	p-(CONHMe)	95	mp 117–119	mp 116	37
11	m-(CONHMe)	78	mp 66–68	mp 67–68	37, 38
12	o-(CONHMe)	84	bp 100–105 (0.3)	bp 175 (14)	38
13	p-(CONHMe)	68	mp 41–42	mp 42	45
14	p-($CH_2CONHMe$)	80	mp 96–97		38
15	p-(SO_2NHMe)	83	mp 96–98.5		39
16	p-(SO_2NMe_2)	90	mp 72–74	mp 71–72	39
17	p-(CF_3)	53	bp 166–168 (760)	bp 168.6 (760)	43

[a] NMR and ir data confirmed the structures of these substituted anisole derivatives.

for the para-, meta-, and ortho-substituted anisoles examined in this study. On the basis of the para-substituted anisole results it was found that the substituents having stronger ortho-directing ability than the methoxy group were the following: $-CH_2NMe_2$, -CONHMe, $-SO_2NHMe$, and $-SO_2NMe_2$. Substituents which were inferior ortho directors relative to the methoxy group were the following: $-CH_2CH_2NMe_2$, $-CF_3$, $-NMe_2$, and -F.

The ortho-directing ability of the methoxy, dimethylamino, and fluoro substituents apparently involved both coordination and inductive effects. If coordination effects alone were considered the relative order of directing would be $-NMe_2 > -OCH_3 > -F$. Inductive and resonance effects would predict $-F > -OCH_3 > -NMe_2$. However, the observation that $-OCH_3 > -NMe_2$, -F suggests that both effects may be operative in these cases.

The para-situated methoxy group was found to have a significant effect upon (1) benzyl proton acidities of compounds 7 and 9 and (2) the carbonyl electrophilicity of amide **10.**

TMEDA has been found to be effective in increasing the rate of certain ortho-directed metalation reactions and was shown in certain cases to alter the site of metalation.

Experimental Section

General. *n*-Butyllithium (1.6 M in hexane) used in the following reactions was purchased from the Foote Mineral Co. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA) (bp 120–122 °C) was obtained from Aldrich Chemical Co. and was redistilled with the fraction bp 120.5–121.0 °C being collected. The redistilled TMEDA was stored over Linde 4A molecular sieves under an atmosphere of argon. The ether used as a reaction solvent was Matheson Coleman and Bell "absolute" grade and was stored over Linde 4A molecular sieves. Tetrahydrofuran (THF) used as solvent was filtered through activated alumina immediately before use.

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., Alfred Bernhardt Laboratories, Mulheim, West Germany, and Joseph Nemeth Laboratory, Urbana, Ill. Melting points were determined on a Hoover melting point apparatus and are corrected. Column chromatographies were performed on Matheson Coleman and Bell activated alumina using redistilled solvents. Thin layer chromatographies were performed on E. Merck silica gel G using ethyl acetate as solvent.

All ir spectra were obtained on a Perkin-Elmer Model 137 Infracord using the 6.246-μ band of polystyrene as a reference. All NMR spectra were obtained on a Varian A-56/60 spectrometer using Me_4Si as an internal standard. Integrations used to report deuterium incorporation were accurate to ±0.04 proton, judging from the accuracy obtained for the integration of protons in known pure compounds.

All yields are expressed as percent conversion, i.e., no effort was made to assess the amount of recovered starting materials.

Preparation of Substituted Anisole Derivatives, 1–19. Aminoanisoles. *N,N*-Dimethylanisidines **1–3** were obtained in fair yield by treatment of the corresponding anisidine with dimethyl sulfate.[33] *p*-Methoxy-*N,N*-dimethylbenzylamine (**4**) was prepared from the corresponding primary amine via the Eschweiler–Clark methylation reaction.[34] The meta and ortho isomers, amines **5** and **6**, were prepared by a procedure involving formation of the *N,N*-dimethylanisamides from the anisic acids and reduction of the amides[35] to the corresponding benzylamines. *p*-Methoxy-*N,N*-dimethylphenethylamine (**7**) was prepared via the Eschweiler–Clark methylation[34] of the corresponding primary amine. The ortho isomer **8** was obtained via a synthetic procedure involving metalation of anisole and condensation of the 2-lithio intermediate with ethylene oxide to give 2-(o-methoxyphenyl)ethanol conversion of the ethanol derivative to the bromide using PBr_3 and conversion of the bromide to amine **8** using dimethylamine.[36] Treatment of 3-(*p*-methoxyphenyl)propanol (Aldrich Chemical Co.) with PBr_3 and subsequent treatment of the intermediate bromide with dimethylamine in ethanol[36] gave 3-(*p*-methoxyphenyl)-*N,N*-dimethylpropylamine (**9**).

Amide Anisoles. *N,N*-Dimethylbenzamides **10–12** were prepared[37,38] from the corresponding anisic acid using thionyl chloride to form the corresponding acid chloride and reaction of the acid chloride with methylamine. Amides **13** and **14** were prepared by usual procedures[37] via *p*-anisyl chloride and 4-methoxyphenylacetyl chloride, respectively.

Sulfonamide Anisoles. Sulfonamides **15** and **16** were prepared[39] by reaction of *p*-methoxybenzenesulfonyl chloride with methylamine and dimethylamine, respectively.

Fluorinated Anisoles. *p*-Methoxybenzotrifluoride (**17**) was prepared by treatment of *p*-chlorobenzotrifluoride with sodium methoxide under pressure at 160 °. Fluoroanisoles **18** and **19** were purchased from Aldrich Chemical Co.

A complete summary of physical properties of the substituted anisole derivatives is presented in Table IX.

General Metalation Procedure—Benzophenone Condensation and D_2O Hydrolysis. Aminoanisoles (1–9). The amine was dissolved in dry ether (2 ml ether/mmol substrate) at room temperature under argon and 1 equiv of 1.6 M *n*-butyllithium in hexane was slowly added. After stirring for the period designated in Table II, a mixture of benzophenone (1.25 equiv) in dry ether was added at a rate sufficient to produce only slight reflux. The reaction solution was stirred for 4 h and then hydrolyzed with water. The ether layer and ether extracts of the aqueous layer were combined and extracted with 10% HCl. The acid layer was separated and neutralized with solid NaOH. Ether extracts of the neutralized portion were dried over $MgSO_4$. After the ether had been removed under vacuum, unreacted starting amine (and TMEDA, where appropriate) was removed by vacuum distillation. The benzophenone condensation product was then purified by the appropriate procedure as designated in Table X.

The D_2O hydrolysis products were formed by adding excess D_2O to the lithiation mixture, extracting with ether, and redistilling the recovered amine. The methiodide salt of the deuterated amine (**1**) was formed by stirring with an ether solution of excess methyl iodide for 12 h. The white precipitate, mp 255 °C dec, was collected and recrystallized from methanol.

When TMEDA was employed in the metalation reaction, the TMEDA/*n*-butyllithium complex was first formed by treating TMEDA in ether with 1 equiv of 1.6 M *n*-butyllithium in hexane.

Table X. Physical Data[c]

Compd	% yield	Mp, °C	Purification[a]
1a	71	145–146	A (100% ethanol)
2a	71	142–143	A (95% ethanol)
3a	56	101–102	A (100% ethanol)
4a	80	128–130	A (100% ethanol)
4b	55	88–89	B[b]
5a	79	104–104.5	A (100% ethanol)
6a	58	bp 180–190 (2.0) C	
7a	60	99–101	A (100% ethanol)
9a	71	Oil	
10a	47	198 dec at 200	A (tetrahydrofuran)
11b	65	222–224	A (100% ethanol)
12b	53	168–170	D (50:50 benzene ligroin)
15a	77	165–167	A (100% ethanol)
16a	62	150–151	A (100% ethanol)
17a	79	104–105	A (hexane)

[a] Purification procedures used: A recrystallization; B, thin layer chromatography; C, vacuum distillation; D, column chromatography (alumina with 6% H_2O). [b] TLC on silica gel G gave two bands upon development with ethyl acetate: band 1 (R_f 0.63), **4a**; band 2 R_f 0.39), **4b**. [c] Satisfactory analytical data (±0.3% for C, H, N, F, and S) were obtained and were submitted for review.

After stirring for 1 h an ether solution of the amine was added and the reaction continued as previously described.

The benzophenone condensation product mixture of amine **6** (1.0 g, 0.003 mol) was treated with excess methyl iodide for 14 h at room temperature. The crystalline product was recrystallized from methanol to give yellow crystals, mp ~250 °C with decomposition. The methiodide was placed in a flask filled with argon and heated at 200–210 °C for 20 min. Boiling ether extracts of the reaction residue gave no cyclic ether, the product to be expected if the predominant isomer were the 6 isomer, **6b**.

Carboxamide Anisoles (10–14). The same procedure was followed as for the amines above except that THF was used as solvent and the reaction temperature was that of the refluxing solvent, i.e., approximately 65 °C. Two equivalents of *n*-butyllithium was required to effect metalation for all compounds of this series except compound **13** since the first equivalent would have been initially consumed in the abstraction of the amide proton. Metalation of **13** was attempted using only 1 equiv of *n*-butyllithium. Metalations using TMEDA were run in refluxing ether since all attempts to effect metalation using TMEDA in THF were unsuccessful.

p-Methoxy-*N*,*N*-dimethylbenzamide (**13**, 7.16 g, 0.04 mol) was dissolved in 80 ml of dry ether and treated with 1.6 M *n*-butyllithium (25 ml, 0.04 mol) at reflux under argon for 0.25 h. Benzophenone (7.28 g, 0.04 mol) in 40 ml of dry ether was added to the cooled mixture and stirred for 4 h. A basic gas was expelled throughout the course of the reaction. The metalation mixture was hydrolyzed with H_2O and extracted with ether. The ether extracts were dried over $MgSO_4$ and stripped to give an oil shown to be a mixture of benzophenone and *p*-methoxyvalerophenone. A comparison of relative proton integrations indicated that 55% of the 10.8 g of total product mixture was *p*-methoxyvalerophenone. This corresponded to 5.95 g (78% yield) of *p*-methoxyvalerophenone. No metalation products were detected.

Repetition of the above metalation procedure for carboxamide **14** followed by D_2O hydrolysis and NMR analysis of the deuterated product indicated 1.00 atom deuterium incorporation at the benzyl position and 0.70 atom deuterium incorporation at the –NH site.

Repetition of the above experiment except for a metalation time of 24 h gave 1.00 atom deuterium incorporation at the benzyl and –NH sites, judging from NMR integration of the deuterated product.

Sulfonamide Anisoles (15, 16). The same procedure as for the amides above was followed except that the metalation was performed at 0–5 °C. Upon condensation with benzophenone the reaction mixture was allowed to warm to room temperature. Sulfonamide **16** required the use of only 1 equiv of *n*-butyllithium.

Fluorinated Anisoles (17–19). The same procedure as for the amines above was followed except that the reaction mixture was refluxed in ether during the metalation step and cooled to room temperature during the benzophenone condensation step.

Using conditions favoring metalation of fluorobenzene,[12] *p*-fluoroanisole (**18**, 6.30 g, 0.05 mol) was dissolved in 100 ml of dry ether and cooled to −63 °C using a $CHCl_3$/liquid N_2 slush. To the cooled solution was added 31.2 ml (0.05 mol) of 1.6 M *n*-butyllithium in hexane. The mixture was stirred at −63 °C for 7 h and then poured in portions into a dry ice/ether slurry under argon. After standing for 12 h the mixture was extracted with ether. The ether layer was extracted with 3 N NaOH and the basic layer separated and neutralized with 6 N HCl. Ether extracts of the neutralized layer were dried over $MgSO_4$ and stripped to yield 2.8 g (55% yield) of valeric acid. *p*-Fluoroanisole (5.5 g, 84% recovery) was isolated from the base-insoluble portion.

Using conditions favoring metalation of anisole,[6,11] *p*-fluoroanisole (3.15 g, 0.025 mol) was dissolved in 59 ml of dry THF under argon. To this solution was added 15.6 ml (0.025 mol) of 1.6 M *n*-butyllithium in hexane and the mixture stirred at room temperature for 5 h. The mixture was poured into a dry ice/ether slurry under argon. After the mixture had stood for 12 h, 50 ml of H_2O was added and the mixture extracted with ether. Basic extraction of the ether layer gave 1.35 g (32% yield) of pale yellow crystals of 5-fluoro-2-methoxybenzoic acid, mp 82–85 °C (lit.[46] mp 87 °C). None of the isomeric product was observed. *p*-Fluoroanisole was recovered in 42% yield along with a small amount of material having a phenolic odor. After metalation using *n*-butyllithium/TMEDA in ether, a basic extraction of the ether layer produced some valeric acid but none of the fluoromethoxybenzoic acid products. Almost quantitative recovery of *p*-fluoroanisole along with a small amount of material having phenolic odor was obtained.

o-Fluoroanisole (**19**, 3.78 g, 0.03 mol) was dissolved in 60 ml of dry THF and treated with 1.6 M *n*-butyllithium (18.7 ml, 0.03 mol) in hexane for 5 h at room temperature under argon. The metalation mixture was poured into a dry ice/ether slurry and left to stand for 12 h. A basic extraction of the ether layer produced a small amount of valeric acid along with 1.2 g (36% yield) of *o*-fluorophenol [bp 180–185 °C (750 mm), lit.[47] bp 46 °C (10 mm)]. No fluoromethoxybenzoic acid products were obtained and only 1.15 g (30%) of the *o*-fluoroanisole was recovered. After metalation using *n*-butyllithium/TMEDA in ether, a basic extraction of the ether layer produced some valeric acid along with 0.6 g (27% yield) of *o*-fluorophenol. Approximately 1.1 g (44%) of *o*-fluoroanisole was recovered from the organic layer. No fluoromethoxybenzoic acid products were detected in the product mixture.

Acknowledgments are made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Thanks are also due Art Langer, Exxon Research and Engineering Co., Linden, N.J., for salient advice on the interpretation of the metalations using TMEDA/*n*-butyllithium reagent.

Registry No.—**1**, 701-56-4; **1a**, 59907-30-1; **2**, 15799-79-8; **2a**, 35339-88-9; **2b**, 59907-31-2; **3**, 700-75-4; **3a**, 35339-89-0; **4**, 15175-54-9; **4a**, 10126-23-5; **4b**, 35339-84-5; **5**, 15184-99-3; **5a**, 10126-27-9; **6**, 58774-83-7; **6a**, 35339-85-6; **6b**, 59907-32-3; **7**, 775-33-7; **7a**, 35339-86-7; **8**, 59907-33-4; **9**, 59907-34-5; **9a**, 59907-35-6; **10**, 3400-22-4; **10a**, 35339-90-3; **11**, 35129-32-9; **11b**, 20144-53-0; **12**, 3400-35-9; **12b**, 20144-51-8; **13**, 7291-00-[illegible]; **14**, 59907-36-7; **15**, 7010-86-8; **15a**, 35339-91-4; **16**, 59907-37-8; **16a**, 59907-38-9; **17**, 402-52-8; **17a**, 59907-39-0; **18**, 459-60-9; **19**, 321-28-8.

Supplementary Material Available. Table XI, ir and NMR spectral data of substituted benzenes (2 pages). Ordering information is given on any current masthead page.

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Directed Metalation Reactions. 7.[1] Directed Metalation of Methoxymethylferrocene: 2- and 1′-Metalated Ferrocene Intermediates

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A unique regiospecific metalation of a substituted ferrocene has been observed in the lithiation of methoxymethylferrocene (MMF, **1**). Approximately equal amounts of 2- and 1′-monometalated intermediates were produced as judged by derivatization experiments. Among the most interesting of the new compounds isolated were 2- and 1′-chloromercurimethoxymethylferrocene (2-ClHg-MMF) and (1′-ClHg-MMF). 1′-ClHg-MMF underwent a transmetalation reaction with *n*-butyllithium to produce a unique ferrocenyllithium derivative, namely, 1′-lithiomethoxymethylferrocene (1′-Li-MMF). Also found to undergo 2 lithiation were ethyoxymethylferrocene (EMF, **5**) and α-methoxyethylferrocene (MEF, **6**). These results are interpreted in terms of coordination of oxygen with a lithium ion in the metalated intermediate.

The displacement of a hydrogen atom from a carbon–hydrogen bond by an alkali metal to give an organometallic intermediate, i.e., metalation, has become of increasing interest to organic chemists. In recent years, the ability of certain groups on aromatic systems to direct lithiation at a position "ortho" to the substituent has been demonstrated to be of synthetic utility, since such a procedure enables a chemist to produce "ortho" disubstituted products virtually uncontaminated by other isomers.[3] More recently, ortho metalation of aromatic systems by various transition metal derivatives has also received attention.[4]

Although many of the early reports focused on the directing ability of amines, several articles dealing with directed metalation of aromatic ethers also appeared. Notable among these were the early studies of Gilman and co-workers on the directed lithiation of dibenzofuran, anisole, and related ethers.[3a] Subsequent papers by other workers have contained suggested mechanism(s)[5a,b,6] and caveats[5c] for the observed ortho lithiation of aryl ethers and these contain estimates of contributions of coordination by oxygen to the overall transition state. In the preceding paper,[1] the methoxy group was found to be intermediate in directing ability among the group of nine directing substituents studied. Moreover, the methoxy group has also been found to direct metalation in other systems, namely, ferrocene[7] and naphthalene.[8] Some evidence for the importance of coordination in the mechanism of directed lithiation by the methoxy group has been inferred from the observed significant decrease in the extent of lithiation of the anisole nucleus by the presence of an ortho *tert*-butyl group.[9]

In our opinion, no unequivocal demonstration of a coordinating direction of lithiation by oxygen has ever been accomplished. Such an example is provided herein, namely, the formation of 2-Li-MMF and 1′-Li-MMF upon metalation of MMF with *n*-butyllithium. Both the regiospecificity of the metalation (no 3 metalation) as well as the observation that the rate is much faster and the extent greater than metalation of ferrocene itself under these conditions[10] dictate a decided

Table I. Time Study of the Metalation of Methoxymethylferrocene (MMF) and Condensation with Benzonitrile

Metalation period, h	% 1,2-disubstituted product isolated	% 1,1′-disubstituted product isolated
0.5	24.5	24.5
1	27.5	24.6
2	32.3	31.1
5	32.4	30.0
10	30.5	26.3
20	25.1	24.5

influence of the methoxymethyl group on the course of the reaction. The fact that the oxygen atom is "insulated" from the ferrocene residue by the presence of a methylene group rules out significant contribution of any type of through-bond electronic effect to the mechanism. Only a coordination contribution is left.

It is also interesting to note that no Wittig rearrangement products were detected during the course of these metalations. Such products have been isolated from lithiation of benzyl ethers.[6]

Results and Discussion

In the dimethylaminomethyl-,[11a] dimethylaminoethyl-,[11b] and *N*-ethylcarboxamidoferrocene systems,[12] metalation with *n*-butyllithium resulted in partitioning between the 2-metalated and 2,1′-dimetalated specie. For this reason, the expected products from the lithiation of MMF were to arise from 2-Li-MMF and 2,1′-diLi-MMF. In addition to products arising from the expected 2-lithio-MMF, concomitant 1′ metalation occurred as indicated by the isolation of six 1′-substituted MMF's in from 11 to 35% yield. This significant 1′ metalation of MMF appears to be a unique metalation pattern which presents the possibility of a new route to 1,1′-heteroannular disubstituted ferrocenes. These observations modify somewhat an earlier communication of ours[13] on this topic, a necessity which has already been alluded to in a paper by Valkovich, Gokel, and Ugi.[14]

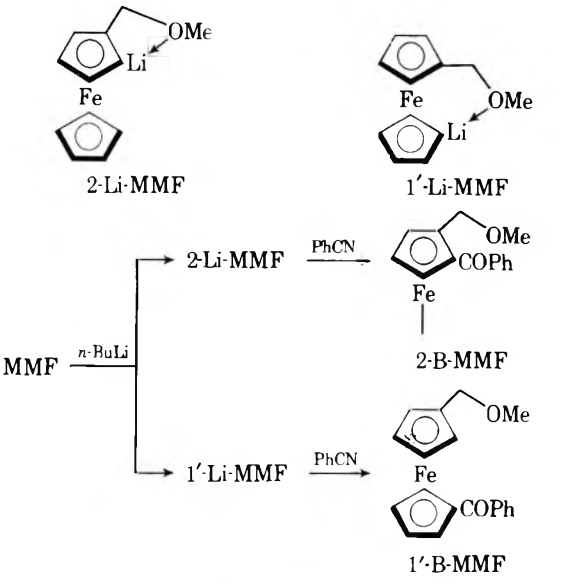
A time study of the metalation of MMF (Table I) indicated that the 2- and the 1′-lithio-MMF were formed at comparable rates and that these intermediates, once formed, were stable within periods of from 0.5 to 20 h. Surprisingly, no significant amounts of products stemming from 2,1′-dilithio-MMF were detected. These data were obtained by isolation of the two monobenzoyl derivatives, 2-B-MMF and 1′-B-MMF, since these isomers could be cleanly separated on a chromatography column. The inferred reaction sequence is outlined in Scheme I.

Condensation with phenyl isocyanate gave a 28% yield of 2-(*N*-phenylcarboxamido)methoxymethylferrocene (2-PC-MMF) and a 17.3% yield of 1′-(*N*-phenylcarboxamido)-methoxymethylferrocene (1′-PC-MMF). The lower yield observed in this reaction is more a demonstration of the difficulty encountered in the purification of these products than of the efficacy of the condensation itself.

The NMR spectrum of 2-PC-MMF displayed an AB quartet for the methylene protons. Magnetic nonequivalence of the methylene-group protons of 1,2-disubstituted ferrocenes was first examined in detail by Smith, McLesky, and Slocum[15] and renders support for the assignment of 1,2 disposition of the substituents in 2-PC-MMF. Magnetic nonequivalence was not observed in the other 1,2-disubstituted products because the resonances for the methylene protons were obscured by the resonances of the ferrocene moiety.

Condensation of the lithio intermediates with benzophenone was reexamined; this reaction also resulted in a mixture

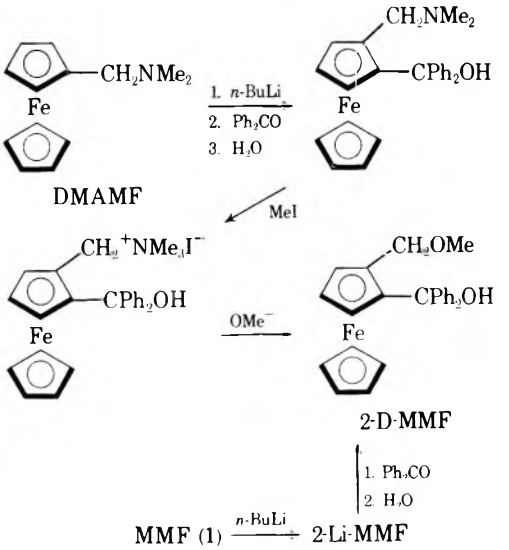
Scheme I



of the products from 2 and 1′ metalation. This is in contrast to our original report[13] in which it was claimed that only 2 lithiation of MMF was observed. The 1,1′ structure for 1′-(α,α-diphenylhydroxymethyl)methoxymethylferrocene was assigned on the basis of its elemental analysis, which indicated that the compound contained one diphenylhydroxymethyl group per molecule, and the absence of absorptions in the 9 and 10 μ region of its ir spectrum. Absorptions at 9 and 10 μ in the ir spectrum of a substituted ferrocene are indicative of the presence of at least one unsubstituted cyclopentadienyl ring.[16]

The 1,2 structure for 2-(α,α-diphenylhydroxymethyl)-methoxymethylferrocene (2-D-MMF) was assigned on the basis of its elemental analysis, the presence of absorptions at 9 and 10 μ in its ir spectrum,[16] and its identity with a sample of the known compound prepared by a route involving the 2 metalation of dimethylaminomethylferrocene (DMAMF).[11a] Since 2 metalation of DMAMF has been unequivocally demonstrated,[11a] the identity of the carbinol ethers prepared by both routes provides additional proof of the 2 metalation of MMF (1). Scheme II outlines both routes used in the synthesis of 2-D-MMF.

Scheme II



In the condensation with carbon dioxide and subsequent reaction with diazomethane, only 1′-(carbomethoxy)hydroxymethylferrocene (1′-C-HMF) was identified. Another

Table II. Products from the Metalation of Methoxymethylferrocene (MMF) and Condensation with Various Electrophilic Reagents

Condensing agent	2 or 1′ derivative	Metalation time, h	Condensation time, h	Yield, % 1,2	Yield, % 1,1′
PhCOPh	$-CPh_2OH$	2.5	4	32.5	34.9
$HgCl_2$	-HgCl	5.0	16	37.5	33.0
PhCN	-COPh	1.0	2	32.4	30.0
PhNCO	-CONHPh	2.0	16	28.8	17.3
1. CO_2 2. CH_2N_2	$-CO_2Me$[a]	3.0	1		15.0
$CH_2CH_2ONO_2$	$-NO_2$	2.5	2.5		10.7

[a] Methoxymethyl group was hydrolyzed during course of reaction and workup to hydroxymethyl group.

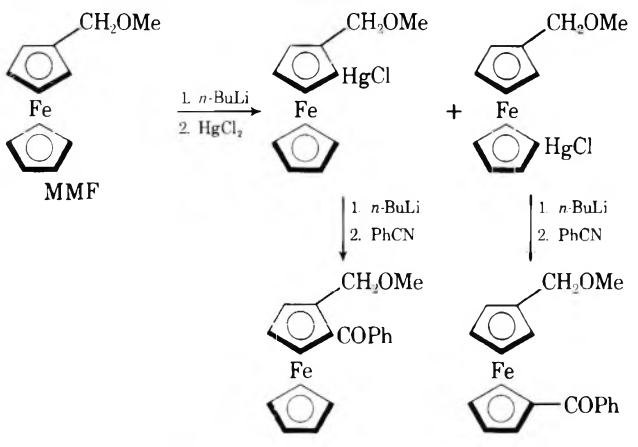
product, presumably the 1,2-disubstituted isomer, was isolated and an ir spectrum obtained, but the compound proved to be too unstable for further analysis. It is not known whether the methoxymethyl group in 1′-C-HMF was cleaved during carbonation, acidification, or chromatography of the product. It is interesting to note here that other attempts to cleave the ether function of several substituted methoxymethylferrocenes by acid or by reaction with lithium metal failed. The spontaneous cleavage which resulted in 1′-C-HMF appears to be a result of the inherent instability of this particular compound relative to its methyl ether under the reaction or isolation conditions utilized and does not constitute a general method of cleavage for ferrocenylmethyl ethers.

Another instance, where only the product resulting from 1′ metalation was isolated, was the condensation with ethyl nitrate to give 1′-nitromethoxymethylferrocene (1′-N-MMF). The 1,1′ structure was assigned on the basis of (1) an NMR spectrum which displayed two downfield two-proton triplets which were assigned to the four protons on the nitro-substituted ring and (2) the absence of absorptions at 9 and 10 μ in its ir spectrum. As was the case in the condensation with carbon dioxide, the isolation of only the 1,1′ derivative was probably due to the instability of the 1,2-disubstituted compound.

Derivatization with mercuric chloride produced 2-(chloromercuri)methoxymethylferrocene (2-ClHg-MMF) and 1′-(chloromercuri)methoxymethylferrocene (1′-ClHg-MMF). These compounds were particularly interesting because they were stable, crystalline solids. More important, the isolation of 1′-ClHg-MMF presented the possibility of the synthesis of 1,1′-disubstituted ferrocenes uncontaminated by the corresponding 1,2-disubstituted compound. It is known that the chloromercuri group in the ferrocene series can be transmetalated by n-butyllithium to give the corresponding lithio intermediate.[17]

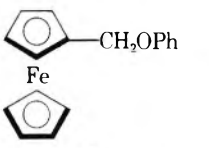
1′-ClHg-MMF was transmetalated by treatment with n-butyllithium to give 1′-Li-MMF uncontaminated by the 2-lithio isomer as demonstrated by derivatization with benzonitrile (Scheme III). No materials other than MMF and 1′-B-MMF were isolated from the chromatographic workup procedure. Use of 1′-ClHg-MMF as an intermediate in the synthesis of 1,1′-disubstituted ferrocenes thus appears feasible. Presumably, 2-ClHg-MMF could be utilized similarly.

Scheme III

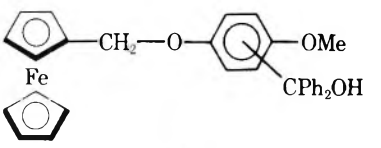


In none of the metalations of MMF were any products isolated which would have resulted from a Wittig rearrangement. Ustynyuk, Perevalova, and Nesmeyanov[18] have shown that the ferrocenylmethyl group stabilizes a carbanionic center to a lesser extent than does the benzyl group. It appears that the ring metalated intermediates formed from lithiation of MMF are more stable than the intermediate, α-Li-MMF, which would be formed prior to Wittig rearrangement. This is exactly the opposite of the stabilities of the anions in the corresponding benzene compounds.[19] A summary of the products from the metalation of MMF can be found in Table II.

In order to investigate the electronic requirements for the metalation of ferrocenylmethyl ethers, a number of related compounds were prepared, treated with n-butyllithium, and condensed with electrophilic reagents. Phenoxymethylferrocene (2) was allowed to react with n-butyllithium for from



2



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2 to 22 h in several experiments, and was condensed with benzophenone or dry ice. From these reactions only phenoxymethylferrocene itself was recovered. An attempt was made to increase the coordinating ability of the phenoxy group by the placing of a p-methoxy electron-donating group of the phenyl nucleus. p-Methoxyphenoxymethylferrocene (3) was found to undergo metalation only in the benzene ring to give, upon condensation with benzophenone, the carbinol 4. It is probable that metalation took place ortho to the methoxy group, since the methoxy group is a known director, but this assignment cannot be substantiated at present.

Ethoxymethylferrocene (EMF, 5) was metalated and condensed with benzophenone. The derivative was found to be 2-(α,α-diphenylhydroxymethyl)ethoxymethylferrocene by its identity with a compound previously studied in our group.[20] No 1′-substituted product was isolated from this reaction.

Substitution of one of the α hydrogens in MMF as in the compound α-methoxyethylferrocene (6) apparently brought significant steric hindrance to the transition state for 2 metalation. Only a 1.7% yield of this lithio intermediate could be detected by carbonation.[21]

Experimental Section

General. All lithiation reactions were run under an atmosphere of argon. n-Butyllithium (1.6 M in hexane) used in the following reactions was purchased from the Foote Mineral Co. $N,N,N'N'$-

Tetramethylethylenediamine (TMEDA) (bp 120–122 °C) was obtained from Aldrich Chemical Co. and was redistilled. The fraction of bp 120.5–121.0 °C was collected and was stored over Linde 4A molecular sieves. Ether used as a reaction solvent was Matheson Coleman and Bell "absolute" grade and was stored over Linde 4A molecular sieves.

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Alfred Bernhardt Laboratory, Mulheim, West Germany. Melting points were determined on a Hoover melting point apparatus and were corrected. Column chromatographies were performed on Matheson Coleman and Bell activated alumina using distilled solvents.

All ir spectra were obtained on a Perkin-Elmer Model 137 Infracord spectrometer using the 6.246-μ band of polystyrene as a reference. NMR spectra were obtained on a Varian A-56/60 spectrometer and a Varian HA-100 using Me_4Si as an internal standard. Physical data of the new compounds isolated can be found in Table III and ir and NMR spectral data for these compounds in Table IV (see paragraph at end of paper regarding supplementary material).

General Lithiation and Condensation Procedure. Methoxymethylferrocene (MMF, 5 mmol) in 100 ml of dry ether was treated dropwise with 8 mmol of 1.6 M *n*-butyllithium in hexane and metalation was allowed to proceed with stirring at 25 °C for 1–5 h. At this point, the condensing agent (8 mmol) in 25 ml of ether was added; the solution was then stirred for an additional 1–15 h. After hydrolysis with 25 ml of water, the aqueous layer was separated and extracted twice with ether and the combined ether extracts dried over anhydrous $MgSO_4$. After removal of the ether the oils were chromatographed on alumina with methylene chloride/petroleum ether as eluent.

Transmetalation of 1′-ClHg-MMF. Condensation with Benzonitrile. 1′-ClHg-MMF (0.46 g, 1.0 mmol) in dry ether was treated with 1 ml (1.6 mmol) of 1.6 M *n*-butyllithium in hexane. The mixture was stirred for 1 h whereupon 0.3 g (3.0 mmol) of benzonitrile was introduced. After stirring for 2 h the reaction mixture was hydrolyzed with 20 ml of water. The aqueous and ether layers were separated, the aqueous layer extracted twice with ether, and the combined ether extracts dried over anhydrous $MgSO_4$. This solution was filtered and the solvent stripped under vacuum to afford a brown oil which was chromatographed on alumina II with CH_2Cl_2/petroleum ether as eluent. MMF (0.15 g, 65%) was eluted with 10% CH_2Cl_2/petroleum ether. A second fraction which was eluted with 30% CH_2Cl_2/petroleum ether gave a red oil upon removal of solvent. An ir spectrum of this oil was identical with that of 1′-B-MMF prepared via the original lithiation route. The yield was 0.1 g (30%).

***p*-Methoxyphenoxymethylferrocene (3). A. Preparation of *p*-Methoxyphenoxymethylferrocene (3).** *p*-Methoxyphenol (70.25 g, 0.566 mol) in a minimum amount of dry ether was lithiated with 100 ml (0.16 mol) of 1.6 M *n*-butyllithium in hexane. This solution was added to a mixture of the methiodide of dimethylaminomethylferrocene (56.25 g, 0.146 mol)[24] in 1 l. of water. The ether was evaporated, and the resulting mixture refluxed for 5 h and allowed to cool. This mixture was extracted several times with ether, and the combined extracts were washed with 5% NaOH solution.

After evaporation of this ether solution under vacuum, a solid was obtained which was recrystallized from hexane (yield 25.5%).

B. Metalation of *p*-Methoxyphenoxymethylferrocene (3). Condensation with Benzophenone to Produce the Diphenylcarbinol Derivative 4. *p*-Methoxyphenoxymethylferrocene (1.61 g, 5.0 mmol) dissolved in 125 ml in dry ether was treated with 1.6 M *n*-butyllithium (3.1 ml, 4.8 mmol) in hexane. The mixture was stirred for 5.5 h, whereupon an ether solution of benzophenone (3.64 g, 20 mmol) was added with stirring being continued overnight. Water was added and the layers were separated. The aqueous layer was extracted twice with ether and the combined ether extracts were dried over anhydrous $MgSO_4$. After filtration and stripping of the solvent, an oil was obtained which was chromatographed on alumina III with CH_2Cl_2/petroleum ether as eluent. After a forerun of benzophenone, a fraction was eluted with 10% CH_2Cl_2/90% petroleum ether which was found to be ether **3** (recovery 0.30 g, 19%). Fraction 2 which was eluted with 30% CH_2Cl_2/70% petroleum ether gave a yellow solid upon evaporation, mp 139–141 °C, after being chromatographed several times and then recrystallized from hexane (yield 0.25%). NMR and elemental analysis data indicated that condensation and, therefore, metalation had taken place on the benzene ring to produce diphenylcarbinol **4**.

Lithiation of Ethoxymethylferrocene (5). Condensation with Benzophenone to Produce 2-(α,α-Diphenylhydroxymethyl)-ethoxymethylferrocene (2-D-EMF). EMF (2.44 g, 10 mmol) in 100 ml of dry ether was treated with 10 ml (16 mmol) of 1.6 M *n*-butyllithium in hexane. The mixture was stirred at room temperature for 5 h. After this time, benzophenone (5.9 g, 32 mmol) in ether was added. After the solution had been stirred for 4 h, water was added, the layers separated, the aqueous layer extracted twice with ether, and the ether combined extracts dried over anhydrous $MgSO_4$. The solution was filtered and stripped of solvent with the resulting oil being crystallized by trituration with petroleum ether. A yellow solid was obtained (yield 31%). Its ir spectrum was identical with that of a known sample of 2-D-EMF.[20]

Metalation of α-Methoxyethylferrocene (MEF, 6). Condensation with Carbon Dioxide to Produce 2-(α-Methoxyethyl)-ferrocene carboxylic Acid (2-ME-FCA). MEF[25] (4.9 g, 0.02 mol) in 200 ml of absolute ether was treated with 25 ml (0.04 mol) of 1.6 M *n*-butyllithium in hexane and the resulting solution stirred for 4 h. The reaction mixture was poured over dry ice/ether and after a time extracted with base. This basic solution was then washed with ether. The combined ether extracts were dried, filtered, and evaporated under vacuum. An oil was obtained which was redissolved in ether. Upon cooling this solution a precipitate appeared which was isolated by suction filtration. Ir and NMR data were consistent with the structure 2-(α-methoxyethyl)ferrocenecarboxylic acid (yield 17%). An analysis was not obtained.

Table III. Physical Data

Registry no.	Compd[a]	Molecular formula	Mp, °C
59922-65-5	2-B-MMF	$C_{19}H_{18}O_2Fe$	Oil
59922-66-6	1′-B-MMF	$C_{19}H_{18}O_2Fe$	Oil
59922-67-7	2-PC-MMF	$C_{19}H_{19}O_2NFe$	Oil
59922-68-8	1′-PC-MMF	$C_{19}H_{19}O_2NFe$	Oil
32914-68-4	2-D-MMF	$C_{25}H_{24}O_2Fe$	109–111
51178-07-5	1′-D-MMF	$C_{25}H_{24}O_2Fe$	Oil
59922-69-9	1′-C-HMF	$C_{13}H_{14}O_3Fe$	Oil
59922-70-2	1′-N-MMF	$C_{12}H_{13}O_3NFe$	64–66
59922-71-3	1′-ClHg-MMF	$C_{12}H_{13}OClHgFe$	105.5–106.5
59922-72-4	2-ClHg-MMF	$C_{12}H_{13}OClHgFe$	152–154
59922-73-5	**3**		98–100
59922-79-1	**4**		139–141
59922-74-6	2-D-EMF		123–125.5
59922-75-7	2-ME-FCA		202 dec

[a] All materials except 2-D-EMF and 2-ME-FCA purified by column chromatography. [b] Satisfactory analytical data (±0.3% for C, H, and in certain cases for N, Fe, and Cl) were obtained with the following exceptions: 2-D-MMF, Fe, 13.09 (13.55); **4**, C, 73.24 (73.67). Elemental analyses were not obtained for 2-PC-MMF, 2-D-EMF, and 2-ME-FCA.

Acknowledgments. We are grateful for partial support of this research by the Office of Research and Projects, Southern Illinois University, and to Dr. C. A. Jennings for help in the preparation of this manuscript.

Registry No.—**1**, 12153-89-8; **2**, 34871-88-0; **5**, 31724-98-8; **6**, 12512-90-2; carbon dioxide, 124-38-9; benzophenone, 119-61-9; ethyl nitrate, 625-58-1; mercuric chloride, 7487-94-7; *p*-methoxyphenol, 150-76-5; dimethylaminomethylferrocene methiodide, 12086-40-7; phenyl isocyanate, 103-71-9; benzonitrile, 100-47-0.

Supplementary Material Available. Table IV, ir and NMR spectral data of 1,2- and 1,1-disubstituted ferrocenes (1 page). Ordering information is given on any current masthead page.

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(2) To whom correspondence should be addressed.
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(21) Mention must be made here that Valkovitch et al.[14] also metalated ether **6** with *n*-butyllithium and have reported isolation of significant yields of all three possible ring metalated derivatives upon condensation with benzophenone. Such discrepancy in yields from the same metalated intermediate is not as unusual as it may seem. We are prompted to report here some unpublished studies[22] involving carbonation of commercial phenyllithium (Ventron Corp.). Repeated attempts to effect this carbonation, either by bubbling CO_2 through the phenyllithium or by pouring the phenyllithium solution over dry ice/ether, afforded only low yields of benzoic acid (<20%). On the other hand, condensation of this same phenyllithium solution with benzophenone under various conditions brought routinely yields of 60–70% of triphenylcarbinol. A similar study by Gilman and co-workers[23] has been published.
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Directed Metalation Reactions. 8.[1] Directed Metalation of 3-Mono- and 2,5-Disubstituted Thiophenes

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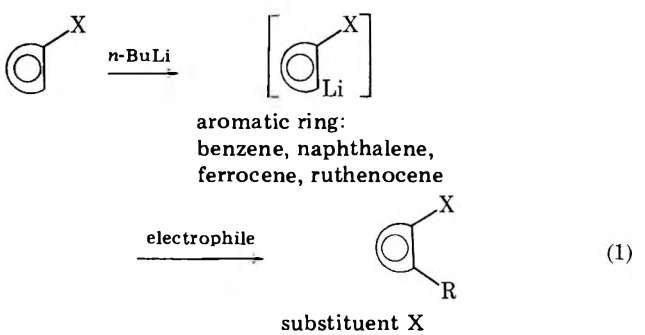
Regiospecific 2 metalation of thiophene has long been known. In this study we have examined the metalation with *n*-butyllithium of thiophenes containing a substituent that directs metalation such that a competition between the directing properties of the sulfur and the substituted group was set up. Results were as follows: (1) 2-Substituted thiophenes were lithiated in the 5 position, i.e., the sulfur atom controlled the site of metalation; (2) if the 5 position was blocked, 3 lithiation was observed; (3) 3-substituted thiophenes were lithiated in the 2 position, a site common to the directing properties of both the substituent and the sulfur moiety. Each of these metalations was surprisingly regiospecific. These lithiation pathways were explored via a number of derivatization and cyclization experiments and can be utilized in the synthesis of a wide variety of 2,3-disubstituted thiophenes. An intriguing dimerization of *N,N*-dimethyl-3-thiophenecarboxamide (**5**) in the presence of *n*-butyllithium to 4,8-dehydrobenzo[1,2-*b*:4,5-*b*′]dithiophene-4,8-dione (**5a**) was discovered.

Directed metalation of *N,N*-dimethylbenzylamine,[3] its ferrocene analogue,[4] and a number of related amines with subsequent treatment with electrophilic reagents has provided a general route to a variety of aromatic amines substituted exclusively in the 2 position.[5] In the preceding paper of this series[1] similar results are recorded for the directed lithiation of methoxymethylferrocene, thereby establishing unequivocally that the ether analogue of the dimethylaminomethyl group can also direct metalation. The 2-metalating ability of the N-substituted carboxamide group on benzene[6] and ferrocene[7] has also been reported. A generalized picture of these transformations is summarized in eq 1.



(1)

The ability of the directed metalation reaction to produce ortho-disubstituted products uncontaminated by other isomers would possess significant synthetic potential for other aromatic systems, notably heterocycles. In this study the utility of this method for the preparation of specific di- and trisubstituted thiophenes is described. These results can be contrasted to those for the electrophilic substitution of thiophenes. Generally for 2-substituted thiophenes, varying amounts of 2,5- or 2,4-disubstituted compounds are obtained depending on the competitive directing influence of the ring sulfur and the 2 substituent.[8] The yield of 2,3-disubstituted thiophenes is improved somewhat for 3-substituted compounds containing ±I + M substituents. For example, 3-methylthiophene gives upon acylation a mixture consisting of 80% 3,2 isomer and 20% 3,5 isomer.[9]

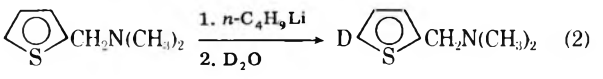
Ideally, directed metalation of a 2-substituted thiophene to give a 3-lithio intermediate would be most desirable, since 2-substituted thiophenes are much more readily available as starting materials. In no instance during this study was this lithiation pattern for 2-substituted thiophenes realized; rather 5 metalation was observed. This suggests that the thiophene sulfur is a stronger director than the carboxamide and dimethylaminomethyl groups, which are among the strongest directors known.[10] Likewise the 2-alkylsulfonamides were found to be weaker directors than the thiophene sulfur, although other reactions at times ensued upon metalation of

N,N-dialkyl-2-thiophenesulfonamides.[11] Blocking the 5 position with an alkyl group or a trimethylsilyl group served to eliminate competition by the 5 position and 3 lithiation was then observed for several 2,5-disubstituted thiophenes. Interestingly, a recent communication[12] has described 3 lithiation of thiophene in 2-(2′-thienyl)pyridine, a surprising observation in view of the results described herein.

For several substituents in the 3 position of thiophene, directed lithiation to the 2 position in high yield was observed.

Results and Discussion

The compound *N,N*-dimethyl-2-thenylamine (2-DTA, **1**) was initially chosen for this study since the dimethylaminomethyl substituent was a well-known director and was easily attached to the thiophene nucleus. However, metalation of this amine followed by condensation of its lithio intermediate with D_2O afforded an 88% recovery of what was found to be 5-deuterio-2-DTA (**1a**) (eq 2). Presumably, interaction



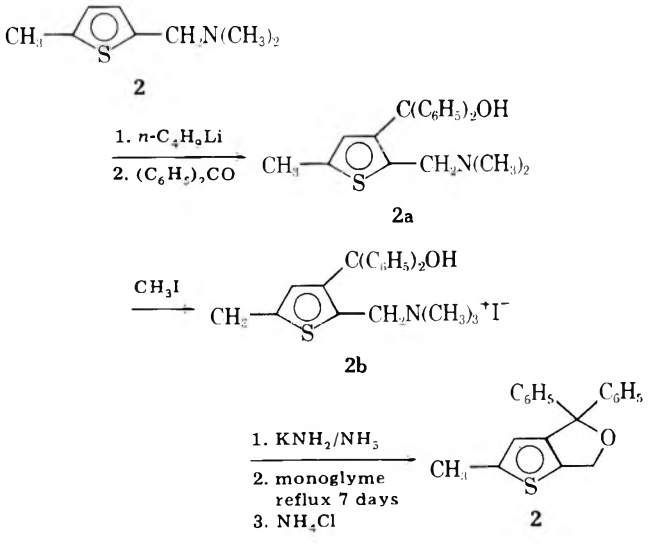
(2)

1 **1a**

between the coordinating nitrogen and the lithium atom must be less important than factors tending to favor substitution adjacent to the sulfur atom. The reactivity of the 5 position in 2-substituted thiophenes has been demonstrated by the fact that 2-alkyl-,[13,14] 2-methoxy-,[14,15] 2-alkylthio-,[16] and 2-alkylsulfonamide[11] derivatives of thiophene are known to undergo metalation in the 5 position. 5-Methyl- (**2**), 5-trimethylsilyl- (**1b**), and 5-formyl-2-DTA (**1c**) were also prepared by 5 lithiation (cf. Experimental Section).

Introduction of a blocking methyl group into the 5 position of 2-DTA to give 5-methyl-2-DTA (**2**) allowed directed lithiation in the 3 position to be easily effected. Metalation of 5-methyl-2-DTA with *n*-butyllithium followed by condensation with benzophenone gave a 65% yield of 5-methyl-3-diphenylhydroxymethyl-2-DTA (**2a**). The orientation of substituents in compound **2a** was verified by cyclization to the phthalan derivative **2c** via treatment of the methiodide **2b** with KNH_2 in liquid ammonia (Scheme I). Ir, NMR, and elemental analytical data supported the structure assigned phthalan **2c**.

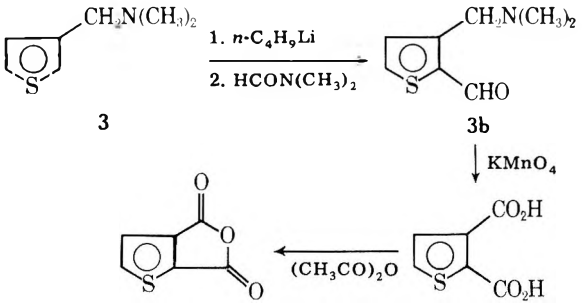
Scheme I



This result suggested a modified route to 2,3-disubstituted thiophenes via directed metalation of appropriate 2,5-disubstituted thiophenes where one substituent was a metalation director and the other was not and in addition could be reversibly removed. Such a removable substituent might be the trimethylsilyl group which is easily cleaved in aromatic systems upon treatment with strong acids.[17] 5-Trimethylsilyl-2-DTA (**1b**) was prepared, treated with *n*-butyllithium, and condensed with benzophenone; however, no condensation product was obtained. Failure of such a stratagem to provide a general route to 2,3-disubstituted thiophenes has also been reported for 5-trimethylsilyl-2-*N,N*-dialkyl thiophenesulfonamides.[11]

With these unsuccessful attempts to prepare 2,3-disubstituted thiophenes a switch in emphasis to the study of the directed metalation of a number of 3-substituted thiophenes was undertaken. Lithiation of *N,N*-dimethyl-3-thenylamine (3-DTA, **3**) with *n*-butyllithium followed by condensation of the lithio intermediate with dimethylformamide gave a 75% yield of 2-formyl-3-DTA (**3b**) (Scheme II). The orientation

Scheme II



of substituents in compound **3b** was confirmed by their oxidation with $KMnO_4$ to give the known 2,3-thiophenedicarboxylic acid[18] in 21% yield. Cyclization of this diacid with acetic anhydride gave the 2,3-anhydride, also a known compound[18] (Scheme II). An NMR spectrum of compound **3b** gave a well-resolved AB pattern for the two ring protons. The coupling constant for these protons was 5.0 Hz which falls in the region observed for a large number of 2,3-disubstituted thiophenes.[19] Spin–spin coupling of 1.0 Hz was also observed between the side-chain hydrogen of the aldehyde group and the 5-position ring proton. Studies by Gronowitz have shown that various 2-thiophenecarboxaldehydes possess a J_{CHO-H_5} = 1.05–1.40 Hz.[19]

The exclusive 2 lithiation observed for 3-DTA indicated that nitrogen coordination with the metalating agent reenforces ring sulfur coordination. At present, one can only speculate at what stage of the metalation reaction nitrogen coordination becomes important or what is the structure of the coordinated species. A complex of the organolithium tetramer and 3-DTA containing a pseudo-six-membered chelated ring could conceivably be formed by transfer of the hydrogen at the 2 position of 3-DTA to a coordinated *n*-butyl group (Scheme III). Some inferential evidence for coordination of 3-DTA with butyllithium has recently been provided by Wiswanathan and Wilkie.[20]

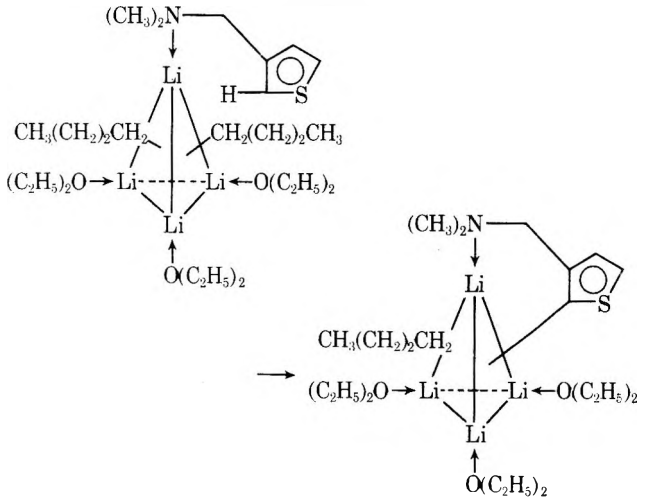
2-Lithio-3-DTA was also treated with D_2O, benzophenone, benzonitrile, *p*-toluenesulfonyl chloride, and *p*-toluenesulfonyl bromide to form 2-deuterio- (**3c**), 2-diphenylhydroxymethyl- (**3a**), 2-benzoyl- (**3d**), 2-chloro- (**3e**), and 2-bromo- (**3f**) 3-DTA, respectively. Physical and spectral data for these compounds are summarized in Tables I and II, respectively (see paragraph at end of paper regarding supplementary material). NMR spectra of these products with the exception of that for the 2-benzoyl derivative exhibited well-resolved AB patterns for the two thiophene ring protons. The coupling constant of these protons in each case was 5 Hz, exactly that observed for a large number of 2,3-disubstituted thiophenes.[19] For 2-benzoyl-3-DTA (**3d**) a resolved AB pattern for the thiophene ring protons was not observed owing to overlap with

Table I. Physical Data of Substituted Thiophenes[c]

Registry no.	Compd	% yield	Mp or bp, °C (mm)	Purification[a]
59906-28-4	**1b**	71	bp 65–67 (0.9)	
59906-29-5	**1c**	40	bp 95–104 (2.5)	
19260-96-9	**2**	86	108–110	B
59906-30-8	**2a**	65	117–118	A (100% ethanol)
59906-31-9	**2b**	98	194	A (100% ethanol)
32281-35-9	**2c**	45	117–119	A (1005 ethanol)
22601-13-4	**3**	42	bp 28–32 (0.12)	
32281-32-6	**3a**	67	88–88.5	A (50:50 petroleum ether/ether, 100% ethanol)
32281-31-5	**3b**	75	bp 62–63 (0.03)	
32281-33-7	**3d**	54	bp 122–124 (0.5)	
59906-32-0	**3e**	25	bp 31–32 (0.6)	
59906-33-1	**3f**	32	bp 59–60 (1.3)	
53229-44-0	**4**	38	bp 26 (0.2)	
59906-34-2	**4a**	46	102–104	A (100% ethanol)
59906-35-3	**4b**	54	bp 122–124 (0.5)	
59906-36-4	**4c**	61	bp 65–68 (0.03)	
59906-37-5	**5**	6.7[b]	bp 89–90 (0.5)	
32281-36-0	**5a**	41	258–260	C (150 °C)
59906-38-6	**6**	13	115–117	A (100% ethanol)
59906-39-7	**6a**	55	107–110	
59906-40-0	**6b**	23	172.5–173 dec	A (50:50 methanol/THF)

[a] Purification methods: A, recrystallization (solvent); B, steam distillation; C, sublimation (temperature). [b] Overall yield in five synthetic steps. [c] Satisfactory analytical data (±0.3% for C, H, and in some cases for N, S, and O) were obtained for compounds **1b, 1c, 2a, 2b, 2c, 3, 3a, 5a, 6,** and **6b** with the following exceptions: **1c**, S, 19.04 (19.39); **2b,** C, 55.04 (54.66), H, 5.95 (5.42); **2c,** C, 77.67 (78.05), O, 5.86 (5.47); **3a,** N, 4.53 (4.15). Elemental analyses were not obtained for the remaining compounds.

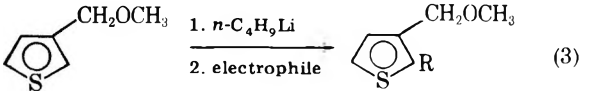
Scheme III



the phenyl proton signals. However, indirect evidence for the site of the benzoyl substituent in **3b** was obtained from the observed downfield shift of the methylene resonance from τ 7.03 in 3-DTA to τ 6.40 in **3b.** This large downfield shift would only be explicable if the benzoyl group were adjacent to the dimethylaminomethyl (DMAM) group. From the metalation patterns observed thus far for thiophenes, the benzoyl group must be positioned at the far more reactive 2 position.

Of interest was the fact that the NMR spectrum of the benzophenone condensation product **3a** exhibited a two-proton methylene resonance at τ 7.03 (upfield τ 0.45 from the methylene singlet in 3-DTA) and a six-proton methyl singlet of the two amine methyls at τ 7.92 (upfield τ 0.09 from the same group in 3-DTA). These upfield shifts can be attributed to the anisotropic effect arising from the geminal phenyl groups situated adjacent to the DMAM group and are diagnostic of the assigned substitution pattern.[10,21]

With the excellent directing ability of the DMAM group in the 3 position of thiophene successfully demonstrated, it was anticipated that the oxygen analogue would similarly coordinate with *n*-butyllithium to afford significant concentrations of an oxygen-directed 2-lithiothiophene. This was realized in the case of 3-thenylmethyl ether (3-TME, **4**). Metalation of 3-TME followed by condensation with benzophenone, dimethylformamide, and dimethyl disulfide afforded good yields of compounds **4a, 4b,** and **4c,** respectively (eq 3).



(3)

4

4a, R = $C(C_6H_5)_2OH$
b, R = CHO
c, R = SCH_3

Physical and spectral data for these compounds are summarized in Tables I and II (see paragraph at end of paper regarding supplementary material). NMR spectra of **4b** and **4c** exhibited well-resolved AB patterns for the two thiophene ring protons.[19] The values of J_{AB}, in each case ca. 5.0 Hz, i.e., that expected for 2,3 disposition of the ring protons, substantiated the indicated substitution pattern of the substituents. For 2-diphenylhydroxymethyl-3-TME the thiophene ring proton resonances were obscured by the phenyl resonances but these same phenyls produced the expected anisotropic effect[21] upon the adjacent methoxymethyl substituent. The methylene protons in **4a** exhibited a resonance at τ 6.00 (upfield τ 0.45 from the methylene resonance in 3-TME). Interestingly, this chemical shift difference is exactly that found between 2-diphenylhydroxymethyl-3-DTA (**3a**) and 3-DTA (**3**) itself. The terminal methyl resonance was shifted from τ 6.63 in the 3-TME to τ 6.92 in 2-diphenylhydroxymethyl-3-TME (Δ = 0.29 τ).

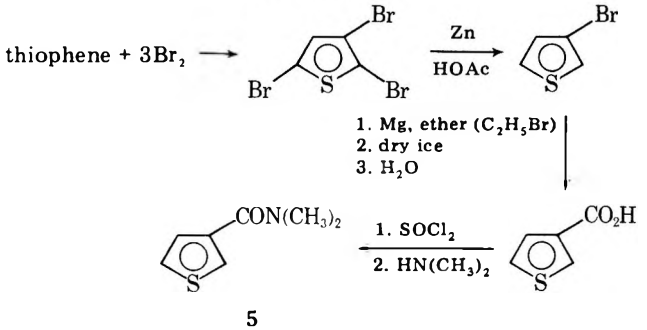
In an attempt to extend these results, *N,N*-dimethyl-3-thiophenecarboxamide (3-DTC, **5**) was prepared and metalated. Before considering the results of its metalation, its multistep synthesis deserves some attention. One of the most suitable methods for preparing 3-substituted thiophenes is that based on the use of 3-bromothiophene. The synthetic route utilized is illustrated in Scheme IV.

A preliminary metalation of 3-DTC followed by hydrolysis

Table III. Experimental Conditions for the Metalation of Various Substituted Thiophenes

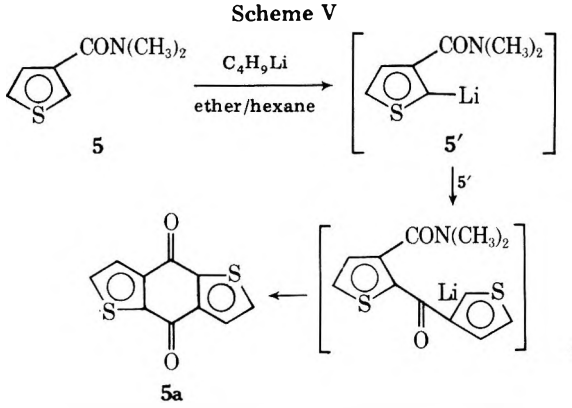
Compd	Substrate:*n*-BuLi: condensing agent	Substituent	Condensing agent (E)	Metalation period, h	Condensation period, h	Temp, °C
1a	1:1:8	2-CH_2NMe_2	D_2O	7	0.5	25–35 (ambient)
1b	1:1.2:1.7	2-CH_2NMe_2	Me_3SiCl	1	12	25–35 (ambient)
1c	1:1.2:1.8	2-CH_2NMe_2	$CHONMe_2$	12	12	25–35 (ambient)
2a	1:10:10	2-CH_2NMe_2; 5-Me	Ph_2CO	4	0.5	25–35 (ambient)
3a	1:1.2:1	3-CH_2NMe_2	Ph_2CO	1	4	25–35 (ambient)
3b	1:1.2:1	3-CH_2NMe_2	$CHONMe_2$	1	5	25–35 (ambient)
3c	1:1.2:6	3-CH_2NMe_2	D_2O	4	1	25–35 (ambient)
3d	1:1.1:1.1	3-CH_2NMe_2	PhCN	1	12	25–35 (ambient)
3e	1:1:1	3-CH_2NMe_2	*p*-$C_7H_7SO_2Cl$	1	3	−70
3f	1:1.2:1.4	3-CH_2NMe_2	*p*-$C_7H_7SO_2Br$	1	3	−70 warm to 25
4a	1:1.2:1.2	3-CH_2OMe	Ph_2CO	1	12	25–35 (ambient)
4b	1:1.1:2	3-CH_2OMe	$CHONMe_2$	1	12	25–35 (ambient)
4c	1:1.1:2	3-CH_2OMe	Me_2S_2	1.5	5	25–35 (ambient)
6a	1:2.4:10	3-COHNMe	D_2O	1	0.25	25–35 (ambient)
6b	1:2.1:1.2	3-CONHMe	Ph_2CO	3	7	25–35 (ambient)

Scheme IV



5

Scheme V



5a

failed to return the original carboxamide. Instead, the lithio intermediate formed, presumably 5′, condensed with itself to form 4,8-dehydrobenzo[1,2-*b*:4,5-*b*′]dithiophene-4,8-dione (**5a**) (Scheme V). The product was deduced to have the structure shown based on the following data: (1) molecular weight and elemental analysis were in accord with theory; (2) its NMR spectrum exhibited two equivalent doublets for the ring protons at τ 2.79 and 3.39 with a coupling constant of 5.0 Hz.[19] In addition a paper published after this work was completed has reported an independent synthesis of this quinone.[22]

With the failure of the 3-*N*,N-dimethylcarboxamide group to effect utilizable metalation in the 2 position of thiophene, our attention was turned to the possible use of the *N*-methylcarboxamide group, for which there was ample precedent in other systems.[6,7] It was anticipated that this substituent would initially undergo N-metalation with *n*-butyllithium thus deactivating the carbonyl group toward nucleophilic attack. 2-Lithiation by a second equivalent of *n*-butyllithium might then be realized. Metalation of *N*-methyl-3-thiophenecarboxamide (3-MTC, **6**) with 2.2 equiv of base followed by hydrolysis with deuterium oxide gave a 55% recovery of 2-deuterio-3-MTC (**6a**). An NMR spectrum of the product showed an AB pattern for the two ring protons with J_{AB} = 5.0 Hz. In the spectrum of 3-MTC itself the downfield proton resonance centered at τ 2.13 can be reasonably assigned to the proton adjacent to both the sulfur atom and the carbonyl. This resonance was not detectable in the product **6a** indicating incorporation of one atom of deuterium at the 2 position of 3-MTC.

Condensation of 2-lithio-3-MTC with benzophenone afforded a 23% yield of 2-diphenylhydroxymethyl-3-MTC (**6b**). The compound's structure was supported by both ir and NMR evidence. The location of the diphenylhydroxymethyl substituent in the 2 position in this molecule can, in addition to being inferred by the previously described deuteration experiment, be substantiated by the upfield shift (τ 0.29) of the methyl group in this compound vs. that of the unsubstituted amide, 3-MTC.[21]

Experimental Section

General. All lithiation reactions were run under dry nitrogen or argon. *n*-Butyllithium (1.6 M in hexane) was purchased from Foote Mineral Co. *N,N,N′N′*-Tetramethylethylenediamine (TMEDA) was obtained from Aldrich Chemical Co. and stored over KOH pellets. Ethers used as reaction solvents were Matheson Coleman and Bell "absolute" grade which was stored over Linde 3A molecular sieves or sodium metal and tetrahydrofuran (THF) which was distilled from lithium aluminum hydride immediately before use. Aldrich Chemical Co. was the supplier of thiophene and 3-methylthiophene. *N*-Bromosuccinimide and benzoyl peroxide were purchased from Matheson Coleman and Bell. The former reagent was recrystallized from H_2O immediately before use. Condensing reagents (benzonitrile, benzophenone, *p*-toluenesulfonyl chloride, and methyl disulfide) were supplied by Matheson Coleman and Bell. Dimethylformamide was purchased from Mallinckrodt Chemical Works and stored over Linde 3A molecular sieves.

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Alfred Bernhardt Laboratories, Mulheim, West Germany. Melting points were determined on a Hoover melting point apparatus and have been corrected. Ir spectra were obtained as Nujol mulls unless otherwise indicated on a Perkin-Elmer Model 137 Infracord spectrometer using the 5.14- and 11.03-μ bands of polystyrene as references. NMR spectra were obtained on a Varian A-56/60 spectrometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on a Varian Aerograph Model 90-P gas chromatograph, using a 10-ft column packed with 6% Apiezon L on Chromosorb W.

General Metalation Procedure. The substrate was dissolved in dry ether (1 ml ether/mmol substrate) at room temperature under nitrogen and 1.6 M *n*-butyllithium in hexane was slowly added. After an appropriate period a condensing agent was added at such a rate as to produce only a slight exotherm. The reaction solution was stirred for a designated period and then with the exception of compound **3d** hydrolyzed with water (dilute acid was used in the case of **3d**). Exact conditions for each metalation are provided in Table III.

Table IV. Study of the Extent of Metalation of *N,N*-Dimethyl-3-thenylamine (3) with Time

Metalation time, h	Yield, g	%	Mp, °C
1	0.52	58	86–88
3	0.58	64	84–87
4	0.60	66	87–88
6	0.61	67	86–88
12	0.56	62	87–88

The workup procedure used for the hydrolyzed mixtures (with the exceptions described below) called for separating the ether layer, then combining it with ether extracts of the aqueous layer. The combined ether extracts were dried over $MgSO_4$ and stripped under vacuum. The condensation product was then purified by the appropriate procedure designated in Table I.

For compounds **2a, 3a, 3e,** and **3f** the ether layer and ether extracts of the aqueous layer were combined and extracted with 10% HCl. The acid layer was separated and neutralized with 10% NaOH. Ether extracts of the neutralized portion were dried over $MgSO_4$. After the ether was removed under vacuum the condensation product was purified as indicated in Table I.

Physical data for various substrates and metalation products are given in Table I. Ir and NMR data are provided in Table II (see paragraph at end of paper regarding supplementary material).

***N,N*-Dimethyl-2-thenylamine (2-DTA, 1).** Thiophene was chloromethylated[23] to give 2-chloromethylthiophene, bp 40–43 °C (6 mm). 2-Chloromethylthiophene (30.2 g, 2.28 mol) was added dropwise to a fourfold excess of dimethylamine. Excess dimethylamine was evaporated and 100 ml of water and 100 ml of ether were added. The ether layer and two ether extracts of the aqueous layer were combined, dried over anhydrous $MgSO_4$, and stripped. A brown oil was obtained which was vacuum distilled to give 18.5 g (57%) of 2-DTA, bp 58–60 °C (8 mm) [lit.[24] 60–61 °C (10 mm)].

5-Methyl-*N,N*-dimethyl-2-thenylamine (2). Aldehyde **1c** (8.0 g, 0.047 mol) was reduced via the Wolff–Kishner reduction method. The product was steam distilled and the fraction boiling at 108–110 °C collected. The yield was 6.6 g (86%) of 5-methyl-*N,N*-dimethyl-2-thenylamine (**2**) [lit.[25] bp 83–84 °C (13 mm)].

Preparation of the Methiodide (2b) of 5-Methyl-3-diphenylhydroxymethyl-2-DTA (2a). Carbinolamine **2a** (1.30 g, 0.0027 mol) was dissolved in 50 ml of acetonitrile and a large excess of methyl iodide (10.0 g, 0.070 mol) was added. After the reaction mixture was refluxed for 6 h, the solvent was stripped under reduced pressure to give 1.80 g (98%) of 5-methyl-3-diphenylhydroxymethyl-*N,N,N*-trimethyl-2-thenylammonium iodide (**2b**). An analytical sample, mp 194 °C dec, was obtained after recrystallization from absolute ethanol.

Cyclization of Methiodide 2b to Produce Ether 2c. A solution of 0.004 mol of KNH_2 in 175 ml of liquid NH_3 was prepared from potassium metal (0.15 g, 0.004 mol) in the manner described by Hauser and Harris.[27] Methiodide **2b** (1.15 g, 0.0024 mol) was added to the stirred solution. After 0.5 h, 50 ml of dry dimethoxyethane was added and the condenser was fitted with a $CaCl_2$ drying tube. After the reaction mixture was refluxed for 7 days evolution of trimethylamine was no longer detected with litmus paper. Excess NH_4Cl was added followed by 100 ml of water. The organic layer was separated, dried over anhydrous $MgSO_4$, and stripped to give a light orange powder. Recrystallization from absolute ethanol gave 0.48 g (45%) of a white powder, mp 117–119 °C. The product was assigned structure **2c** on the basis of its spectral and analytical data.

Preparation of *N,N*-Dimethyl-3-thenylamine (3). A solution of 3-methylthiophene (44 g, 0.45 mol) and benzoyl peroxide (0.8 g) in 150 ml of dry CCl_4 (stored over molecular sieves) was brought to rapid reflux and a mixture of *N*-bromosuccinimide (72 g, 0.4 mol) and benzoyl peroxide (0.8 g) was added portionwise as rapidly as the vigorous foaming would permit. As soon as the foaming from the last addition of *N*-bromosuccinimide had subsided, the flask was cooled and the succinimide filtered off and washed with CCl_4. The filtrate was stripped under reduced pressure and the residue vacuum distilled at 0.12 mm to give 53.0 g (67%) of 3-(α-bromomethyl)thiophene, bp 75–77 °C (1.0 mm) [lit.[28] 75–78 °C (1.0 mm)]. Ir and NMR were in accord with the assigned structure. The 3-(α-bromomethyl)thiophene (10.0 g, 0.056 mol) was added dropwise to 150 ml (2.26 mol) of dimethylamine, then 100 ml of distilled water was added and the reaction mixture was refluxed for 1 h. After standing overnight, the crude product was extracted with ether. The ether extracts were combined, dried over anhydrous $MgSO_4$, and stripped of solvent. Resulting was a light brown oil which was vacuum distilled at 0.12 mm and the fraction boiling between 28 and 32 °C collected. A yield of 7.9 g (42%) of 3-DTA was obtained.

Metalation of *N,N*-Dimethyl-3-thenylamine (3). Time Study. 3-DTA was metalated over a period of 1, 3, 6, and 12 h. Each run was carried out as follows.

To a solution of 3-DTA (0.41 g, 0.0028 mol) in 30 ml of dry ether was added 2.1 ml (0.0034 mol) of 1.6 M *n*-butyllithium. After stirring for between 1 and 12 h, benzophenone (1.24 g, 0.0028 mol) was added and the reaction mixture was stirred for 4 h. The mixture was hydrolyzed with H_2O, the aqueous layer was separated and extracted with ether, and the combined ether extracts in turn were extracted with 10% HCl. The acidic extracts were carefully neutralized with NaOH and extracted once again with ether. These ether extracts were dried over anhydrous $MgSO_4$ and stripped. After the resulting clear, viscous oil had stood overnight under a vacuum, a white solid crystallized. The crude solid was washed several times with petroleum ether.

Table IV gives the melting point and yield of product obtained for each run. The data indicate that metalation is essentially complete after 1 h.

2-Formyl-*N,N*-dimethyl-3-thenylamine (3b). 3-DTA (**3**, 0.67 g, 0.0048 mol) was dissolved in 50 ml of dry ether at room temperature and 3.3 ml (0.0052 mol) of 1.6 M *n*-butyllithium in hexane was slowly added. After stirring for 1 h, dimethylformamide (0.70 g, 0.0096 mol) dissolved in 10 ml of dry ether was slowly added and the solution stirred for 5 h. To the resultant cloudy mixture 50 ml of water was added and the ether layer was separated, dried over anhydrous $MgSO_4$, and stripped. The resulting light brown oil was vacuum distilled at 0.03 mm and the fraction boiling between 62 and 63 °C collected. A yield of 0.60 g (75%) of 2-formyl-3-DTA (**3b**) was obtained.

Oxidation of 2-Formyl-3-DTA (3b) to 2,3-Thiophenedicarboxylic Acid. Carboxaldehyde **3b** (1.1 g, 0.0065 mol) was added to 20 ml of 0.5 N NaOH, the mixture was cooled to 20 °C, and $KMnO_4$ (3.6 g, 0.023 mol) was slowly added with stirring. After stirring for an additional 1 h at room temperature, Na_2SO_3 (0.5 g, 0.004 mol) was added, whereupon MnO_2 precipitated and was filtered off; the remaining reaction mixture was extracted twice with ether. The ether layer was separated, dried over anhydrous $MgSO_4$, and stripped of solvent. No unreacted starting material was recovered. After the aqueous layer had been acidified with 10% HCl, it was extracted with ether. These ether extracts were dried over anhydrous $MgSO_4$ and stripped to give 0.3 g (21%) of 2,3-thiophenedicarboxylic acid, mp 268–270 °C (lit.[18] 270 °C dec).

Formation of 2,3-Thiophenedicarboxylic Acid Anhydride (TCA). 2,3-Thiophenecarboxylic acid (0.23 g, 0.0013 mol) was treated with 4.8 ml (0.051 mol) of acetic anhydride and the solution refluxed for 30 min. Excess acetic anhydride was boiled off under reduced pressure. The resulting crude solid was sublimed at 85 °C (0.4 mm) to give 0.10 g (50%) of the anhydride, mp 137–138 °C (lit.[18] mp 140 °C).

Preparation of 2-Chloro-*N,N*-dimethyl-3-thenylamine (3e). 3-DTA (**3**, 1.1 g, 0.0078 mol) was dissolved in 50 ml of dry ether and 4.9 ml (0.0078 mol) of 1.6 M *n*-butyllithium was added. After stirring for 1 h, the reaction flask was placed in a dry ice–acetone bath and *p*-toluenesulfonyl chloride (1.48 g, 0.0078 mol) was slowly added. After stirring for 3 h at −70 °C, 100 ml of H_2O was added. The aqueous layer was separated and extracted with ether and the combined ether extracts extracted with 10% HCl. The combined acid extracts were carefully neutralized with NaOH and this neutralized solution was extracted with ether. The combined ether extracts were dried over anhydrous $MgSO_4$ and filtered and the solvent stripped under vacuum. The resulting dark brown oil was vacuum distilled at 0.6 mm to give one fraction, bp 31–32 °C. A yield of 0.34 g (25%) of 2-chloro-3-DTA (**3e**) was obtained. A similar synthesis of the 3-bromo analogue utilizing *p*-toluenesulfonyl bromide prepared by the method of Kovar et al.[29] yielded 2-bromo-3-DTA.

Preparation of 3-Thenyl Methyl Ether (4). Sodium methoxide was prepared by reacting sodium metal (2.3 g, 0.10 mol) with 100 ml of absolute methanol at room temperature. To this solution, 3-(α-bromomethyl)thiophene (10.5 g, 0.059 mol) was added and the resulting mixture was refluxed for 7 h. The mixture was concentrated to 20 ml and extracted with ether. The combined ether extracts were washed once with water, dried over anhydrous $MgSO_4$, and filtered and the solvent removed under vacuum. Distillation of the resultant oil gave 2.9 g (38%) of 3-TME (**4**), bp 26 °C (0.2 mm) [lit.[30] bp 65–67 °C (17 mm)].

Preparation of *N,N*-Dimethyl-3-thiophenecarboxamide (3-DTC, 5). Thiophene (282 g, 3.35 mol) was treated with bromine (1620 g, 10.05 mol) in chloroform to give 876 g (82%) of 2,3,5-tribro-

mothiophene, bp 150–152 °C (16 mm) [lit.[31] bp 120–122 °C (11 mm)]. The latter compound (642 g, 2.0 mol) was debrominated by treatment with zinc (392 g, 6.0 mol) and 350 ml of acetic acid to give 233 g (72%) of 3-bromothiophene, which was isolated by steam distillation (lit.[32] bp 159–160 °C). The Grignard reagent was prepared via the entrainment method by reacting 3-bromothiophene (40 g, 0.25 mol) with magnesium metal (36.5 g, 1.5 mol) and ethyl bromide (138 g, 1.25 mol) in dry ether. After refluxing several hours the reaction mixture was poured over a dry ice/ether slurry. Workup gave 13 g (41%) of 3-thiophenecarboxylic acid, mp 136–137.5 °C (lit.[33] mp 137.5–138.5 °C). The carboxylic acid (13 g, 0.102 mol) was treated with 37.7 g (0.329 mol) of thionyl chloride to afford 9.1 g (62%) of 3-thenoyl chloride, mp 50–52 °C (lit.[34] mp 51–52 °C). A solution of 2.5 g (0.017 mol) of 3-thenoyl chloride in 20 ml of benzene was slowly added to a large excess of dimethylamine. After stirring overnight the crude product was taken up in ether and washed once with water. The ether layer was dried over anhydrous $MgSO_4$ and stripped of solvent. The resultant oil was vacuum distilled at 0.5 mm to give a single fraction boiling at 89–90 °C. A yield of 1.2 g (45%) of 3-DTC (**5**) was obtained.

Metalation of *N,N*-Dimethyl-3-thiophenecarboxamide (5) and Hydrolysis with H_2O. 3-DTC (**5**, 0.90 g, 0.0058 mol) in 50 ml of dry ether was treated with 4.0 ml (0.0066 mol) of 1.6 M *n*-butyllithium with stirring. After 10 min a light yellow precipitate formed. The reaction mixture was stirred for another 10 min and then hydrolyzed with water. A white, crystalline material precipitated from the resulting mixture which was isolated by filtration. Ether extracts of the aqueous layer did not give any further product. The filtered solid was sublimed at 150 °C (0.2 mm) to give 0.26 g (41%) of 4,8-dehydrobenzo[1,2-*b*:4,5-*b'*]dithiophene-4,8-dione, mp 258–260 °C (lit. mp 258–260 °C).[22]

***N*-Methyl-3-thiophenecarboximide (3-MTC, 6).** A solution of 3-thenoyl chloride (9.1 g, 0.062 mol) in 50 ml of benzene was added slowly to 31 g (0.40 mol) of 40% methylamine. After the reaction mixture was refluxed for 45 min, the benzene layer was separated, washed once with water, and dried over anhydrous $MgSO_4$ and the solvent stripped under vacuum. A white powder was obtained which was recrystallized from ethanol to give 1.1 g (13%) of 3-MTC (**6**), mp 115–117 °C.

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Registry No.—**1**, 26019-17-0; D_2O, 7789-20-0; benzophenone, 119-61-9; benzonitrile, 100-47-0; *p*-toluenesulfonyl chloride, 98-59-9; *p*-toluenesulfonyl bromide, 1950-69-2; *N,N*-dimethylformamide, 68-12-2; dimethyl disulfide, 624-92-0; 2-chloromethylthiophene, 765-50-4; dimethylamine, 124-40-3; 3-methylthiophene, 616-44-4; 3-(α-bromomethyl)thiophene, 34846-44-1; 2,3-thiophenedicarboxylic acid, 1451-95-2; TCA, 6007-83-6; thiophene, 110-02-1; 2,3,5-tribromothiophene, 3141-24-0; 3-bromothiophene, 872-31-1; 3-thiophenecarboxylic acid, 88-13-1; 3-thenoyl chloride, 41507-35-1.

Supplementary Material Available. Table II, ir and NMR spectral data of substituted thiophenes (1 page). Ordering information is given on any current masthead page.

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The Reaction of Dialkylcopper Lithium Reagents with 3-Halo-2-acylaminoacrylic Acids

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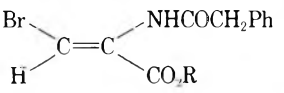
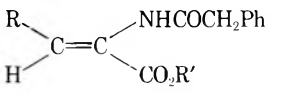
The reaction of Me_2CuLi and n-Bu_2CuLi with some 3-halo-2-acylaminoacrylic acid derivatives has been studied. Reaction of (*Z*)-3-bromo-2-(2-phenylacetamido)acrylic acid (**1**) with Me_2CuLi yielded (*Z*)-2-(2-phenylacetamido) crotonic acid (**3**), while the reaction with n-Bu_2CuLi gave a 2:1 mixture of *Z* and *E* isomers, **5** and **6**, of 2-(2-phenylacetamido)hept-2-enoic acid. In each case, the reduction product, 2-(2-phenylacetamido)acrylic acid (**4**), was formed as a minor product. The (*Z*)-3-chloroacrylate **7**, upon reaction with Me_2CuLi, gave the (*Z*)-crotonate **8**, while a 3:1 *Z* to *E* mixture of the 3-bromoacrylates **9** and **10**, yielded a product mixture of the (*Z*)- and (*E*)-crotonates 8 and **11**. These reactions thus occur by replacement of the vinylic halogen and proceed with complete or predominant retention of configuration about the double bond.

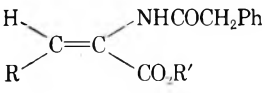
The synthetic utility of dialkylcopper lithium reagents, R_2CuLi, is well known[1] and of current interest. R_2CuLi reagents are known to undergo direct displacement of vinylic halogen by an alkyl group[2] and also to effect conjugate addition to enone systems.[3] We have studied the reaction of Me_2CuLi and n-Bu_2CuLi with 3-halo-2-acylaminoacrylic acid derivatives as a possible route for preparation of dehydroamino acids substituted in the β position with various alkyl groups and to establish the stereochemical course of the reaction. The reaction of cuprate reagents with cyclic β-halo-α,β-unsaturated ketones recently has been reported.[4]



1, R = H
2, R = Me



3, R = Me; R′ = H
4, R = H; R′ = H
5, R = n-Bu; R′ = H



6, R = n-Bu; R′ = H

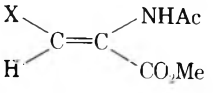
Results and Discussion

Products of the Reaction. (*Z*)-3-Bromo-2-(2-phenylacetamido)acrylic acid (**1**),[5] upon treatment with 5 equiv of ethereal Me_2CuLi in tetrahydrofuran at 0 °C, yielded a mixture for which TLC analysis revealed four components, two of which were present in minor amounts. The NMR spectrum of the mixture established the two major products to be the crotonic acid **3** of *Z* configuration and the acrylic acid **4**[6] in a 3:1 ratio. Use of only 2 equiv of Me_2CuLi furnished a more homogeneous product mixture containing only small amounts of **4**, from which **3** was obtained in 52% yield by one recrystallization from ethyl acetate.

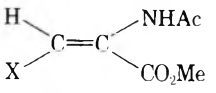
Isomerization has been reported to occur in reactions of R_2CuLi with vinyl halides[7] and α,β-acetylenic esters,[8] and likely proceeds via intermediate vinyl cuprates. To check if this were occurring, the reaction of **1** with Me_2CuLi was carried out at lower temperatures. No reaction was observed at −78 °C and it was necessary to raise the temperature to approximately −40 °C before significant reaction occurred. Then, only the *Z* isomer was observed in the NMR spectrum of the product mixture. It should be pointed out that the *Z* isomer of 2-acylaminocrotonates has been reported[9,10] to be the more stable isomer. Thus, isomerization may not be occurring in this case as the (*Z*)-3-bromoacrylates yield directly the more stable vinyl cuprate and, subsequently, crotonate of *Z* configuration.

Treatment of the 3-bromoacrylic acid **1** with an excess of n-Bu_2CuLi in tetrahydrofuran–hexane at −40 °C gave a mixture composed of six components, four of which were identified as being the heptenoic acids **5** and **6**, the acrylic acid **4**, and recovered reactant **1**. The heptenoic acids **5** and **6** typically comprised 30–60% of the product mixture and were present in an approximate ratio of 2:1, respectively. The acids **5** and **6** were each separated, though in low yield, from the product mixture by preparative TLC. The formation of the acrylic acid **4** in the above reactions, in which bromine has been replaced by hydrogen, was not unexpected as similar reduction products resulting from apparent halogen–metal exchange reactions have been reported.[2,7,11] Likewise, the nonstereospecificity as observed in reaction of **1** with n-Bu_2CuLi has been observed previously in reactions of R_2CuLi with β-halo-α,β-unsaturated sulfones[12] and β-acetoxy-α,β-unsaturated carbonyl compounds.[13]

Methyl (*Z*)-2-acetamido-3-chloroacrylate (**7**) underwent reaction with Me_2CuLi in an analogous manner as **1** to yield the (*Z*)-2-acetamidoacrylate **8**. When an approximate 3:1 isomeric mixture of the 3-bromoacrylates **9** and **10** was allowed to react with Me_2CuLi, a mixture of *Z* and *E* isomers 8 and **11** was obtained. The ratio of **8**:**11** could not readily be determined from the NMR spectrum of the mixture; however, the *Z* isomer **8** was the predominant product. The reactions of **1**, **7**, **9**, and **10** thus appear to be stereospecific with retention of configuration, a result consistent with previous studies.[2,7,14]



7, X = Cl
8, X = Me
9, X = Br



10, X = Br
11, X = Me

The possibility exists that the above 3-alkyl products are formed by a sequence of conjugate addition and elimination rather than by substitution. Casey has proposed[13] an addition–elimination sequence in the reactions of R_2CuLi with β-acetoxy-α,β-unsaturated esters. We have observed that the acrylic acid **4** did not undergo conjugate addition upon reaction with Me_2CuLi, in agreement with previous results reported[15] for α,β-ethylenic carboxylic acids. Thus, unless the 3-bromo group in **1** has an effect of enhancing conjugate addition, the above results, while not ruling out an addition–elimination process, indicate that conjugate addition may not be a significant reaction pathway in this system. Also, for-

Table I. Shift Values and Configurational Assignments for β-Haloacrylates

Registry no.	Compd	Solvent	Chemical shift, δ, of vinylic proton	Configuration
60084-43-7	**9**	$CDCl_3$	7.17	*Z*
		TFA	7.80	
60084-44-8	**10**	$CDCl_3$	7.48	*E*
		TFA	7.51	
60084-45-9	**2**	$CDCl_3$	7.04	*Z*
		TFA	7.77	
60084-46-0	**1**	TFA	7.94	*Z*
60084-47-1	**7**	$CDCl_3$	6.97	
		TFA	7.55	*Z*

mation of the acrylate **4** in these reactions is consistent with at least a portion of the reaction proceeding by a substitution process.

Stereochemistry of Reactants and Products. The stereochemistry of reactants and products involved in this study was established by use of NMR spectroscopy. Previous studies[9,16] have shown that for 2-acylaminoacrylate or crotonate derivatives, a vinylic proton cis to the acylamino group is downfield compared to a proton trans to that function. In the preparation of reactant **1**, only one geometrical isomer was obtained. Other 3-haloacrylic acids related to **1** that have been reported[5,17] also appear to be single isomers of unspecified configuration. However, Kishi and co-workers[18] recently obtained a 2:1 mixture of the *Z* and *E* isomers **9** and **10**. Following Kishi's procedure, we prepared **9** and **10** and have assigned stereochemistry to these isomers based upon the shift positions of the vinylic protons. In agreement with the previous assignment,[18] **9** is of the *Z* configuration and has the vinylic proton, being trans to the acylamino function, absorbing at higher field relative to the olefinic shift position of the *E* isomer **10** (Table I).

Reactant **1** was converted to the methyl ester **2** by methylation with dimethyl sulfate. Comparison of the NMR spectra of **2**, taken in both $CDCl_3$ and trifluoroacetic acid (TFA), with those of **9** and **10** established **2**, and consequently **1**, as being of the *Z* configuration. The *Z* isomers **2**, **7**, and **9** all showed a significant downfield shift of the vinylic proton in TFA compared to $CDCl_3$, as has been observed[9] for the *Z* isomers of crotonic acid derivatives (see Table I).

Relevant NMR data and resulting stereochemical assignments for the 3-alkylacrylates prepared in this study are given in Table II. Configuration previously has been assigned[9] to crotonates **8** and **11** in which the *Z* isomer has both the vinylic and β-methyl protons high field relative to the *E* isomer when measured in $CDCl_3$. As previously noted[9] for spectra measured in TFA as solvent, the relative positions of the β-methyl protons in the two geometrical isomers are unchanged, while the vinylic proton of the *Z* isomer is shifted downfield and the corresponding proton in the *E* isomer is shifted upfield. The net result is that the relative positions of the isomeric vinylic protons are switched in TFA relative to their positions in $CDCl_3$ and the *Z* isomer now has the low-field vinyl absorption. Since compounds **3**, **5**, and **6** were insoluble in $CDCl_3$, their spectra were measured in TFA as solvent. Comparison of the chemical shift values of **3** with **8** clearly showed **3** to have the *Z* configuration. Likewise, the relative positions of the β-methylene and vinylic protons in **5** and **6** readily allowed assignment of *Z* and *E* configuration, respectively, to these substances (see Table II).

Table II. Shift Values and Configurational Assignments for β-Alkylacrylates

Registry no.	Compd	Solvent	Chemical shift, δ: β-Me or -CH_2	Vinylic H	Configuration
60084-48-2	**3**	TFA	1.91	7.40	*Z*
60084-49-3	**5**	TFA	2.24	7.34	*Z*
60084-50-6	**6**	TFA	2.77	6.95	*E*
60027-59-0	**8**	$CDCl_3$	1.71	6.72	*Z*
		TFA	1.85	7.18	
60027-53-4	**11**	$CDCl_3$	2.02	6.90	*E*
		TFA	2.13	6.68	

Experimental Section

The melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected. Thin layer chromatography was done on commercially available silica gel plates with fluorescent indicator (Brinkman F-254 and 60F-254). Preparative TLC was done on 20 × 20 cm, 2-mm thick plates. The solvent systems used were A, $CHCl_3$–AcOH (95:5); B, $CHCl_3$–MeOH–AcOH (10:5:1); C, $CHCl_3$–EtOH (1:1). The compounds were located under uv irradiation and with iodine vapor. The NMR spectra were determined on a Varian Associates XL-100-12, 100 MHz, or Varian EM-360, 60 MHz, spectrophotometer, with Me_4Si as an internal reference. Solvents were removed in vacuo on a Büchi rotary evaporator. Elemental analyses were performed at M-H-W Laboratories, Garden City, Mich. Reagents used were of reagent or spectroscopic grade.

The air-sensitive alkyllithium and dialkylcopper lithium reagents were handled according to established techniques.[19] The MeLi and n-BuLi solutions were purchased from Alfa Products and were used untitrated. Both solutions were stored at room temperature and the n-BuLi solution was stored in a desiccator. Ultrapure grade cuprous iodide was purchased from Ventron, Alfa Products, and stored in a desiccator. THF was distilled from $LiAlH_4$ prior to use and stored over 5A molecular sieve.

Reaction of 1 with Me_2CuLi. To a three-neck round-bottom flask fitted with nitrogen inlet and outlet tubes and a septum capped addition funnel was added 1.58 g (8.82 mmol) of anhydrous CuI. The reaction flask was flamed out both before and after the addition of the CuI and allowed to cool under a dry, oxygen-free nitrogen flow. THF (24.5 ml) was added to the flask and the resulting slurry was stirred magnetically and cooled to 0 °C in an ice bath. A solution of MeLi (11.0 ml of 1.65 M) in ether was added dropwise over 20 min to yield a light brown solution approximately 0.25 M in Me_2CuLi. A solution of **1**[5] (0.500 g, 1.76 mmol) in 8.5 ml of THF was added over 20 min and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of 2 ml of 3 N HCl. The mixture was allowed to warm to room temperature and was added with stirring to 125 ml of 3 N HCl, followed by extraction with 5 × 30 ml of $CHCl_3$. The combined organic extracts were filtered by suction and dried over $MgSO_4$ with simultaneous treatment with charcoal. Following filtration, the solvent was removed in vacuo to yield 0.376 g of a white solid, mp 175–177 °C dec. TLC (solvent A) showed the presence of four components, two of which seemed to be present in minor amounts. NMR analysis of the crude product mixture established that the major components were the crotonic acid **3** and the acrylic acid **4**, these being present in a ratio of 3:1, respectively. No peaks were observed that could be assigned to the other geometrical isomer of **3**. The identity of the acrylic acid **4** also was established by TLC comparison with an authentic sample[6] in three different solvent systems. The crotonic acid **3** was isolated by recrystallization from ethyl acetate; one recrystallization gave material melting at 194–195 °C dec and in a yield of 39%. This material still contained a small amount of **4** as shown by TLC analysis. An analytical sample of **3** was prepared by additional recrystallizations from ethyl acetate: mp 198–199 °C dec; TLC R_f 0.17 (A), 0.69 (B); NMR (TFA) δ 1.91 (d, 3 H, CH_3, J = 7 Hz), 4.01 (s, 2 H, CH_2Ph), 7.40 (q, 1 H, vinyl, J = 7 Hz) overlapped with 7.46 (s, 5 H, Ph), 7.84 (s, 1 H, NH).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.44; H, 6.13; N, 6.17.

Reaction of **1** with 2 equiv of Me_2CuLi as used above resulted in negligible formation of **4**; one recrystallization of the product mixture from ethyl acetate gave crotonic acid **3** in 52% yield.

Treatment of **1** as above, except that the reaction was run at −78 °C for 2 h in a dry ice–acetone bath, gave upon workup mainly recovered reactant **1** as shown by TLC and NMR analysis. When the reaction was carried out at −40 to −50 °C and for reaction periods of 45–90 min, the product mixture was composed of reactant **1** and the

Z isomer **3**. None of the *E* isomer was detected in the NMR spectrum of the product mixture.

Reaction of 1 with *n*-Bu_2CuLi. Anhydrous CuI (1.68 g, 8.82 mmol), treated as above, was suspended in 27 ml of anhydrous THF and cooled to −40 °C in a dry ice–2-propanol bath. A solution of *n*-BuLi (8.5 ml of 2.1 M) in hexane was added dropwise over a 20-min period to produce a dark brown solution approximately 0.25 M in *n*-Bu_2CuLi. A solution of **1** (0.500 g, 1.76 mmol) in 10 ml of THF was added dropwise over 20 min, following which the reaction was allowed to proceed for an additional 1 h and then quenched at −40 °C by dropwise addition of 2.5 ml of 3 N HCl over an 8-min period. The mixture was stirred for 10 min at −40 °C, after which the cooling bath was removed and the mixture allowed to warm to room temperature. The reaction mixture was poured with stirring into 120 ml of 3 N HCl and the resulting mixture was filtered by suction through a pad of Celite. The filtrate was extracted with 5 × 30 ml of $CHCl_3$ and the combined organic extracts were simultaneously treated with charcoal and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo to give 0.414 g of a yellow solid, mp 140–155 °C dec. TLC (solvent A) showed the presence of six components, two of which were identified as being **1** and **4** by TLC comparison with authentic samples. NMR analysis of the mixture showed it to consist of the heptenoic acids **5** and **6**, the acrylic acid **4**, the reactant **1**, plus unidentified components. The ratio of **5**:**6**, as measured from the NMR spectrum of the product mixture, varied in different runs from approximately 2:1 to 3.6:1, with the total combined yield of **5** and **6** varying from 30–60%. Compounds **5** and **6** were separated by preparative TLC using solvent A. Each 2-mm silica gel plate was treated by application of 150 mg of sample in 1.5 ml of THF followed by multiple developments to effect separation. The appropriate bands were removed from each plate and extracted with three portions of MeOH. The extracts were filtered several times utilizing Celite to remove traces of silica gel and the solvent was removed in vacuo.

The lower band material proved to be the *Z* isomer and was obtained as a light yellow oil in 11% yield from **1**, which after dissolution in $CHCl_3$, filtration, and evaporation of the filtrate in vacuo yielded a glassy solid. Trituration of this solid with ether followed by two recrystallizations from 2-propanol gave a white solid, mp 205–206 °C dec. TLC and NMR analysis indicated this material to be homogeneous; however, two attempts to obtain satisfactory analytical data were unsuccessful, each analysis varying from the other. TLC R_f 0.18 (A), 0.35 (C); NMR (TFA) δ 0.95 (m, 3 H, CH_3), 1.45 (m, 4 H, $-CH_2CH_2-$), 2.24 (q, 2 H, $-CH_2C=$, J = 7 Hz), 4.00 (s, 2 H, $-COCH_2-$), 7.34 (t, 1 H, vinyl, J = 7 Hz) overlapped with 7.46 (s, 5 H, Ph), 7.78 (s, 1 H, NH).

The *E* isomer was isolated from an upper band of the preparative plate as a light yellow solid, mp 155–158.5 °C, 14% yield from **1**. This material was recrystallized twice from water and dried in a vacuum desiccator over P_2O_5 to give a white solid: mp 164–165 °C dec; R_f 0.36 (A), 0.50 (C); NMR (TFA) δ 1.0 (m, 3 H, CH_3), 1.5 (m, 4 H, $-CH_2CH_2-$), 2.77 (q, 2 H, $-CH_2C=$, J = 7 Hz), 3.98 (s, 2 H, $-COCH_2$), 6.95 (t, 1 H, vinyl, J = 7 Hz), 7.43 (m, 5 H, Ph), 8.06 (s, 1 H, NH).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.13; H, 7.20; N, 5.28.

Methyl 3-Bromo-2-(2-phenylacetamido)acrylate (2). Following the basic methylation procedure of Rothstein,[20] a mixture of **1** (1.00 g, 3.52 mmol), Na_2CO_3 (0.219 g, 2.07 mmol), NaOMe (0.223 g, 4.13 mmol), and Me_2SO_4 (0.67 g, 5.31 mmol) in 10 ml of anhydrous MeOH was heated at reflux for 1.75 h. After cooling to room temperature, 4 ml of water was added, the mixture was stirred for 30 min and filtered by suction, and the solvent was removed in vacuo. The residue was extracted with three portions of $CHCl_3$ and the combined extract was dried over $MgSO_4$. Filtration and removal of the solvent in vacuo gave 0.686 g (65%) of a pale yellow solid, mp 96–97.5 °C. Recrystallization from ether furnished product melting at 97.5–98 °C (lit.[5] 100–101 °C, prepared by esterification of **1** with diazomethane): R_f 0.40 (A); NMR ($CDCl_3$) δ 3.71 (s, 2 H, $-CH_2Ph$), 3.78 (s, 3 H, OCH_3), 6.92 (s, 1 H, NH), 7.04 (s, 1 H, vinyl), 7.36 (s, 5 H, Ph); NMR (TFA) δ 3.98 (s, 2 H, $-CH_2Ph$), 4.00 (s, 3 H, OCH_3), 7.45 (s, 5 H, Ph), 7.74 (s, 1 H, NH), 7.77 (s, 1 H, vinyl).

Methyl 3-Chloro-2-acetamidoacrylate (7). In 500 ml of dry CCl_4 (stored over Linde 3A molecular sieves) was dissolved 28.6 g (20 mmol) of methyl 2-acetamidoacrylate.[21] Chlorine gas was passed into the stirred solution at room temperature until a permanent yellow color developed, then the yellow solution was stirred for 10 min at room temperature. The solvent was removed in vacuo to yield a colorless oil. The oil was dissolved in 500 ml of dry CH_3CN (stored over Linde 3A) and 23.2 g (20.7 mmol) of 1,4-diazabicyclo[2.2.2]octane was added to the solution. The reaction mixture was stoppered and stirred for 1 h at room temperature. The precipitated hydrochloride salt was filtered and the solvent removed in vacuo to yield a brown precipitate. The precipitate was extracted three times with 100 ml of cold EtOAc and the combined extract filtered through Celite. The EtOAc was removed in vacuo to yield a brown oil which solidified upon standing overnight. The brown solid was recrystallized from Et_2O to yield a white solid. Additional crops were obtained after treatment of the Et_2O solution with Norit at room temperature. Recrystallization of the combined crops from Et_2O afforded **7** in 41% yield (14.6 g): mp 96–97 °C; NMR ($CDCl_3$) δ 2.13 (s, 3 H, Ac), 3.83 (s, 3 H, Me ester), 7.00 (s, 1 H, vinylic), and a broad band centered at 7.50 (1 H, NH).

Anal. Calcd for $C_6H_8ClNO_3$: C, 40.58; H, 4.54; N, 7.89. Found: C, 40.64; H, 4.60; N, 7.88.

Reaction of β-Chloroacrylate 7 with Me_2CuLi. A solution of **7** (0.30 g, 1.69 mmol) in 5.2 ml of THF was added dropwise over a period of 10 min to 2 equiv of Me_2CuLi, prepared as described above from 0.64 g (3.36 mmol) of CuI and 4.1 ml (6.72 mmol) of 1.65 M ethereal MeLi, in 15 ml of THF at 0 °C. The reaction was allowed to proceed for 2 h at 0 °C and then the mixture was worked up as above except that the acidic aqueous phase was saturated with NaCl prior to extraction with $CHCl_3$. A light yellow oil (0.26 g) was obtained, the NMR spectrum of which, upon comparison with reported spectral data,[9,10] showed this material to be the *Z* isomer **8**.

Preparation of (*Z*)- and (*E*)-2-Acetamido-3-bromoacrylic Acid Methyl Esters (9 and 10). Following the method of Kishi,[18] methyl 2-acetamidoacrylate[20] (0.50 g, 3.49 mmol) in 20 ml of CH_2Cl_2 was treated dropwise with a solution of bromine in CH_2Cl_2 until a permanent color persisted. After stirring at room temperature for 10 min, 0.39 g (3.48 mmol) of 1,4-diazabicyclo[2.2.2]octane was added and the reaction mixture was stirred for an additional 40 min. The precipitate was filtered through Celite and the solvent removed in vacuo to yield an oil. The oil was dissolved in 75 ml of anhydrous Et_2O, the resulting precipitate was removed by filtration, and the solvent was removed in vacuo to yield 0.58 g of an oil. The NMR spectrum of this oil was consistent for a mixture of **9** and **10** in an approximate ratio of 3:1, plus other unidentified components. Preparative TLC using $CHCl_3$–AcOH (95:5) as elutant effected separation of **9** and **10** for which the first and second bands above the origin corresponded to **9** and **10**, respectively: NMR ($CDCl_3$) (*Z* isomer) δ 2.13 (s, 3 H, acetyl), 3.80 (s, 3 H, methyl ester), 7.10 (s superimposed on broad peak, 2 H, vinylic and amide protons); (*E* isomer) δ 2.13 (s, 3 H, acetyl), 3.92 (s, 3 H, methyl ester), 7.78 (broad s, 1 H, NH), 8.00 (s, 1 H, vinylic proton). We have observed that the shift positions of the vinylic protons for mixtures of **9** and **10** were not reproducible among various samples; however, the relative positions of the vinylic protons for the two isomers did not change.

Reaction of a Mixture of 9 and 10 with Me_2CuLi. A 3:1 mixture of **9** and **10** (0.57 g, 2.57 mmol) was treated with 2 equiv of Me_2CuLi in THF as described above for **7**. An NMR spectrum of the crude reaction product showed both crotonates **8** and **11** to be present; a determination of the relative amounts of these isomers was not practical owing to the lack of separation between isomeric peaks and to overlap with absorption caused by impurities present in the sample.

Attempted Conjugate Addition of Me_2CuLi to Acrylic Acid 4. The acrylic acid **4** (0.500 g, 2.44 mmol) was treated with an excess of Me_2CuLi in the same manner as described above for the reaction of Me_2CuLi with the 3-bromoacrylic acid **1**. Following workup, TLC and NMR analysis on the crude reaction mixture established that the reactant **4** was the major component with two other minor components being present. The NMR spectrum did not show any peaks assignable to an ethyl group, as would be expected for any products formed by conjugate addition.

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Registry No.—**7** HCl, 60084-51-7; Me_2CuLi, 15681-48-8; *n*-Bu_2CuLi, 24406-16-4; methyl 2-acetamidoacrylate, 35356-70-8.

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Solvents for Aromatic SRN1 Reactions[1a]

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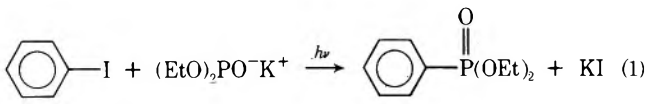
Whereas previously aromatic SRN1 reactions were conducted almost exclusively in ammonia, it is now found that dimethyl sulfoxide is a good solvent for photostimulated reactions of diethyl phosphite ion, thiophenoxide ion, and acetone enolate ion with iodobenzene. Yields in the iodobenzene–diethyl phosphite ion reaction were also high in acetonitrile and dimethylformamide and fairly good in *tert*-butyl alcohol, but poor in hexamethylphosphoric triamide and some other common dipolar, aprotic solvents. In *tert*-butylamine, attempted reactions with thiophenoxide and acetone enolate ions were not very satisfactory, but iodobenzene as well as *m*-bromoiodobenzene underwent rapid photostimulated reaction with diethyl phosphite ion. In water, poor yields were obtained in photostimulated reactions of thiophenoxide ion with two substrates which were the more reactive of several tried.

The SRN1 mechanism of aromatic substitution, first recognized in 1970,[2] involves radical and radical anion intermediates and electron transfer steps but the overall consequence is that of nucleophilic substitution. A representative reaction is that of iodobenzene with potassium diethyl phosphite (eq 1).[3]



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1 2

Other nucleophiles successfully involved in aromatic SRN1 reactions include arenethiolate ions,[4] the amide ion,[2,5] ketone enolate ions,[6-10] α-cyanoalkyl carbanions,[2,11] picolyl anions,[12] and several carbanions of other sorts.[8] The mechanism tolerates substituents such as alkyl, alkoxy, and carboxylate ($-COO^-$) groups and is remarkably insensitive to the steric effects of groups ortho to the site of substitution. These reactions usually require stimulation, for purposes of chain initiation, by photons or electrons.

The SRN1 mechanism of substitution was initially discerned for certain reactions at aliphatic sites by Kornblum[13] and Russell[14] and their associates and has recently been reviewed as a mechanism of substitution at saturated carbon by Kornblum.[15] As a radical chain mechanism, it involves initiation, propagation, and termination steps but, since the initiation and termination steps are not very well understood and probably vary in character from case to case, we sketch in Scheme I only the probable cycle of propagation steps. In Scheme I, ArX is a generalized aromatic substrate and Y^- a generalized nucleophile.

Liquid ammonia has been the solvent for nearly all the aromatic SRN1 reactions reported from this laboratory. Bunnett and Sundberg[9] did report a few experiments on the use of other solvents for the reaction of bromobenzene with potassium acetone enolate. The investigations of Kornblum and Russell and their co-workers were conducted mainly in dipolar aprotic solvents such as dimethylformamide (DMF), dimethyl sulfoxide (Me_2SO), and hexamethylphosphoric triamide (HMPT). In order to assess the utility of diverse solvents for aromatic SRN1 reactions, we carried out the studies now described.

Scheme I

$$[ArX]\cdot^- \rightarrow Ar\cdot + X^- \quad (2)$$

$$Ar\cdot + Y^- \rightarrow [ArY]\cdot^- \quad (3)$$

$$[ArY]\cdot^- + ArX \rightarrow [ArX]\cdot^- + ArY \quad (4)$$

General Considerations. An obvious requirement is that a solvent should dissolve the reactants, usually a nonpolar organic compound and an alkali metal salt of an anionic nucleophile. Another, for photostimulated reactions, is that the solvent be transparent to the light which provokes reaction, which is probably about 300–380 nm.

Most of the nucleophiles that have been successfully involved in aromatic SRN1 reactions are highly basic. The acidity of the solvent must be low enough so that it does not protonate the nucleophile very much under the reaction conditions. Also, a rather acidic solvent might protonate one of the radical anion intermediates, especially $[ArY]\cdot^-$, in the manner of the Birch reduction.[16] Inasmuch as electron transfer steps are involved, solvents which accept electrons readily (e.g., nitrobenzene) or irreversibly (CCl_4) are unlikely to be satisfactory.

Solvents with which aryl radicals can readily react, especially to abstract hydrogen atoms, present a problem inasmuch as the by-product radicals from hydrogen atom abstraction

Table I. Photostimulated Reaction of Iodobenzene with Potassium Diethyl Phosphite in Diverse Solvents

Registry no.	Solvent	Irradiation time, h	Product yields, % I^- [a]	Product yields, % 2 [b]	Color after irradiation
7664-41-7	Ammonia	0.75	99	96	Colorless
75-65-0	*t*-BuOH[c]	2.0	63	31	Nearly colorless
	t-BuOH[d]	4.5	81	74	Nearly colorless
67-68-5	Me_2SO	4.0	100	68	Pale yellow
90-72-2	DMF	4.5	94	63	Pale yellow-brown
680-31-9	HMPT	4.5	30	4	Yellow
75-05-8	CH_3CN	4.0	98	94[e]	Yellow
127-19-5	$CH_3CON(CH_3)_2$	4.5	72	53	Pale gray
872-50-4	*N*-Methyl-2-pyrrolidone	4.5	24	10	Yellow-orange
110-71-4	$CH_3OCH_2CH_2OCH_3$	4.5	73	56	Colorless
	50% Me_2SO–50% *t*-BuOH	4.5	74	48	Pale yellow
126-33-0	Sulfolane[f]	4.5	28	20[g]	Yellow

[a] By titration with $AgNO_3$. [b] By isolation and weighing unless otherwise noted. [c] Mallinckrodt AR grade, without further purification. [d] Specially purified; see Experimental Section. [e] Yield by GLC, with phenanthrene as internal standard. [f] Tetramethylenesulfone. [g] Yield estimated from GLC.

might not lead back into the propagation sequence. Whether hydrogen abstraction from the solvent is a serious complication or not depends on the relative rates of two alternative pathways available to the aryl radical: reaction with nucleophile (step 3) to continue the propagation cycle, or reaction with solvent leading usually to termination. Methanol, which may be taken to represent alcohols with α-hydrogen atoms, is a good hydrogen atom donor to aryl radicals and the methoxide ions present in basic methanol are better yet,[17] but the by-product formaldehyde radical anions ($\cdot CH_2O^-$) can sometimes lead back into the SRN1 propagation cycle.[18]

Finally, important for preparative applications are practical considerations such as cost, ease of purification, and convenience of product isolation.

Results

Reactions of Iodobenzene with Potassium Diethyl Phosphite (eq 1). A series of experiments is summarized in Table I. In these experiments iodobenzene and a twofold excess of the nucleophile in the listed solvent in a Pyrex flask were exposed to the light of "350-nm" fluorescent lamps in a Rayonet photochemical reactor for the times shown. All the yields listed are based on iodobenzene provided at the beginning of the reaction.

It is noteworthy that iodide ion release was in excess of 90% in ammonia, Me_2SO, DMF, and acetonitrile. However, the yields of diethyl phenylphosphonate (2) isolated from reactions in Me_2SO and DMF were appreciably lower. The reason, we believe, is that relatively large amounts of water were used when the crude 2 was extracted into diethyl ether causing some losses of 2 because of its appreciable solubility in water.

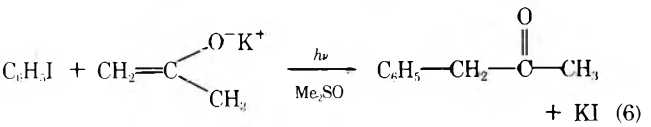
The times of irradiation chosen, mostly 4.0 or 4.5 h, were rather long in order to provide reactions an ample opportunity to occur. They do not represent the results of optimization efforts. In the case of solvent Me_2SO, subsequent quantitative studies[19] show that under typical conditions reaction is complete in 40 min or less.

Small amounts of by-products were detected in some cases, notably in *tert*-butyl alcohol and acetonitrile solvents.

Reactions in Dimethyl Sulfoxide. Iodobenzene was observed to react with a 2.5-fold excess of potassium thiophenoxide during 2-h irradiation to release 66% of iodide ion and form 65% of diphenyl sulfide (eq 5), leaving 34% of the iodobenzene unreacted.[20] No by-products were detectable. An identical reaction mixture kept for 2 h in the dark underwent virtually no reaction. In an experiment of similar design, except that all reagents were used "from the shelf" without further purification, iodide ion release during 2-h irradiation was 51% but the yield of diphenyl sulfide was only 37%.

$$C_6H_5I + C_6H_5S^-K^+ \xrightarrow[Me_2SO]{h\nu} C_6H_5\text{-}S\text{-}C_6H_5 + KI \quad (5)$$

The reaction of iodobenzene with acetone enolate ion (eq 6) was much faster; it was complete after 1-h irradiation. With a 4:1 ratio of enolate to iodobenzene, the yield of phenylacetone was 81% and of 1,1-diphenyl-2-propanone, 11%. A mere trace of benzene was detectable. When the ratio of enolate reagent to iodobenzene was 8:1, the yield of phenylacetone rose to 88% and only 4% of diphenylation occurred. In a further experiment with a 4:1 reactant ratio, 55% release of iodide ion was observed during only 12-min irradiation, but remarkably a similar sample kept for 12 min in the dark furnished 31% of iodide ion. A significant dark reaction is indicated.



Reactions in *tert*-Butylamine (*t*-BuNH$_2$). This solvent seemed attractive, a priori, because of its low acidity and its lack of hydrogen atoms readily abstractable by radicals. Its resemblance to ammonia is obvious, but it was expected better to dissolve organic compounds.

Of four nucleophiles that were tried, namely the diethyl phosphite, acetone enolate, thiophenoxide, and *tert*-butylamide ions, only one underwent SRN1 reactions satisfactorily in *t*-$BuNH_2$. Potassium diethyl phosphite reacted with iodobenzene during 60-min irradiation according to eq 1, releasing 94% of iodide ion and affording a 76% isolated yield of 2. The same nucleophile reacted with *m*-bromoiodobenzene during 60-min irradiation to form tetraethyl *m*-phenylenebisphosphonate[3] in high yield together with a small amount of diethyl *m*-bromophenylphosphonate, liberating bromide and iodide ions to the extents of 89 and 100%, respectively.

Because iodobenzene reacted with $(EtO)_2PO^-K^+$ so attractively in *t*-$BuNH_2$, the reaction was investigated more closely in the hope that it might be suitable for quantitative study. With only eight of the usual 16 lamps in place in the reactor, the reaction was nearly complete in 20 min. A plot of percent iodide ion formed vs. time was nearly linear although there was a slight lag within the first 4 min in the manner of an induction period. Such behavior indicates that the reaction is zero order in iodobenzene.

Nevertheless, there are disadvantages to this system for purposes of meticulous measurements. For one thing, solu-

Table II. Photostimulated Reactions of Nucleophiles with Aromatic Substrates in Water Solution

Registry no.	Substrate	Nucleophile[a]	Irradiation time, min	Halide ion yield, %	Products and yields
98-04-4	$C_6H_5NMe_3^+I^-$	PhS^-(930-69-8[f])	150		Ph_2S, 1%
19095-34-2	p-$IC_6H_4NMe_3^+I^-$	PhS^-	100	100	p-$C_6H_4(SPh)_2$, 12% p-$PhSC_6H_4NMe_3^+I^-$, 38% p-$PhSC_6H_4NMe_2$, trace p-$IC_6H_4NMe_2$, trace PhSSPh, trace
2532-17-4	o-$IC_6H_4COO^-Na^+$	PhS^-	180	11	[b]
2532-18-5	m-$IC_6H_4COO^-Na^+$	PhS^-	180	12	[b]
60118-02-7	p-$IC_6H_4CH_2COO^-Na^+$	PhS^-	200	26	[b]
60118-03-8	p-$IC_6H_4OCH_2COO^-Na^+$	PhS^-	180[c]	43	p-$PhSC_6H_5OCH_2COOH$,[d] 6% $C_6H_5OCH_2COOH$, 4% p-$IC_6H_4OCH_2COOH$, 55%
	p-$IC_6H_4NMe_3^+I^-$	$PhSO_2^-$ (873-55-2)	180	5	[b]
	p-$IC_6H_4NMe_3^+I^-$	$CH_2NO_2^-$ (25854-38-0)	150	0	[b]
	$C_6H_5NMe_3^+I^-$	$CH_2NO_2^-$	Na(Hg)[e]		$C_6H_4CH_2NO_2$, nil
	p-$IC_6H_4NMe_3^+I^-$	$CH_2NO_2^-$	Na(Hg)[e]	5	[b]

[a] Nucleophiles supplied as sodium salts. [b] Not investigated. [c] "300-nm" lamps used. [d] Isolated as the methyl ester. [e] Sodium amalgam, without irradiation. [f] Registry number.

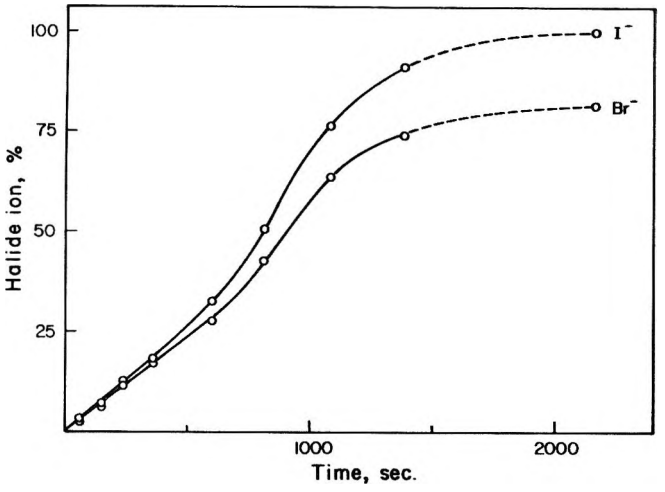


Figure 1. Rates of halide ion release in photostimulated reaction of m-bromoiodobenzene with potassium diethyl phosphite in *tert*-butylamine.

tions of $(EtO)_2PO^-K^+$ in t-$BuNH_2$ were somewhat cloudy. Also, potassium iodide began to precipitate after about 15% reaction.

The reaction of m-bromoiodobenzene with $(EtO)_2PO^-K^+$ in t-$BuNH_2$ was also observed closely. Samples were taken at intervals, quenched with acid, and analyzed for both bromide and iodide ions by potentiometric titration. The results are presented in Figure 1. It is noteworthy that formation of iodide and bromide ions was closely coupled, rather than sequential, with iodide ion being formed in somewhat greater amount.

It was shown that t-$BuNH_2$ does not react with $(EtO)_2PHO$, $(EtO)_2PO^-K^+$, or 2 under the conditions of our reactions.

Potassium and lithium acetone enolates, formed in t-$BuNH_2$ by reaction of acetone with t-BuOK and butyllithium, respectively, were soluble but reacted very slowly with iodobenzene. During 200-min irradiation, reaction with the potassium enolate formed only 46% of iodide ion together with 31% of phenylacetone. The lithium enolate, during 120-min exposure to light, generated only 29% of iodide ion and 18% of phenylacetone.

Both *tert*-butylammonium thiophenoxide and potassium thiophenoxide were found to be insoluble in t-$BuNH_2$. Irradiation of a mixture of the former with iodobenzene in t-$BuNH_2$ gave only a trace of diphenyl sulfide. The lithium salt of thiophenol is soluble in t-$BuNH_2$ but irradiation of a solution of it and iodobenzene for 120 min gave only 36% of iodide ion and a low yield (about 12%) of diphenyl sulfide.

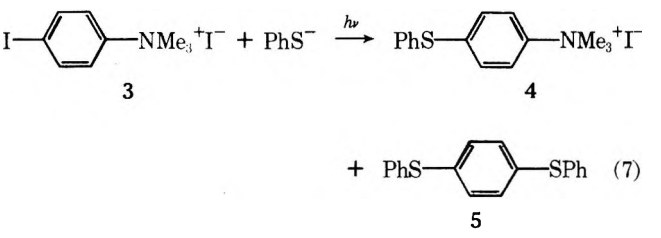
A solution of lithium *tert*-butylamide and iodobenzene in t-$BuNH_2$ was irradiated for 70 min. Iodide ion release was 98% and an 82% isolated yield of *N-tert*-butylaniline was obtained. However, our finding that quantitative release of iodide ion also occurred in the dark suggested that reaction occurred via the intermediacy of benzyne.[21] This interpretation was supported by observation that lithium *tert*-butylamide and bromomesitylene in t-$BuNH_2$, irradiated for 120 min, formed only 5% of bromide ion. Bromomesitylene is structurally unable to afford an aryne intermediate.

Reactions in Water. Investigations in this solvent were limited to substrates soluble in it.

Because water is rather acidic, only a few of the nucleophiles that have been found reactive in aromatic SRN1 reactions can be provided in aqueous solution. Most of our experiments, which are summarized in Table II, concerned thiophenoxide ion as nucleophile. A few concerned the anion of nitromethane, which is reported[22] to react with phenyl radical in aqueous medium to form the radical anion of phenylnitromethane. One experiment was performed with benzenesulfinate ion as nucleophile; its participation in aliphatic SRN1 reactions has been described,[23] although it has never been observed to engage in such substitutions at aromatic carbon.

The first experiment in Table II involves the photostimulated interaction of thiophenoxide with phenyltrimethylammonium ion, which earlier[7] was found to react with acetone enolate ion in ammonia, under irradiation, to form phenylacetone. Scarcely any reaction occurred during 2.5-h illumination, and only 1% of diphenyl sulfide was obtained.

In ammonia, p-iodophenyltrimethylammonium ion (3)



(7)

reacts with thiophenoxide ion under irradiation to form bissulfide **5** in 95% yield, both the iodine atom and the trimethylammonio group being replaced.[24] The same reaction in water (Table II) is less straightforward. Although the covalently bound iodine atom was released quantitatively, only 12% of **5** was obtained together with 38% of *p*-thiophenoxyphenyltrimethylammonium ion (**4**), which represents replacement of the iodine atom only, and trace amounts of tertiary amines formed by demethylation of **3** and **4**. Much tar was formed, amounting to about 20% of the mass of the **3** used.

Upon being irradiated in the presence of thiophenoxide ion for 3 h or more, the anions of *o*- and *m*-iodobenzoic acid and of *p*-iodophenylacetic acid released only about a quarter or less of their iodine atoms as iodide ion; other products were not sought. Under irradiation by "300-nm" lamps, the anion of *p*-iodophenoxyacetic acid was somewhat more reactive, 43% of iodide ion being formed, but the yield of the thiophenoxy deiodination product was only 6%. There was also 4% of phenoxyacetic acid, the deiodination product, as well as 55% of recovered starting material and some tar. Also with "300-nm" illumination, sodium *p*-iodophenylacetate behaved very similarly.

A single attempt to observe a photostimulated substitution reaction between benzenesulfinate ion and *p*-iodophenyltrimethylammonium ion was fruitless. Likewise, no evidence of substitution could be found from the interaction of this substrate with the anion of nitromethane, either under stimulation by photons or by electrons from sodium amalgam. Phenyltrimethylammonium ion failed to form phenylnitromethane when exposed to the nitromethane anion in the presence of sodium amalgam.

Discussion

Of solvents for aromatic SRN1 reactions other than ammonia, Me_2SO appears to be the best on the basis of evidence now available. Photostimulated reactions of iodobenzene with the diethyl phosphite, thiophenoxide, and acetone enolate ions, and of bromobenzene with the last of these, all occur in high yield in Me_2SO. In this laboratory Me_2SO has become the solvent of choice for quantitative kinetic or photochemical studies.

There are some disadvantages to Me_2SO. Methods for its purification are laborious and there is evidence[19] that impurities in incompletely purified Me_2SO can significantly affect reaction rates or quantum yields. Also, product isolation from Me_2SO is rather inconvenient.

One of the reasons that Me_2SO is so satisfactory is its low reactivity as a hydrogen atom donor toward aryl radicals. Of more than 100 substances of diverse structure and functional type whose hydrogen donor reactivity toward phenyl radical was measured by Bridger and Russell,[25] Me_2SO was the least reactive but for one. Me_2SO is a good solvent for organic compounds as well as for many salts.

Nevertheless, ammonia is the solvent of choice for preparative work. Its advantages include low cost, ease of purification, and convenience of product isolation, besides its favorable chemical characteristics. The special techniques for handling this low-boiling solvent (−33 °C) are easily learned and do not substantially interfere with its use for preparative purposes.

Although experience with other dipolar, aprotic solvents is limited mainly to reactions with diethyl phosphite ion, we consider the evidence in Table I to be very significant, at least insofar as the less satisfactory solvents are concerned, because SRN1 reactions with this nucleophile are exceptionally fast and clean in ammonia and Me_2SO. In the experiments of Table I, a superb nucleophile was provided and irradiation was conducted for rather a long time; a solvent that fails to support reaction in high yield under such conditions is truly unpromising.

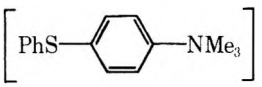
The unsatisfactoriness of HMPT is especially worthy of note. In another study,[9] bromobenzene and potassium acetone enolate failed to react in HMPT during 65 min irradiation.

Acetonitrile and DMF stand out in Table I as rather good solvents, and merit further attention.

In *tert*-butylamine solvent, the main difficulty appears to be the low solubility of many salts. Potassium diethyl phosphite is, however, soluble, and its reactions with iodobenzene and *m*-bromoiodobenzene occurred rapidly and in high yield.

It is unclear why reactions in water (Table II) were so poor. Perhaps the identity of products which escaped isolation would provide a clue.

The fact that **3** afforded mainly **4** in water but mainly **5** in ammonia[24] may be taken to indicate that zwitterionic radical **6** in ammonia almost exclusively expels trimethylamine to yield the *p*-thiophenoxyphenyl radical, which continues to



6

form **5**, whereas **6** in water preferentially transfers an electron to **3**, leaving **4** as a stable product.

Experimental Section

Instrumentation. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were determined on JEOL Minimar or Varian A-60A instruments. Infrared spectra were taken on a Perkin-Elmer 237B spectrometer. Gas chromatographic analyses were performed using a Hewlett-Packard 5750 flame ionization instrument, and reaction yields were calculated by standard methods using internal standards with peak areas suitably corrected for molar response. Iodide titrations were carried out potentiometrically using a Corning Model 7 pH meter with silver and glass electrodes. Photochemical reactions were carried out in a Rayonet Model RPR-100 reactor equipped normally with 16 "350-nm" lamps.

Materials. Commercially available solvents and most reagents were purified prior to use by distillation or crystallization unless otherwise noted. *tert*-Butyl alcohol was repetitively partially frozen, the remaining liquid discarded each time, then refluxed over sodium and distilled. Me_2SO, DMF, HMPT, and 1,2-dimethoxyethane were dried over calcium hydride and distilled. Acetonitrile was distilled from phosphorus pentoxide. *N,N*-Dimethylacetamide and *N*-methyl-2-pyrrolidone were dried over $CaSO_4$ and distilled. Tetramethylenesulfone was dried over BaO at 140 °C for 8 h and distilled. Commercial anhydrous ammonia was distilled from sodium directly into the reaction flask. *tert*-Butylamine was freshly distilled prior to use.

Iodobenzene was dried and distilled, and stored protected from light. Diethyl phosphonate (Aldrich) was dried over CaH_2 and distilled. Thiophenol was freshly distilled each week. Spectrograde acetone was used without further purification.

Reactions of Iodobenzene with Potassium Diethyl Phosphite. Typical Procedure. A 250-ml, three-neck flask equipped with magnetic stirrer, nitrogen inlet, and dry ice condenser was constantly swept with dry nitrogen. Potassium *tert*-butoxide (3.36 g, 0.03 mol) was placed in the flask and 120 ml of DMF was added. After the solid had dissolved, 4.15 g (0.03 mol) of diethyl phosphite was added, followed by 3.06 g (0.015 mol) of iodobenzene. The resulting clear and nearly colorless solution was irradiated in a Rayonet reactor for 4 h. The solution was concentrated to about 10 ml and taken up in 150 ml of ether and 20 ml of water. The organic layer was separated and the aqueous layer was extracted five more times with ether. The combined ether extracts were washed with 20 ml of saturated NaCl solution and dried (Na_2SO_4). After removal of the ether, the crude product was distilled to give 2.03 g (68%) of diethyl phenylphosphonate as a colorless liquid: NMR δ_{CCl_4} (Me_4Si) 1.3 (t, 6 H), 4.1 (m, 4 H), and 7.4–7.9 (m, 5 H, Ar); ir (film) λ_{max} 1250 (P=O), and 1205 cm^{-1} (P–O–C).

The aqueous layer was acidified with 6 M nitric acid and titrated for iodide ion: 0.936 equiv of iodide ion was found per mole of iodobenzene used.

Reactions in Dimethyl Sulfoxide. Typical Procedure. Potassium *tert*-butoxide (2.30 g, 20.5 mmol) was placed in a nitrogen-

flushed three-neck flask fitted with condenser and nitrogen inlet and 50 ml of Me_2SO was added. Acetone (1.16 g, 20 mmol) was added, followed by 500 mg (2.45 mmol) of iodobenzene. The solution turned yellow immediately. After irradiation for 60 min, the brown solution was cooled, diluted with water, and thrice extracted with ether. Analysis of the aqueous phase showed 2.46 mmol of iodide ion. The ether layer was analyzed by GLC (Carbowax 20M column, biphenyl internal standard), and phenylacetone (2.16 mmol, 88%) and 1,1-diphenylacetone (0.086 mmol, 3.5%) were found.

Reaction of Iodobenzene and Potassium Acetone Enolate in *tert*-Butylamine. Typical Procedure. Potassium *tert*-butoxide (2.30 g, 20.5 mmol) was dissolved in 50 ml of *tert*-butylamine, and 1.16 g (20 mmol) of acetone and 1.00 g (4.90 mmol) of iodobenzene were added. The solution, under nitrogen atmosphere, was irradiated with 300-nm lamps for 200 min. Ammonium nitrate (1.8 g) was added and the solvent was evaporated on a warm water bath. The product was taken up in ether and water and the aqueous phase was extracted with two further portions of ether. The combined ether fractions were dried ($MgSO_4$), and analyzed by GLC. The yield of phenylacetone was 1.5 mmol (31%). Titration of the aqueous fraction with silver nitrate solution showed 0.46 equiv of iodide ion.

Kinetic Procedure in *tert*-Butylamine. In a nitrogen flushed flask was placed 1.68 g (15 mmol) of potassium *tert*-butoxide and 125 ml of *tert*-butylamine and 2.00 g of diethyl phosphite was added. After the solid dissolved, aryl halide was added. Aliquots (5 ml) were transferred to screw-cap test tubes which were then flushed with nitrogen and placed in a Rayonet reactor with a merry-go-round apparatus. The reactor was started and tubes were removed at timed intervals, quenched with ammonium nitrate, heated to remove solvent, and titrated for free halide ion.

Reaction of Iodobenzene and Lithium *tert*-Butylamide. To 50 ml of *tert*-butylamine under nitrogen was added 20 mmol of *n*-butyllithium followed by 1.00 g (4.9 mmol) of iodobenzene. A 2.00-ml aliquot was removed and placed in a foil-wrapped screw-cap test tube to check the dark reaction. The solution was irradiated for 70 min and then diluted with water and extracted twice with ether. The combined ether fractions were washed with water (three times), dried, and concentrated. Distillation of the resulting oil gave *N*-*tert*-butylaniline (600 mg, 4.03 mmol, 82%): bp 69 °C (5 mm) [lit.[26] 92.5–93 °C (19.5 mm)]; NMR δ_{CCl_4} (Me_4Si) 1.27 (s, 9 H), 3.23 (s, broad, 1 H), and 6.5–7.2 (m, 5 H); ir (film) λ_{max} 690, 746, 1224, 1500, 1608, 2970, and 3415 cm^{-1}.

Titration of the aqueous layer showed 0.98 equiv of iodide ion.

The aliquot kept in the dark was worked up in a similar manner. Titration showed 1 equiv of iodide ion and GLC analysis showed only *N*-*tert*-butylaniline.

***p*-Iodophenyltrimethylammonium iodide**[27] was prepared from *p*-iodo-*N*,*N*-dimethylaniline[27] and methyl iodide in methanol. After refluxing for 6 h, the precipitated product was filtered and recrystallized twice from hot water: mp 196–198 °C dec; NMR (Me_2SO-d_6) δ (Me_4Si) 3.61 (s, 9 H), 7.78 (AB doublet, J = 9 Hz, 2 H), and 8.07 (AB doublet, 2 H).

Reaction of *p*-Iodophenyltrimethylammonium Iodide (3) with Sodium Thiophenoxide in Water. To a solution of **3** (0.51 g, 1.31 mmol) in 50 ml of doubly distilled water (heat) and 25 ml of 2 M sodium hydroxide, thiophenol (1.25 g, 11.4 mmol) was added and the system was purged with nitrogen. A 2-ml aliquot was removed and wrapped with foil to check the dark reaction, and the remaining solution was irradiated for 180 min at 350 nm. After cooling, the yellow, turbid solution was extracted with ether (three times), and the combined ethereal fractions were dried and concentrated. There remained 220 mg of a dark brown oil which was analyzed by GLC (SE-54 column). At least eight peaks were observed and the following compounds identified: diphenyl sulfide (25 mg), *p*-di(thiophenoxy)benzene (**5**) (43.3 mg, 0.15 mmol, 12%), and small amounts (10–15 mg) of diphenyl disulfide, and *p*-thiophenoxy-*N*,*N*-dimethylaniline. The latter compound was identified by acid extraction of the ether-soluble material. GLC analysis of the acid-soluble extract also revealed a trace of *p*-iodo-*N*,*N*-dimethylaniline.

The aqueous solution was acidified with acetic acid and extracted with ether (three times) to remove excess thiophenol. A 10-ml aliquot was titrated for iodide ion: 2.00 equiv of iodide was found. Titration of the foil-wrapped aliquot removed before irradiation (dark reaction) showed 1.02 equiv of iodide.

The water-soluble product of another experiment was isolated in two ways. (1) The aqueous solution was concentrated to about half its original volume and sodium iodide was added. A precipitate formed and the solution was filtered. Further concentration yielded two more portions of the water-soluble product. The product so obtained contained a mixture of compounds and was typically about 60% substitution product as judged by comparison of the Ph–S NMR singlet with the trimethylammonio peaks. The product was dissolved in Me_2SO-d_6 and methylene chloride was added as an internal standard. With this method of product isolation being used, 3.55 mmol of **3** reacted to give 1.18 mmol (33%) of **4**. The presence of this product was confirmed by comparison of spectra with those of an authentic sample. The other products were not identified. (2) Tetraphenylborate isolation:[28] addition of an aqueous solution of sodium tetraphenylborate to the aqueous solution above gave an immediate precipitate of ammonium tetraphenylborate salts. The product isolated in this way was examined by NMR (Me_2SO-d_6), and the amount of substitution product estimated by comparing the Ph–S singlet to the trimethylammonio peaks. The yield of substitution product observed in several experiments ranged from 25 to 38%.

***p*-Thiophenoxy-*N*,*N*-dimethylaniline.** *N*,*N*-Dimethylaniline (20.0 g, 0.165 mol) was dissolved in 200 ml of anhydrous ether under nitrogen. Benzenesulfenyl chloride (8.0 g, 0.055 mol) in 100 ml of ether was added slowly. After 1–2 min the solution became perceptibly lighter in color and anilinium hydrochloride began to precipitate. After 2-h refluxing, the ether was removed, water was added, and the residue was steam distilled to remove the excess aniline. Upon cooling, the residue remaining solidified. It was taken up in ether, dried, and concentrated. Dilution with petroleum ether gave white crystals (6.8 g, 0.03 mol, 55%): mp 66.5–67 °C (lit.[29] 66–67 °C); δ_{CCl_4} (Me_4Si) 2.97 (s, 6 H), 7.15 (s, PhS, 5 H), 6.68 (AB doublet, 2 H), and 7.42 (AB doublet, J = 9 Hz, 2 H).

***p*-Thiophenoxyphenyltrimethylammonium Iodide (4).** *p*-Thiophenoxy-*N*,*N*-dimethylaniline (2.0 g, 8.73 mmol) in 15 ml of methanol and methyl iodide (1.24 g, 8.73 mmol) were refluxed for 2 h. No precipitate appeared. The solution was cooled in ice water; crystals appeared as a rigid mass filling the liquid volume. NMR analysis of the solid showed only partial conversion to the quaternary ammonium salt. More methyl iodide was added (0.75 g) and the solution was refluxed for an additional 1 h. A few drops of 1 M sodium methoxide in methanol were added until the yellow color was discharged, and the product, which crystallized upon cooling, was filtered, washed with small portions of methanol and with ether, and dried. The yield was 0.95 g (2.56 mmol, 29%): mp 179.5–180.5 °C; NMR $\delta_{Me_2SO\text{-}d_6}$ (Me_4Si) 3.63 (s, 9 H), 7.40 (AB doublet, J = 9 Hz, 2 H), 7.52 (s, PhS, 5 H), and 8.00 (AB doublet, 2 H); ir λ_{max} (KBr) 699, 752, 840, 935, 1015, 1130, 1400, 1445, 1480, 1495, 1590 and 3010 cm^{-1}.

Anal.[30] Calcd for $C_{15}H_{18}INS$: C, 48.53; H, 4.89; S, 8.64. Found: C, 48.25; H, 4.78; S, 8.90.

Reaction of *p*-Iodophenoxyacetic Acid with Sodium Thiophenoxide. 4-Iodophenoxyacetic acid (1.00 g, 3.60 mmol) in 125 ml of 0.8 M sodium hydroxide and thiophenol (2.5 g, 22.7 mmol) were irradiated under nitrogen for 3 h (300 nm). The solution was acidified and the thiophenol was extracted with three portions of ether. The combined ether extracts were dried and concentrated to give 1.04 g of an oily yellow solid. Titration of the aqueous layer indicated 0.433 equiv of iodide (43% reaction). The acidic product was dissolved in methanol, a drop of concentrated sulfuric acid was added, and the solution was refluxed for 1 h, diluted with water, and extracted with ether. Concentration gave 0.97 g of a yellow oil. GLC analysis (SE-54 column, 4 ft × 0.125 in.) showed three peaks: methyl *p*-iodophenoxyacetate (1.98 mmol, 55%), methyl phenoxyacetate (0.14 mmol, 4%), and methyl *p*-thiophenoxyphenoxyacetate (0.23 mmol, 6%). The methyl *p*-thiophenoxyphenoxyacetate was identified by preparative GLC isolation by means of a 3 ft × 0.25 in. 2.5% SE-54 column at 250 °C. The material collected had NMR δ_{CCl_4} (Me_4Si) 3.75 (s, 3 H, OCH_3), 4.55 (s, 2 H, CH_2), 6.97 (AB doublet, J = 9 Hz, 2 H), 7.13 (s, 5 H, PhS), and 7.38 (AB doublet, 2 H); ir λ_{max} (CCl_4) 826, 1080, 1210 (broad), 1435, 1495, 1600, 1751 cm^{-1} (C=O); MS *m/e* 274 (M^+), 201, 184, 109.

Reaction of *p*-Iodophenyltrimethylammonium Iodide with Nitromethane Anion and Sodium Amalgam.[31] The iodide (500 mg, 1.29 mmol) was dissolved in 100 ml of 0.5 M sodium hydroxide. Nitromethane (1.13 g, 18.5 mmol) was added and the system purged with nitrogen. Sodium amalgam (2%, 2.0 g, 1.74 mmol) was added in small portions over about 25 min with vigorous mechanical stirring. After 1 h of additional stirring, the solution was acidified with 10% sulfuric acid and extracted with ether. Analysis of the aqueous layer showed 1.05 equiv of iodide ion.

Registry No.—**1**, 591-50-4; **2**, 1754-49-0; **4**, 60118-04-9; potassium diethyl phosphite, 54058-00-3; lithium *tert*-butylamide, 31828-54-9; *N*-*tert*-butylaniline, 937-33-7; *p*-iodo-*N*,*N*-dimethylaniline, 698-70-4; *p*-thiophenoxy-*N*,*N*-dimethylaniline, 42881-80-1; *N*,*N*-dimethylaniline, 121-69-7; benzenesulfenyl chloride, 931-59-9; *p*-iodo-

phenoxyacetic acid, 1878-94-0; methyl-*p*-thiophenoxyphenoxyacetate, 60118-05-0.

References and Notes

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Chemical Consequences of Hydride Addition to Aromatic Olefins

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The scope and synthetic applications of hydride addition to aromatic olefins have been studied. Many aromatic olefins are reduced by $LiAlH_4$ in tetrahydrofuran (THF), 1,2-dimethoxyethane, *p*-dioxane, or diglyme at 65–150 °C. Hydride addition to 1,1-diarylethylenes is accelerated by THF and other solvents, as compared with diethyl ether, and by electron delocalizing or cyclic, relatively rigid, aromatic groups. Substituents which increase the electron density at the double bond, or form steric hindrance, decelerate the hydride addition. o-MeO and especially *o*-Me_2N groups accelerate the reaction, probably by coordination with the lithium ion and displacing solvent molecules in both the transition state and the generated carbanions. 2,2-Diarylpropanes are efficiently obtained from 1,1-diarylethylenes, $LiAlH_4$, and anisole in THF, while 1,1-diarylethanes are produced in diglyme at 140–150 °C. A novel specific carbon–carbon bond formation is utilized for the diarylpropanes synthesis, involving methylation of the intermediate carbanions by anisole. Anthracene and phenanthrene are reduced by $LiAlH_4$ in diglyme, the former giving eventually 9,9,10,10-tetramethyl-9,10-dihydroanthracene. *cis*-Stilbene undergoes competing reduction and isomerization to *trans*-stilbene when heated with $LiAlH_4$ in diglyme; the latter ultimately gives 1,2-diphenylethane.

It has generally been accepted[1,2] that nonfunctionalized aromatic olefins do not react with $LiAlH_4$. The hydride addition to dibenzofulvene[3] has been interpreted as evidence for the high polarity of the exocyclic double bond of this special olefin. Transformation of cinnamyl alcohols to phenylcyclopropanes,[4] 1-phenylpropyne to *n*-propylbenzene,[4f] cinnamaldehyde to dihydrocinnamyl alcohol, and reduction of some unsaturated azabicyclic systems,[5] effected by $LiAlH_4$, have indicated that suitable functionalization of an olefin might enable hydride addition across a carbon–carbon double bond to occur. However, these latter reactions have been shown to be specific examples of intramolecular reactions.[4e] Recently, it has been found that aromatic compounds bearing an exocyclic double bond, such as substituted 9-methylenexanthenes[6] and methylenebenzanthrene,[7] react with $LiAlH_4$ under mild conditions. Furthermore, alternate aromatic olefins, such as 1,1-diphenylethylene,[8,9] are converted by $LiAlH_4$ in THF to the corresponding benzylic carbanions. Possible synthetic applications of these carbanions have briefly been outlined.[8,10] Similar findings have been reported[11] for the reduction of some aromatic olefins with sodium bis(2-methoxyethoxy)aluminum hydride. We now wish to present new data[12] concerning the scope of hydride addition to aromatic olefins, substituent and solvent effects, and some synthetic applications associated with this reaction.

Substituent and Geometry Effects. We have studied the hydride addition to aromatic olefins using $LiAlH_4$ in several ethereal solvents and temperatures. Reaction progress was followed by ^1H NMR spectroscopy and final products were isolated, purified, and characterized by standard techniques.

Generally, substituents which increase the electron density at the double bond or cause steric hindrance decelerate the hydride addition to an aromatic olefin. Electron-delocalizing, and cyclic, relatively rigid aromatic groups accelerate the reaction. Half-lives of some representative olefins in the presence of $LiAlH_4$ in refluxing THF (65 °C) are given in Table I. The hydride addition to 1,1-di-*o*-anisylethylene (**2**) is considerably faster than it is to 1,1-di-*p*-anisylethylene (**3**) in refluxing THF. A similar ortho effect is exhibited by 1-(*o*-anisyl)-1-phenylethylene[10] and especially 1-(*o*-dimethylaminophenyl)-1-phenylethylene ($T_{1/2}$ **31**/$T_{1/2}$ **30** = 40).

This rate-enhancing phenomenon exhibited by *o*-MeO[13] and *o*-Me_2N might be associated with the hydride attack (the "activated complex") as well as the stabilization of the generated carbanion (the "product"). The o-MeO group, e.g., might replace a solvent molecule[14,18] in the transition state, thus placing the hydride closer to the double bond and consequently enhancing the reaction rate. Similarly, intramolecular stabilization could be extended to the carbanion by

Table I. Half-Lives (h) of Olefins in the Presence of Excess $LiAlH_4$ at 65 °C in THF

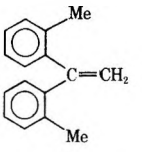
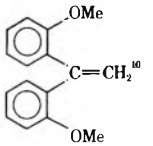
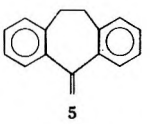
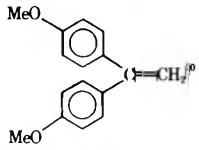
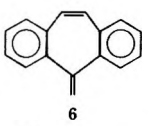
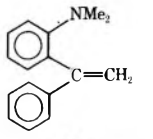
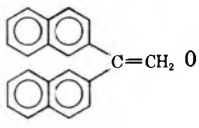
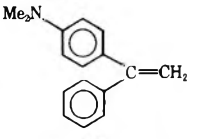
$Ph_2C{=}CH_2$ (1)	0.33 ± 0.03	 (4)	1.60 ± 0.1
 (2)	1.50 ± 0.1	 (5)	0.20 ± 0.02
 (3)	30 ± 2	 (6)	0.14 ± 0.01
 (30)	0.21 ± 0.01	 (7)	0.03 ± 0.008
 (31)	8.5 ± 0.5		

Table II. Half-Lives (h) of Olefins in the Presence of Excess $LiAlH_4$ at 150 °C in Diglyme

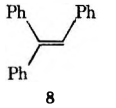
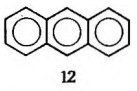
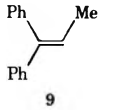
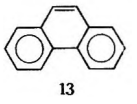
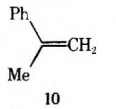
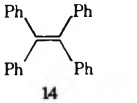
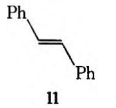
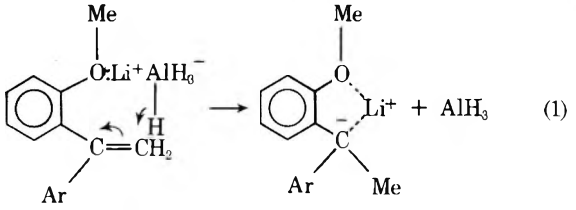
 (8)	1.0 ± 0.1	 (12)	0.40 ± 0.03
 (9)	1.2 ± 0.1	 (13)	14 ± 1
 (10)	1.2 ± 0.1	 (14)	18 ± 1
 (11)	1.5 ± 0.1		

Table III. Half-Lives (h) of 1,1-Diphenylethylene in the Presence of Excess $LiAlH_4$ in Some Ethereal Solvents at 17 °C

Tetrahydrofuran	2.5 ± 0.1	*p*-Dioxane	22 ± 2
1,2-Dimethoxyethane	3.5 ± 0.1	Diethyl ether	>>50
Diglyme	6.5 ± 0.2	Anisole	No reaction after 50 h

formation of a contact ion pair, such as the one shown in eq 1 (see also later). The more pronounced ortho effect of the Me_2N group, as compared with MeO, further substantiates



(1)

the above interpretation, since the former is a stronger base than the latter.

Analogous contact ion pairs structures have been suggested[14] for 9-(ω-methoxyethyl)- and 9-(ω-dimethylaminoethyl)fluorenyllithium salts in THF.

The data in Table I also suggest that the hydride addition rate is markedly influenced by the geometry of the olefins. It should be noted that the steric factor is twofold. Apart from the straightforward steric hindrance to the hydride attack, the aromatic ring in the transition state should be properly oriented in order to effectively stabilize the generated carbanion. Orthogonal alignment of the aromatic ring with respect to the carbanion provides maximum resonance stabilization of the negative charge.[15]

Another example of the geometry effect is offered by the stilbene isomers. *cis*-Stilbene is reduced to 1,2-diphenylethane by $LiAlH_4$ in diglyme faster than *trans*-stilbene when the reaction is started at 20 °C and gradually heated to 150 °C. This is in accord with the reported[16] vinyl isotopic exchange for *cis*-stilbene, proceeding at a rate ca. 10 times faster than the exchange for *trans*-stilbene. However, the hydride addition to *cis*-stilbene is complicated by the base-catalyzed[17] cis–trans isomerization. This hydride-induced isomerization becomes faster than the hydride addition to *cis*-stilbene at 150 °C in diglyme; the half-life time with a large excess of $LiAlH_4$ at 28 °C in diglyme is 4 h.

The rate of hydride addition to aromatic olefins is sensitive to the substituents on the aromatic rings. Moreover, substituents on the double bond might even inhibit the reaction, as is the case with α-*tert*-butylstyrene and 1,1-diphenyl-2-methylpropene. The substituents on the double bond induce both steric and electronic effects which are not easily distinguishable. However, some of the more hydride-resistant olefins can be reduced by $LiAlH_4$ in diglyme at 140–165 °C. Comparative data are shown in Table II.

While cumene is easily prepared in a good yield by the $LiAlH_4$ reduction of α-methylstyrene (**10**) in diglyme, styrene itself is almost completely polymerized by the hydride in either THF or diglyme. Phenanthrene and especially anthracene represent aromatic hydrocarbons which can be reduced by $LiAlH_4$ in diglyme to the corresponding 9,10-dihydro derivatives. However, anthracene yields eventually 9,9,10,10-tetramethyl-9,10-dihydroanthracene (see later). Tetraphenylethylene (**14**) suffers a reductive cleavage,[11] under our reaction conditions, and eventually methylation to yield mainly 2,2-diphenylpropane, together with 1,1-diphenylethane and 1,1-diphenylcyclopropane as by-products. 1,1,2,2-Tetraphenylethane and diphenylmethane are intermediates in this reaction.[11] Consequently, it appears that the approaching hydride is capable of polarizing a nonpolar double bond conjugated with an aromatic ring, probably with the solvent participation.

Solvent Effects and Synthetic Applications. It has already been noted[9,10] that hydride addition to **1** is considerably faster in THF than it is in diethyl ether. We have now examined the relative rate of this reaction in several ethereal solvents. The half-lives of **1** in the presence of a large excess of $LiAlH_4$ in several solvents under a dry nitrogen atmosphere at 17 °C are given in Table III. Hydride addition to **1** is fastest in THF, while diethyl ether and especially anisole are less suitable or even inhibit the reaction, in the latter solvent.

This solvent effect implies that THF provides a better solvation of the transition state complex associated with the hydride-induced polarization of the double bond and/or a better stabilization of the intermediate benzylic carbanions. This is consistent with our observations[8] that the highly reactive 9-methylenexanthenes and also the dibenzofulvenes do react with $LiAlH_4$ in diethyl ether. This view is in accord

with a recent report[18] which has revealed the formation of solvent separated ion pairs and triple ions for $LiAlH_4$ in THF, but larger aggregates of contact ion pairs appear to be formed for $LiAlH_4$ in diethyl ether. The solvent separated ion pairs of $LiAlH_4$ in THF would presumably be the more reactive species. It has also been suggested[4d] that intramolecular hydride transfer from aluminum to an olefinic carbon is facilitated by stronger Lewis bases, probably through coordination with aluminum. Furthermore, evidence has been presented[18] for the ability of the oxygen of the methoxy group to coordinate the lithium ion and displace solvent molecules in ethereal solutions of $LiAl(OMe)_2H_2$. This also substantiates our interpretation concerning the o-MeO and Me_2N effects discussed above.

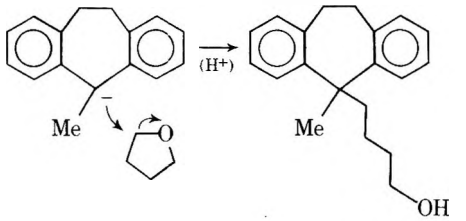
The solvent for the hydride addition reaction is sometimes dictated by the olefin. However, the solvent and temperature might determine the reaction products. Proton abstraction from the solvent is a well-known[19,20] side reaction of benzylic carbanions, regardless of their mode of formation. This reaction is usually described[21,22] as α-metalation of the ether (solvent), followed by olefin and lithium alkoxide, e.g., formation as shown in eq 2.

$$RCH_2CH_2OR' + Ar_2MeCLi \longrightarrow \underset{\mathbf{15}}{Ar_2MeCH}$$

$$+ RCH_2\underset{\displaystyle Li}{\underset{|}{C}}HOR' \longrightarrow RCH{=}CH_2 + LiOR' \quad (2)$$

The deprotonation reaction, leading to 1,1-diarylethanes **15**, is almost as fast as the hydride addition reaction in diglyme at 150 °C. The blood-red benzhydrylic carbanions, initially formed, were decolorized rapidly by proton abstraction from the diglyme, confirmed by the absence of deuterium in the products after D_2O quenching of the reaction mixture. Deprotonation of refluxing *p*-dioxane by these carbanions is ca. 10^2 slower and that of refluxing THF is the slowest. It may well be mainly a temperature effect. The fast deprotonation of diglyme by the carbanions was used to a good advantage for the preparation of pure **15**. This was especially important in the case of the anisylethylenes, where partial demethylation of the MeO groups by the carbanions accompanied the hydride addition reaction in THF (see also later).

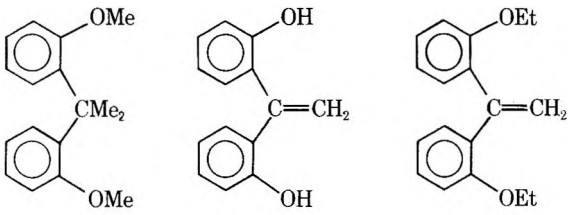
A different mode of cleavage for THF,[23] not involving enolate formation, was revealed in the $LiAlH_4$ reduction of **5** through isolation of the by-product **16**.[9] The alcohol **16** could



(3)

16

have been formed by a nucleophilic attack of the corresponding carbanion (or anion radical[27]) on the α carbon of THF as shown in eq 3. Stabilization of the intermediate alkoxide would support this type of reaction. Indeed, during the hydride addition to the anisylethylenes, e.g., **2**, in THF, an appreciable quantity of 2,2-di-o-anisylpropane (**17**) is formed together with 1,1-di-o-hydroxyphenylethylene (**18**), after hydrolysis. This nucleophilic displacement of alkoxide, leading to a carbon–carbon bond formation, does not occur with phenetole derivatives. Thus, **19** yields only the corresponding 1,1-diarylethane upon refluxing with $LiAlH_4$ in either THF or *p*-dioxane for 24 h.



17 **18** **19**

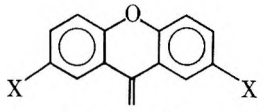
The above specific demethylation reaction was used for syntheses of 2,2-diarylpropanes, such as **17**. While hydride addition to the aromatic olefins does not occur in anisole,[4d] it takes place in a THF–anisole mixture. The intermediate carbanions demethylate the anisole, giving eventually the corresponding 2,2-diarylpropanes.

$$Ar_2MeC^- \quad Me{-}OPh \longrightarrow Ar_2CMe_2 + PhO^- \quad (4)$$

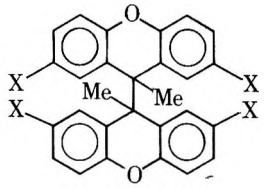
Partial demethylation of diglyme by some of the more crowded carbanions, competing with deprotonation, has also been found at elevated temperatures and relatively long reaction times. Consequently, 30% of 1,2,2-triphenylpropane and 17% of 2,2-diphenylbutane were obtained in the reductions of **8** and **9** in diglyme at 150 °C, in addition to 70% of 1,1,2-triphenylethane and 83% of 1,1-diphenylpropane, respectively. Especially facile methylation by diglyme was found in the case of anthracene (9,9,10,10-tetramethyl-9,10-dihydroanthracene being the major product after 2 h at 150 °C).

Other useful synthetic applications have also been briefly explored. Quenching the hydride addition reaction with solid CO_2 leads to a carboxylic acid. Specifically labeled compounds are obtained by using $LiAlD_4$ instead of $LiAlH_4$ in the reactions described above. Alternatively, reductions with either $LiAlH_4$ or $LiAlD_4$ in THF followed by D_2O quenching lead to the corresponding mono- or dideuterated derivatives. However, highly pure α-deuteration (by D_2O quenching) should be carried out in THF-d_8, thus avoiding contamination through proton abstraction from THF.

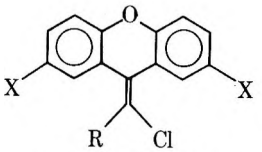
The reactions of $LiAlH_4$ with 9-methylenexanthenes **20–22** without exclusion of air lead to dimerization of the intermediate carbanions to **23–25**, respectively. These dimerization reactions might proceed through oxygen-induced electron



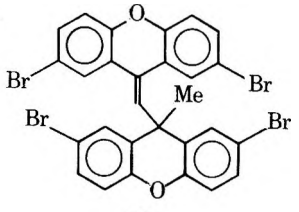
20, X = H
21, X = Me
22, X = Br



23, X = H
24, X = Me
25, X = Br



26, X = F; R = H
27, X = F; R = Me
28, X = Br; R = H



29

transfer in the carbanions to anion radicals.[22,24,25] A side reaction involving dimer formation (2,2,3,3-tetraphenylbutane) in the $LiAlH_4$ reduction of **1** has also been found.[8] The tendency of stabilized anion radicals to dimerize has been reported.[26]

We have already described[6] two examples of hydride addition to **26** and **27** eventually yielding a condensation product, such as **29**. We now can add **28** to this reaction type, noting that diethyl ether should be used as the solvent, thus preventing partial hydrogenolysis of the aromatic bromide, occurring in THF. It has been suggested[6] that the final condensation step leading to the olefins such as **29** is a nucleophilic displacement of chloride by an intermediate carbanion. In view of the possible anion radical nature of the intermediates obtained upon hydride addition to aromatic olefins, the radical anion substitution mechanism[27] might be involved in the above displacement reaction.

Experimental Section

All melting and boiling points are uncorrected. Organic solutions were dried over $MgSO_4$ and Na_2CO_3. The ^1H NMR spectra were determined at 60 MHz with a JEOL C-60 HL spectrometer in CCl_4 solution, unless otherwise stated. The chemical shift values are expressed in δ values (ppm) relative to Me_4Si internal standard.

The mass spectra were obtained with an Hitachi (Perkin-Elmer) Model RMU-6. Unless otherwise stated all reactions involving $LiAlH_4$ or organometallic intermediates were performed under a dry nitrogen atmosphere. Elemental analyses found values for all the new compounds were within ±0.3% of the calculated values.

Compounds **1**, **8–14**, *cis*-stilbene, and styrene were commercially available. They were purified either by careful fractional distillation or recrystallization. 9-Methylenexanthenes were prepared as described elsewhere.[28] 1,1-Diarylethylenes were prepared from aryl Grignard[29] reagents or aryllithium reagents[30] which were obtained by the methods described in the references cited, and acetophenone or ethyl acetate, followed by dehydration with acetic anhydride. Alternatively, a diaryl ketone was added to an alkyl Grignard reagent, and the crude product was similarly dehydrated. The following two procedures are representative examples.

1,1-Bis(*o*-ethoxyphenyl)ethene (19). An *n*-hexane solution of *n*-butyllithium (140 ml of 2 N) was added dropwise to a stirred solution of 36.6 g of phenetole in 100 ml of dry THF and 120 ml of dry diethyl ether. The resulting mixture was refluxed for 2 h and cooled and then 12.8 g of ethyl acetate (distilled over P_2O_5) was added during 30 min, followed by 1-h reflux. Usual workup gave a solid residue, a sample of which melted at 136° (EtOH). This crude alcohol, thus obtained, was refluxed for 5 h with 100 ml of acetic anhydride and then evaporated under reduced pressure.

The crude product yielded 26.5 g of **19** after recrystallization from EtOH: mp 99 °C; mol wt 268 (mass spectrum); δ 0.98 (6 H, t, Me), 3.64 (4 H, q, CH_2), 5.28 (2 H, s, vinyl CH_2), 6.40–7.10 (8 H, m, ArH).

5-Methylene-5*H*-dibenzo[*a*,*d*]cycloheptene (6). Methylmagnesium iodide was prepared from 17 g of MeI and 2.9 g of finely divided Mg in 100 ml of diethyl ether. 5*H*-Dibenzo[*a*,*d*]cyclohepten-5-one (20.6 g) in 50 ml of dry THF was added to the clear solution of the Grignard reagent, at 7–10 °C, with external cooling. The resulting solution was refluxed for 1 h and hydrolyzed with a cold aqueous solution of NH_4Cl. The usual workup gave the expected carbinol (mp 112–114 °C), which was refluxed for 2 h with 100 ml of acetic anhydride. Evaporation under reduced pressure and recrystallization from 95% EtOH yielded 15 g of **6**, mp 118 °C.[31]

Half-Lives Measurements Procedure. The required solvent (30 ml) and $LiAlH_4$ (1.0 g) were equilibrated with magnetic stirring at a suitable temperature under a positive nitrogen pressure, and then 2.0 g of an olefin was added. At various time intervals, a 0.5-ml aliquot of the reaction mixture was pipetted into 20 ml of chilled hydrochloric acid (1 N), or sodium hydroxide (3 N) in the case of an amino olefin, to quench the reaction. Extraction with CCl_4, drying over Na_2CO_3, evaporation, and dissolution in 0.5 ml of CCl_4 containing 1% Me_4Si were followed by an NMR analysis. When diglyme was used as the solvent, the CCl_4 extract was dried over neutral alumina. Each half-life measurement was repeated at least twice.

1,1-Diphenylethane and 2,2,3,3-Tetraphenylbutane. 1,1-Diphenylethylene (**1**, 5.0 g), $LiAlH_4$ (2.0 g), and 50 ml of dry THF were refluxed for 3 h, cooled, and decomposed slowly by adding to ice-cold 1 N hydrochloric acid (200 ml). Extraction with $CHCl_3$ followed by standard workup yielded 4.0 g of 1,1-diphenylethane:[11] bp 85 °C (0.3 mmHg); δ 1.53 (3 H, d, Me, J = 7.0 Hz), 4.01 (1 H, q, CH, J = 7.0 Hz), 7.03 (10 H, s, Ph).

The nonvolatile residue from the distillation yielded 0.5 g of 2,2,3,3-tetraphenylbutane, after recrystallization from EtOH: mp 122 °C;[32] δ 1.96 (6 H, s, Me), 6.80–7.35 (20 H, m, Ph); mass spectrum *m/e* (rel intensity) 362 (19, M^+), 168 (100, $C_{13}H_{12}^+$), 167 (23), 166 (20).

1,1-Diphenyl-2-deuterioethane. **1** (2.0 g) and $LiAlD_4$ (0.5 g) in THF (20 ml) were treated as above, giving 1.5 g of the desired product: bp 87 °C (0.5 mmHg); δ 1.56 (2 H, dt, CH_2D, J_{HH} = 7.0, J_{HD} = 1.5 Hz), 4.05 (1 H, t, CH, J = 7.0 Hz), 7.10 (10 H, br s, Ph); mass spectrum *m/e* (rel intensity) 183 (29, M^+), 167 [100, $(M - CH_2D)^+$], 165 (26, $C_{13}H_9^+$), 154 (24, $C_{12}H_{10}^+$).

1,1-Bis(*p*-methoxyphenyl)ethane. $LiAlH_4$ (0.5 g), **3** (2.0 g), and 20 ml of diglyme were heated for 5 min at 140 °C, cooled, and decomposed with 100 ml of ice-cold 1 N hydrochloric acid. The product was extracted with $CHCl_3$, yielding, after recrystallization from EtOH, 1.7 g: mp 67 °C;[33] δ 1.57 (3 H, d, MeCH, J = 7.0 Hz), 3.76 (6 H, s, MeO), 4.02 (1 H, q, CH, J = 7.0 Hz), 6.73 (4 H, d, ArH, J = 9.0 Hz), 7.05 (4 H, d, ArH, J = 9.0 Hz); mass spectrum *m/e* (rel/intensity) 242 (31, M^+), 227 [100, $(M - Me)^+$].

1,1-Bis(*p*-methoxyphenyl)-2-deuterioethane. $LiAlD_4$ (0.5 g), **3** (2.0 g), and 20 ml of diglyme were treated as above, giving 1.6 g of deuterated product: mp 66 °C (EtOH); δ 1.53 (2 H, dt, CH_2D, J_{HH} = 7.0, J_{HD} = 1.5 Hz), 3.62 (6 H, s, MeO), 4.00 (1 H, t, CH, J = 7.0 Hz), 6.65 (4 H, d, ArH, J = 9.0 Hz), 6.98 (4 H, d, ArH, J = 9.0 Hz); mass spectrum *m/e* (rel intensity) 243 (28, M^+), 227 [100, $(M - CH_2D)^+$].

5-Methyl-5*H*-dibenzo[*a*,*d*]cycloheptene. Diglyme (20 ml) and $LiAlH_4$ (1.0 g) were held at 140 °C when 2.0 g of **6** were added. After 2 min, the reaction mixture was rapidly cooled and 15 ml of ethyl acetate was added, followed by 50 ml of 1 N hydrochloric acid. Extraction with 2 × 50 ml of *n*-hexane yielded 1.5 g of a 1:1 mixture of geometrical isomers, mp 56 °C (MeOH).[34] A, δ 1.28 (3 H, d, Me^{ax}, J = 7.0 Hz), 4.07 (1 H, q, CH^{eq}, J = 7.0 Hz), 6.78 (2 H, s, CH=CH), 7.14 (8 H, m, ArH); B, δ 1.81 (3 H, d, Me^{eq}, J = 7.0 Hz), 3.42 (1 H, q, CH^{ax}, J = 7.0 Hz), 7.00 (2 H, s, CH=CH), 7.14 (8 H, m, ArH); mass spectrum *m/e* (rel intensity) 206 (33, M^+), 191 [100, $(M - Me)^+$].

Hydride Addition to 1,1-Bis(o-methoxyphenyl)ethene (2) in THF. **2** (4.0 g), $LiAlH_4$ (2.0 g), and 100 ml of dry THF were refluxed for 24 h, cooled, and carefully decomposed with 200 ml of hydrochloric acid. The products were extracted with $CHCl_3$ which was washed with aqueous NaOH. The organic extract yielded 2.0 g of 2,2-bis(o-methoxyphenyl)propane: mp 93 °C (EtOH); δ 1.68 (6 H, s, MeC), 3.28 (6 H, s, MeO), 6.60–7.40 (8 H, m, ArH); mass spectrum *m/e* (rel intensity) 256 (60, M^+), 241 [37, $(M - Me)^+$], 133 (41), 121 (100), 105 (65), 91 (50), 77 (28).

The NaOH solution was acidified and extracted with $CHCl_3$, giving 0.4 g of 1,1-bis(o-hydroxyphenyl)ethene (**18**): mp 134 °C (CCl_4); δ 5.35 (2 H, br s, HO, exchangeable with D_2O), 5.58 (2 H, s, CH_2), 6.80–7.30 (8 H, m, ArH); mass spectrum *m/e* (rel intensity) 212 (29, M^+), 195 [100, $(M - OH)^+$].

2,2-Diphenylpropane. **1** (5.0 g), $LiAlH_4$ (2.0 g), THF (50 ml), and anisole (50 ml) were refluxed for 4 h, cooled, and then decomposed as above, including washing of the extract with aqueous NaOH, from which phenol could be isolated. Distillation gave 4.5 g of 2,2-diphenylpropane:[11] bp 90 °C (0.3 mmHg); δ 1.61 (6 H, s, Me), 7.14 (10 H, s, Ph); mass spectrum *m/e* (rel intensity) 196 (30, M^+), 181 [100, $(M - Me)^+$].

2-Phenyl-2-(*p*-methoxyphenyl)propane. This compound was prepared as described above, using 1-phenyl-1-(*p*-methoxyphenyl)-ethene (4.0 g), $LiAlH_4$ (2.0 g), THF (40 ml), and anisole (40 ml) and 6-h reflux: bp 115 °C (0.3 mmHg) (3.1 g); δ 1.58 (6 H, s, MeC), 3.64 (3 H, s, MeO), 6.50–7.15 (9 H, m, ArH); mass spectrum *m/e* (rel intensity) 226 (12, M^+), 211 [37, $(M - Me)^+$], 181 (30), 167 (28), 165 (27), 136 (32), 122 (91), 121 (100), 107 (36), 94 (25), 91 (45), 77 (61).

2,2-Bis(*o*-ethoxyphenyl)propane was similarly prepared from **19** (4.0 g), in 80% yield: mp 83 °C (EtOH); δ 0.84 (6 H, t, $MeCH_2$, J = 7.0 Hz), 1.65 (6 H, s, MeC), 3.52 (4 H, q, CH_2, J = 7.0 Hz), 6.45–7.40 (8 H, m, ArH).

5,5-Dimethyl-5*H*-10,11-dihydrodibenzo[*a*,*d*]cycloheptene. **5** (5.0 g), $LiAlH_4$ (2.0 g), THF (40 ml), and anisole (40 ml) were refluxed for 2 h, cooled, and decomposed with 200 ml of 1 N hydrochloric acid. The products were extracted with $CHCl_3$, washed with aqueous NaOH, dried over Na_2CO_3, and evaporated under reduced pressure. *n*-Hexane (15 ml) was added to the residue and upon cooling, 0.6 g of a solid separated and was filtered off. This solid, mp 102 °C (*n*-hexane), was identified as **5-methyl-5-(ω-hydroxybutyl)-5*H*-10,11-dihydrodibenzo[*a*,*d*]cycloheptene:** δ 0.90–1.60 (5 H, m, CH_2CH_2 + HO), 1.88 (3 H, s, Me), 2.10–2.37 (2 H, m, CH_2C), 2.72–3.70 (4 H, m, 10,11-CH_2CH_2), 3.50 (2 H, t, CH_2O), 7.05–7.53 (8 H, m, ArH); mass spectrum *m/e* (rel intensity) 280 (1, M^+), 207 [100, $(M - C_4H_9O)^+$].

The *n*-hexane solution yielded 4.0 g of the desired product as an oil: δ 1.85 (6 H, s, Me), 3.28 (4 H, s, CH_2), 6.90–7.50 (8 H, m, ArH); mass spectrum *m/e* (rel intensity) 222 (28, M^+), 207 [100, $(M - Me)^+$].

This compound was further characterized by its transformation to **5,5-dimethyl-5*H*-dibenzo[*a*,*d*]cycloheptene,** as follows. The above dihydro derivative (3.0 g), *N*-bromosuccinimide (2.5 g), dibenzoyl peroxide (70 mg), and CCl_4 (50 ml) were refluxed for 1.5 h. The bromination was accompanied by spontaneous dehydrobromination. The filtered solution was washed with aqueous $NaHCO_3$, and with $NaHSO_3$, followed by water. The desired product (2.3 g) was obtained after elution with petroleum ether (bp 40–60 °C) from a short neutral alumina (20 g) column. It solidified upon standing: mp 46 °C;[34] δ 1.65 (6 H, s, Me), 6.90 (2 H, s, CH=CH), 7.05–7.48 (8 H, m, ArH); mass spectrum *m/e* (rel intensity) 220 (31, M^+), 205 [00, $(M - Me)^+$].

1,1,2-Triphenylethane and 1,2,2-Triphenylpropane. 8 (2.0 g), $LiAlH_4$ (1.0 g), and diglyme (40 ml) were refluxed for 1.5 h. Careful acid hydrolysis and extraction with $CHCl_3$ yielded 1.9 g of a mixture from which 1,2,2-triphenylpropane crystallized upon addition of *n*-hexane (10 ml). Recrystallizations from *n*-hexane and then from EtOH gave 0.5 g of the pure compound: mp 115 °C;[35] δ 1.53 (3 H, s, Me), 3.40 (2 H, s, CH_2), 6.50–7.20 (15 H, m, Ph); mass spectrum *m/e* (rel intensity) (M^+ was not observed) 181 [100, $(M - PhCH_2)^+$], 167 (26), 103 (27). 1,1,2-Triphenylethane (1.1 g) was obtained from the original *n*-hexane solution upon evaporation and recrystallization from EtOH: mp 53 °C;[36] δ 3.30 (2 H, d, CH_2, J = 8.0 Hz), 4.15 (1 H, t, CH, J = 8.0 Hz), 7.15 (15 H, br s, ArH).

9,9,10,10-Tetramethyl-9,10-dihydroanthracene. Anthracene (2.0 g), $LiAlH_4$ (1.0 g), and diglyme (30 ml) were heated for 6 h at 150 °C, cooled, and decomposed with 200 ml of 1 N hydrochloric acid. The crystalline product was collected by filtration and yielded 1.7 g: mp 166–167 °C[37] after recrystallization from EtOH; δ 1.64 (12 H, s, Me), 7.00–7.50 (8 H, m, ArH).[24] NMR analysis of an aliquot of the reaction mixture, pipetted 0.5 h from the start, revealed that 9,10-dihydroanthracene was the major component of the reaction mixture at that time: δ 3.85 (4 H, s, CH_2), 7.15 (8 H, m, ArH).

5-Methyl-5*H*-10,11-dihydrodibenzo[*a*,*d*]cycloheptene-5-carboxylic Acid. 5 (2.0 g), $LiAlH_4$ (0.5 g), and THF (40 ml) were refluxed for 40 min, cooled, and decomposed with solid CO_2. Acidification with 1 N HCl, filtration, dissolution in 1 N NaOH, and acidification of the clear basic solution yielded 1.1 g of the desired acid: mp 260 °C (EtOH); δ ($CDCl_3$) 2.15 (3 H, br s, Me), 2.85–3.43 (4 H, m, CH_2CH_2), 7.00–7.30 (8 H, m, ArH); mass spectrum *m/e* (rel intensity) 252 (17, M^+), 237 [40, $(M - Me)^+$], 207 [100, $(M - CO_2H)^+$], 192 (25), 191 (26), 129 (39), 91 (34).

Preparation of 9,9′-Dimethyl-9,9′-bixanthyls. The appropriate 9-methylenexanthene (2.0 g), $LiAlH_4$ (1.0 g), and 50 ml of THF (or diethyl ether for the 2,7-dibromoxanthenes) were refluxed for 2 h without exclusion of air. The usual workup gave the following compounds.

A. 9,9′-Dimethyl-9,9′-bixanthyl (23), mp 153 °C (EtOAc), was prepared in 75% yield from **20:** δ ($CDCl_3$) 1.68 (6 H, s, Me), 6.40–7.20 (16 H, m, ArH); mass spectrum *m/e* (rel intensity) 390 (2, M^+), 195 (62), 194 (100), 181 (60), 165 (37).

B. 2,2′,7,7′,9,9′-Hexamethyl-9,9′-bixanthyl (24), mp 145 °C (EtOH), was prepared in 60% yield from **21:** δ ($CDCl_3$) 1.52 (6 H, br s, 9,9′-Me), 2.16 (12 H, s, MeAr), 6.43 (4 H, br s, H-1,8), 6.86 (4 H, d, H-4,5), 7.04 (4 H, dd, H-3,6) (J_{HH} = 7.0 and 2.0 Hz, respectively); mass spetrum *m/e* (rel intensity) 446 (1, M^+), 223 (100, $M/2^+$), 222 (68, $C_{16}H_{14}O^+$), 209 (57, $C_{15}H_{13}O^+$).

C. 2,2′,7,7′-Tetrabromo-9,9′-dimethyl-9,9′-bixanthyl (25), mp 167 °C (EtOAc), was prepared from **22,** in 50% yield: δ ($CDCl_3$) 1.73 (3 H, s, Me), 1.80 (3 H, s, Me), 6.95–7.80 (12 H, m, ArH).

2,7-Dibromo-9-(2′,7′-dibromo-9′-methyl)xanthylmethylenexanthene (29). This compound, mp 202 °C (MeOH–EtOAc), was prepared by the usual procedure, under N_2 atmosphere, from **28,** in 50% yield: δ ($CDCl_3$) 1.78 (3 H, s, Me), 6.40 (1 H, s, H-11), 6.80–7.50 (11 H, m, Ar-H), 7.90 (1 H, d, H-1).

2-Phenylpropane. 10 (5.0 g), $LiAlH_4$ (2.0 g), and diglyme (40 ml) were heated for 3 h at 150 °C, cooled, and decomposed with 200 ml of 1 N HCl. Extraction with hexane (100 ml), drying over neutral alumina, and distillation gave 3.1 g of 2-phenylpropane: bp 152 °C; δ 1.24 (6 H, d, Me, J = 7.0 Hz), 2.39 (1 H, septet, CH, J = 7.0 Hz), 7.25 (5 H, br s, Ph).

Only a trace of phenylethane could be detected by ^1H NMR spectroscopy upon application of this procedure to styrene. Changing the solvent to THF mainly gave again polymerization of styrene.

Reduction of Tetraphenylethene (14) with $LiAlH_4$ in Diglyme. 14 (2.0 g), $LiAlH_4$ (1.0 g), and diglyme (30 ml) were heated at 150 °C. At various time intervals, a 1.0-ml aliquot of the reaction mixture was pipetted into 20 ml of chilled 1 N HCl. Extraction with CCl_4, drying over Na_2CO_3 and neutral alumina, evaporation, and dissolution in 0.5 ml of CCl_4 were followed by an NMR analysis. Representative results are given in Table IV.

Table IV. Products Formed from 14 and $LiAlH_4$ at 150 °C along the Reaction Coordinate

Time from start, h	Consumption of 14, %	Compd, mol %			
		$Ph_2CHCHPh_2$	Ph_2CHMe	Ph_2CMe_2	
18	50	31	53	6	10
28	60	3	36	36	25
120	100	1	5	71	23

9,10-Dihydrophenanthrene. 13 (5.0 g), $LiAlH_4$ (2.5 g), and diglyme (30 ml) were refluxed for 36 h, cooled, and decomposed with 200 ml of 1 N HCl. Extraction with 2 × 50 ml of $CHCl_3$, drying over neutral alumina (20 g), and fractional distillation yielded 9,10-dihydrophenanthrene (3.5 g): bp 180 °C (25 mmHg); δ 2.84 (4 H, s, CH_2) 7.20–7.85 (8 H, m, ArH).

Registry No.—**1,** 530-48-3; **2,** 28358-60-3; **3,** 4356-69-8; **4,** 2919-19-9; **5,** 2732-90-3; **6,** 2975-79-3; **7,** 39799-27-4; **8,** 58-72-0; **9,** 778-66-5; **10,** 98-83-9; **11,** 103-30-0; **12,** 120-12-7; **13,** 85-01-8; **14,** 632-51-9; **17,** 56751-16-7; **18,** 56751-18-9; **19,** 56751-13-4; **20,** 55164-22-2; **21,** 55164-24-4; **22,** 55164-25-5; **23,** 55164-28-8; **24,** 60047-59-0; **25,** 60047-60-1; **28,** 55517-21-0; **29,** 60047-61-2; **30,** 10482-83-4; **31,** 22057-80-3; phenetole, 103-73-1; ethyl acetate, 141-78-6; 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, 2222-33-5; 1,1-diphenylethane, 103-29-7; $LiAlH_4$, 16853-85-3; 2,2,3,3-tetraphenylbutane, 10496-82-9; 1,1-diphenyl-2-deuterioethane, 4416-97-1; $LiAlD_4$, 14128-54-2; 1,1-bis(*p*-methoxyphenyl)ethane, 10543-21-2; 1,1-bis(*p*-methoxyphenyl)-2-deuterioethane, 60047-62-3; 5-methyl-5*H*-dibenzo[*a*,*d*]cycloheptene, 56175-82-7; 2,2-diphenylpropane, 778-22-3; 2-phenyl-2-(*p*-methoxyphenyl)propane, 6623-93-4; 1-phenyl-1-(*p*-methoxyphenyl)ethene, 4333-75-9; 2,2-bis(*o*-ethoxyphenyl)propane, 60047-63-4; 5,5-dimethyl-5*H*-10,11-dihydrodibenzo[*a*,*d*]cycloheptene, 60047-64-5; 5-methyl-5-(ω-hydroxybutyl)-5*H*-10,11-dihydrodibenzo[*a*,*d*]cycloheptene, 60047-65-6; 5,5-dimethyl-5*H*-dibenzo[*a*,*d*]cycloheptene, 50356-63-3; 1,1,2-triphenylethane, 1520-42-9; 1,2,2-triphenylpropane, 16874-18-9; 9,9,10,10-tetramethyl-9,10-dihydroanthracene, 24269-10-1; 5-methyl-5*H*-10,11-dihydrodibenzo[*a*,*d*]cycloheptene-5-carboxylic acid, 60047-66-7; 2-phenylpropane, 98-82-8.

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Photoinduced Rearrangement and Related Reactions of Ethyl *N*-Phenylcarbamate

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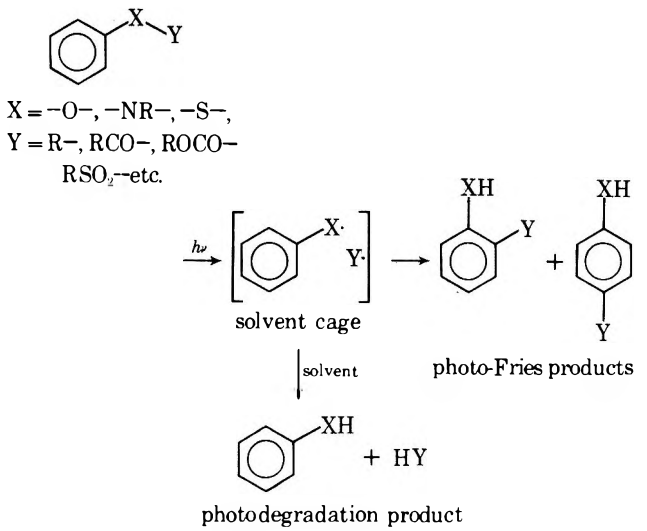
The photoinduced transformation of ethyl *N*-phenylcarbamate (1) to ethyl *o*-aminobenzoate (2), ethyl *p*-aminobenzoate (3), and aniline (4) is concentration dependent. At low concentrations, aniline is the exclusive nonpolymeric product. At higher concentrations of 1, all three products are observed with 2 predominant, but the photoyield is reduced. The results are attributed to the formation of hydrogen-bonded aggregations at higher concentrations which favors similar rearrangement as observed in photo-Fries reactions and to the photolability of 3 and 4.

Since the initial discovery of the photo-Fries rearrangement by Anderson and Reese in 1960,[1] similar reactions are found to be fairly general for aromatic systems linked to a carbonyl or sulfonyl group through a heteroatom, particularly O, N, or S. Scheme I depicts the overall reaction types observed along with the generally accepted mechanism involving initial light induced homolytic cleavage of the X–Y bond followed by rearrangement of the resulting biradical to the observed ortho and para products. In addition, cleavage products resulting from hydrogen atom abstraction by the intermediate radicals usually accompany the rearrangement products. However, the absence of crossover products[2c] has led to the suggestion[2a] that the rearrangements proceed by intramolecular 1,3 and 1,5 sigmatropic shifts, but this interpretation has been questioned.[3] On the other hand, the absence of crossover products from radicals may be explained if such intermediates are trapped in a solvent cage.[4] The degradation products resulting from hydrogen abstraction evidently result from escape of the radicals from the cage. This is consistent with the observation that the ratio of rearrangement to degradation products is enhanced in viscous solvents in which the cage should be more efficient.[5,6] In fact, no degradation products were observed at all in a polyethylene matrix.[7]

Scheme I

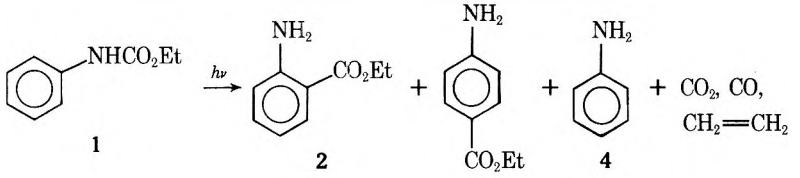


Our interest in the photodegradation of polyurethanes prompted this present investigation of the photochemistry of ethyl *N*-phenylcarbamate (1) as a model representative. Irradiation of 1 under a variety of conditions has been previously reported[8–12] to afford a combination of photoinduced rearrangements and photodegradation products as summarized in Table I. As seen, the percent conversion of 1 is consistently low and the ratio of degradation to rearrangement products appears to be nearly independent of solvent viscosity and irradiation time.

Recently, Schwetlick and co-workers[11,13,14] have examined the photoproducts carefully for a variety of *N*-phenylcarbamates and measured the quantum yields in different solvents. Their results were ascribed to a combination of N–C bond cleavage (Scheme I) and C–O bond cleavage which affords an amido radical which further dissociates to the anilino radical and carbon monoxide; the former eventually gives aniline and/or polymers.

A systematic analysis of the concentration dependence of the carbamates on the overall photoyields and relative ratios of the photoproducts has not been attempted. Such an investigation should provide clues as to the nature of the intermediates and whether the process is concerted or one involving biradical intermediates. Secondly, the photostabilities of the products have not been investigated. Recent work[16] on

Table I. Irradiation of Ethyl *N*-Phenylcarbamate (1)



1 2 3 4

Irradn source[a]	Time, h (temp, °C)	Concn of 1	% convn	% yields[b] 2	3	4	Others	Ref
B	96 (25)	0.25 M (*t*-BuOH)	5	53	14	10		8
A	95 (65)	0.066 M (C_2H_5OH)	14	37	8	30		9
A	48 (60)	Molten, under O_2	7	37	3	34	Azo compd	10
B	6 (20)	1.5×10^{-2} (several solvents)	17–30	24–43	16–34	5–19		11
C	8 (25)	10^{-2} (*i*-PrOH)	8	23	29	24		12

[a] Source A, low-pressure Hg lamp; source B, medium-pressure Hg lamp; source C, high-pressure Hg lamp. [b] The percent yields were determined by GLC.

Table II. Photolysis[a] of Ethyl *N*-Phenylcarbamate (1)

Entry	Solvent	Concn, M	Time, h	% conversion of 1	Yield, %[b] 2	3	4	% loss[c] of 1	Solvent dimers 5, 6 (mole ratio)[d]
				A. Neutral Medium					
1	Ethanol	10^{-3}	3	99	0	0	Tr	99	5 (9)
2	Ethanol	10^{-3}	24	99	0	0	0	99	5 (9)
3	Ethanol	2×10^{-3}	10	56.7	0	0	Tr	56.7	5 (9)
4	Ethanol	$3.5(10^{-3})$	24	60	0	0	Tr	60	5 (9)
5	Ethanol	6×10^{-3}	24	45	2.5	0.5	1	41	
6	Ethanol	10^{-2}	36	29	2.5	1.5	1	13	
7	Ethanol	10^{-2}	24	20	3	3	1	13	5 (9)
8	Ethanol	5×10^{-2}	24	7					
9	Cyclohexane	10^{-3}	24	99	0	0	0	99	6 (0.5)
10	Cyclohexane	$2.5(10^{-3})$	24	74	21	16	4	33	6 (0.5)
11	Cyclohexane	5×10^{-3}	24	55	10	7	2	36	6 (0.5)
12	Cyclohexane	10^{-2}	24	32	7	4	1	20	6 (0.4)
13	Cyclohexane	2×10^{-2}	24	18	4	3	2	8	6
14	Cyclohexane	5×10^{-2}	24	8	2	2	2	2	6
				B. Acid Medium					
15	Ethanol	$3.3(10^{-2})$	72	7	2	0.8	2	2	
16	Ethanol	8×10^{-2}	72	4	0.8	0.2	1	2	
17	Cyclohexane	5×10^{-3}	72	16	2.3	1	7.5	5	
18	Cyclohexane	5×10^{-3}	72	15	4	0	6	5	

[a] Photolysis was carried out in cell of 100-ml capacity under nitrogen. A Hanovia low-pressure mercury lamp (90% emission at 2537 Å) was used and the temperature varied from 42 to 48 °C. [b] Based on the internal standard used during GLC analysis. (See Experimental Section.) [c] Percent loss is the difference between the percent conversion of 1 and the combined percentage yields of 2, 3, and 4 and it is indicative of the polymeric material formed from 1. [d] Mole ratio refers to the number of moles of *meso*- and *dl*-2,3-butanediol (5) or cyclohexylcyclohexane (6) formed per mole of 1 converted.

the photolysis of aniline has demonstrated a two-electron ionization process giving rise to anilinium ion and solvated electrons.

In order to gain further insight into the above questions, a systematic investigation of the photolysis of 1 was undertaken in the polar protic solvent ethanol and the nonpolar aprotic solvent cyclohexane.

Results and Discussion

As a initial probe, a 5×10^{-5} M solution of 1 in ethanol was irradiated at 2537 Å using uv spectroscopy to monitor the disappearance of starting material. Surprisingly, in contrast to reports of others, at 42 °C the half-life for conversion of 1 was only ca. 2.5 h. Even more unexpectedly, the photorearranged products 2 and 3 were completely absent as evident from the lack of characteristic absorptions at 330 and 290 nm, respectively. Concentration of the reaction solution and subsequent analysis by GLC indicated trace amounts of aniline (4) but no evidence for 2 and 3. The bulk of the products appeared to be nonvolatile, colored, polymeric materials which could not be characterized.

In view of the divergence of the above results from those previously reported, the concentration dependence of the conversion of 1 was followed by GLC and the results summarized in Table II. In 10^{-3} to 3.5×10^{-3} M ethanolic solutions, 1 was completely consumed within 24 h but only aniline (4) was produced and only in trace quantities with no evidence for rearrangement products 2 and 3. However, significant amounts of *meso*- and *dl*-2,3-butanediol (5) were detected, apparently arising from dimerization of solvent (vide infra). As the concentration of 1 in ethanol was increased (to 6×10^{-3} M), photoinduced rearrangement products began to appear with the ortho (2) predominating. As the concentration of 1 was further increased, the yield of the para product 3 improved; however, the yield of aniline was essentially constant at about 1%. In addition, the percent conversion of 1 dra-

Table III. Relative Photostabilities[a] of Aromatic Amines

Entry	Amine	Solvent	Concn, M	% lost[b]	Solvent dimer (mole ratio)[c]
1	2	Ethanol	5×10^{-3}	12	5 (trace)
2	2	Cyclohexane	10^{-2}	2	None
3	3	Ethanol	5×10^{-3}	86	5 (3.0)
4	3	Cyclohexane	10^{-2}	43	6 (0.2)
5	4	Ethanol	10^{-2}	100	5 (1.9)
6	4	Cyclohexane	10^{-2}	90	6 (0.025)
7	1			97	
	2	Ethanol	4×10^{-3}	9	
	3		each	65	
	4			99	
8	2			1	
	3	Cyclohexane	4×10^{-3}	16	
	4		each	63	

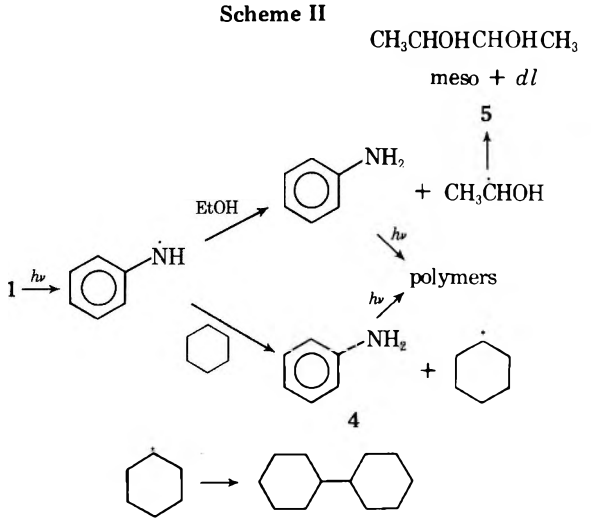
[a] Photolysis was carried out in a cell of 100-ml capacity under nitrogen for 24 h. A Hanovia low-pressure mercury lamp (90% emission at 2537 Å) was used. The temperature varied from 42 to 48 °C. [b] Based on the internal standard used during GLC analysis. (See Experimental Section.) [c] Mole ratio refers to the number of moles of *meso*- and *dl*-2,3-butanediol (5) or cyclohexylcyclohexane (6) formed per mole of amine destroyed.

matically dropped as photo-Fries products 2 and 3 began to appear.

In cyclohexane, similar results were obtained except that photoproducts 2 and 3 began to appear at lower concentrations (2.5×10^{-3}); solvent dimer [cyclohexylcyclohexane (6)] was also produced.

Ostensibly, the formation of dimeric products 5 and 6 is indicative of hydrogen abstraction from ethanol and cyclohexane, respectively. Photoinduced rearrangement products do not involve hydrogen abstraction from solvent, but the formation of aniline from anilino radicals does. The miniscule amounts of aniline produced implies that it is probably consumed in a subsequent polymerization step as illustrated in Scheme II.

Scheme II



Indeed, under identical photolytic conditions, aniline in ethanol was completely destroyed forming polymeric products and 2,3-butanediols (5); 2 mol of 5 were produced per mole of 4 (Table III, entry 5). In cyclohexane, the disappearance of aniline occurred more slowly and 6 was produced only in small quantities (Table III, entry 6). Ethyl *p*-aminobenzoate (3) also reacted under photolysis (entries 3 and 4, Table III). However, the ortho isomer 2 was quite stable with only ca. 2 and 12% losses of 2 observed in cyclohexane and ethanol, respectively (Table III, entries 1 and 2). Similarly, irradiation of a mixture of 1, 2, 3, and 4 resulted in the complete destruction of 4 in ethanol (64% in cyclohexane) and, again, the least affected compound was the ortho derivative 2 (entries 7 and 8, Table III). From these observations, it appears that the photoinduced rearrangement products previously reported are not the primary products of photolysis and further, the predominance of the ortho isomer 2 is evidently an artifact, arising from selective destruction of the para product and of aniline. The mechanism for the photodestruction of aniline in ethanol (at 77 K) has been investigated by Alfimov[15] and appears to involve a two-quanta photoionization process to yield anilinium ions and solvated electrons. The latter, upon warming, produced $CH_3\dot{C}HOH$ radicals which were identified by EPR. In our case, these radicals evidently dimerize to observed *meso*- and *dl*-butanediols (5). Ethyl *p*-aminobenzoate (3) probably undergoes a similar reaction, but is considerably deactivated by the electron-withdrawing ester group. The unusual photostability of 2 can be accounted for in terms of a mechanism involving prototropy rather than ionization as with 3 and 4. Photolysis of 2 may result in the transfer of a proton from the amine nitrogen to the carbonyl oxygen giving rise to the unstable imino enol which spontaneously reverses back to 2 in a thermal process. Similar processes are well known in a number of ortho-substituted aromatic systems.[16]

Photostability of 2 also provides a handle for estimating the lower concentration limit for 1 at which the rearrangement pathway begins to operate (ca. 6×10^{-3} M in ethanol and ca. 2.5×10^{-3} M in cyclohexane). Since 2 is absent at lower concentrations, a concerted sigmatropic mechanism for photoinduced rearrangement may be ruled out since intramolecular process should be quite competitive at low concentrations.

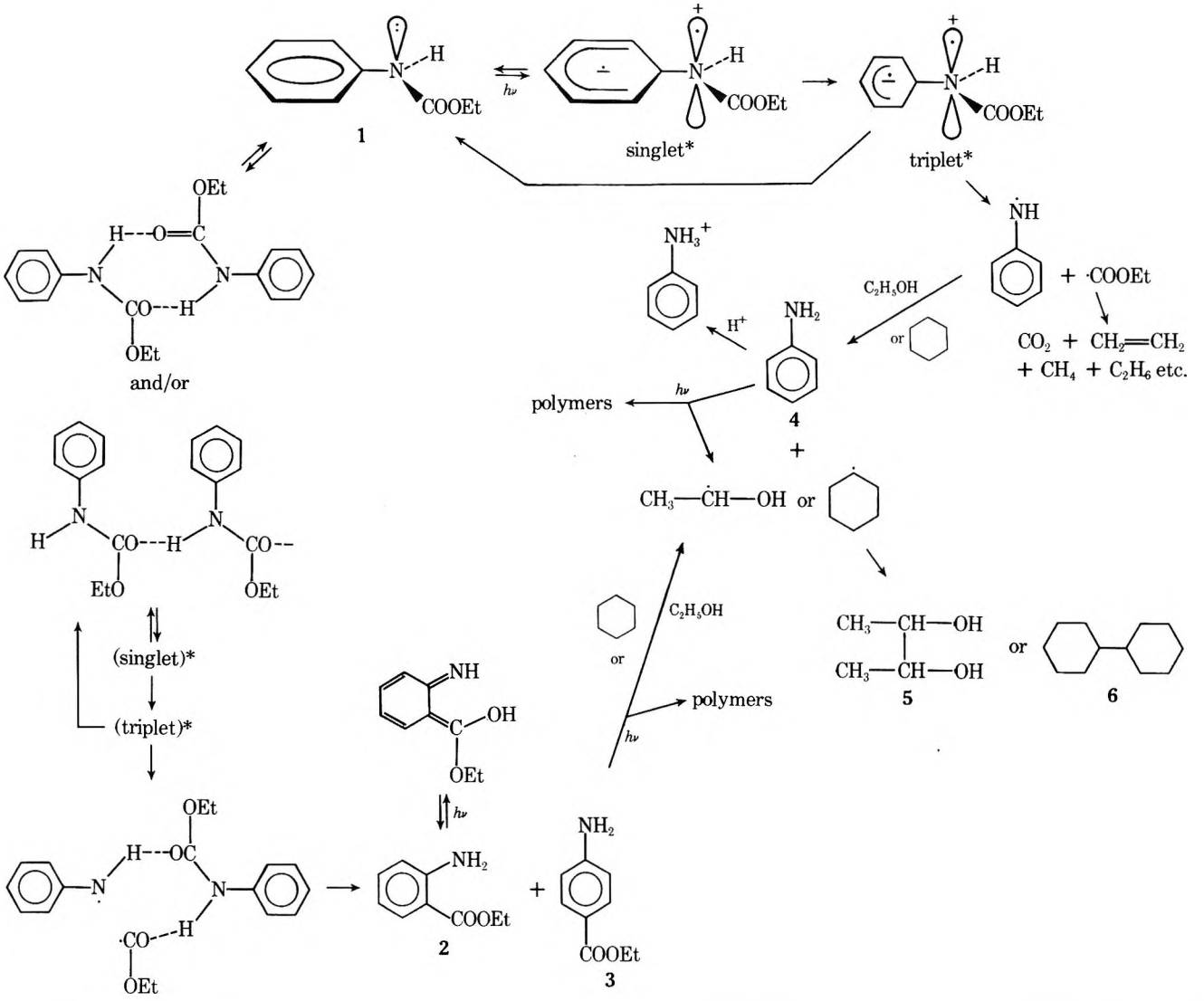
The direct formation of aniline from 1 at low concentrations was demonstrated by trapping the primary photolysis products in the presence of HCl as the amine salts which prevents subsequent decay. As expected, aniline is the major product during the photolysis of 1 in ethanol in the presence of HCl even in concentration ranges as high as 3.3×10^{-2} and 8.0×10^{-2} M (Table II, entries 15 and 16). In cyclohexane, in the same concentration ranges, rearrangement competes more efficiently with photodegradation to aniline (Table II, entries 17 and 18).

The low yields of photoproducts at higher concentrations of 1 may arise from self-quenching of a triplet excited state. Such a state has been implicated by Beachell and Chang[10] on the basis that the oxygen absorption rate of 1 during photolysis was enhanced by triplet sensitizers.[10b] In fact, the photoreaction of 1 was suppressed in the presence of a triplet quencher (naphthalene) even at low dilution. The theoretical rationale for triplet state participation in the photo-Fries rearrangement has been provided recently by Dauben, Salem, and Turro.[17]

In N-substituted anilines, the rate of formation as well as the lifetime of the triplet states[18] is increased compared to those in aniline. In 1, a triplet excited state geometry will aid in weakening the N–C bond through hyperconjugative effect of the π electrons of the benzene ring. (See Scheme III.) Such a bond weakening is not possible in the singlet excited state. However, the longer lifetime also makes the triplet state vulnerable to possible self-quenching by other nonexcited molecules of 1. The amine products 2, 3, and 4 should also be efficient as triplet quenchers.[19]

At low concentrations (10^{-3} M) the reactant molecules are solvent separated and the efficiency of a bimolecular

Scheme III



quenching process will decrease accordingly. The bond cleavage at N–CO bond can now occur producing the anilino and ethyl carboxylate radicals. The anilino radical may abstract a hydrogen from the solvent forming aniline while the carboxylate radical probably undergoes further cleavage producing carbon dioxide and ethyl radicals. This process is exothermic by 7 kcal/mol[11] (activation energy of ca. 1 kcal/mol[20]). The ethyl radical is converted principally to ethylene, hydrogen, and methane.[11]

At higher concentration, 1 forms cyclic hydrogen-bonded dimers as well as chain polymers. This aspect has been studied in detail by Zharkov and Rudnevskii.[21]

In hydrogen-bonded aggregates there is greater scope for photo-Fries type rearrangement; however, there is also an increased possibility for self-quenching. Thus, the appearance of the photorearrangement products is accompanied by a corresponding decrease in photoyields (Table II). Further, 1 will form hydrogen-bonded clusters at a lower concentration in apolar solvents such as cyclohexane than in the polar protic solvent ethanol. Thus, rearrangement products should appear at lower concentration levels in cyclohexane than in ethanol and this is indeed observed.

The above mechanistic details are presented in Scheme III. The results seem best accommodated by the assumption that an equilibrium exists between the monomers and hydrogen-bonded polymers of 1 which controls the product distribution. Viscosity seems to play a minor role. At low concentrations monomers predominate. The number of photons per mole of 1 is high and the percentage conversion of 1 is also substantial.[23] Aniline is the only product formed in substantial quantities but it is destroyed in a subsequent photochemical step. As the concentration of 1 increases, the equilibrium shifts in favor of hydrogen-bonded clusters and photo-Fries products begin to form. However, bimolecular quenching also becomes efficient and the photoyield goes down; the number of photons per mole of 1 also decreases. Such a decrease not only cuts down the yield of products but also their subsequent photodestruction. (See Table III, entries 7 and 8.) At long exposure times, the percentage of the ortho isomer 2 will increase relative to 3 and 4 because of its optical stability. A steady state mechanism will operate maintaining the concentrations of 3 and 4 at a constant level.

Summary. Among compounds undergoing photoinduced rearrangement, ethyl *N*-phenylcarbamate (1) is apparently a special case. The extent of photoconversion is concentration dependent possibly because of the involvement of a triplet excited state. At low concentrations, only aniline (4) is formed through hydrogen abstraction from surrounding solvent molecules. At higher concentrations, 1 forms hydrogen-bonded clusters which undergo essentially photo-Fries type rearrangement; however, these clusters are also vulnerable to self-quenching and hence the photoyields are low. Unless protonated by an acid, aniline is completely decomposed to polymeric material in a subsequent photoionization process. Ethyl *p*-aminobenzoate (3) is also degraded, but to a smaller extent. The ortho isomer 2 is however stable probably because

of its conversion to a conjugated imino enol which cannot undergo photoionization. It is unlikely that **2** and **3** are formed in concerted sigmatropic rearrangements.

Experimental Section

Commercial ethyl *N*-phenylcarbamate was decolorized by activated carbon in refluxing ethanol and purified by sublimation, mp 52 °C (lit.[10] 52 °C). Aniline and ethyl *o*-aminobenzoate was distilled before use and ethyl *p*-aminobenzoate was purified by crystallization in ethanol. A mixture of *meso*- and *dl*-2,3-butanediol was prepared by the reduction of 2,3-butanedione with lithium aluminum hydride in refluxing ether.

Photochemical Apparatus. A 100-ml photocell was employed which was provided with a 24/40 joint for inserting a Hanovia low-pressure mercury lamp (2.5 W) emitting 90% of radiations of 2537 Å. The cell was provided with an air-tight condenser and flushed with nitrogen before and during photolysis. The solution in the cell was stirred magnetically. The cell was wrapped in aluminum foil.

After photolysis, the solution was concentrated[24] on a rotary evaporator and was directly analyzed in a gas chromatograph using a 6-ft 20% Carbowax (20M) column (0.125 in. diameter) operating between 170 and 210 °C. Sulfolane was used as an internal standard whenever necessary and the response ratios were evaluated from pure authentic samples. The experimental results are summarized in Table II. When photolyzed in the presence of an acid (usually HCl, 10^{-1} M) the photoproducts were basified and extracted with ether. The ether solution was dried ($MgSO_4$), concentrated, and analyzed as before.

Kinetic Runs. The photocell was similar to the one described above. A 5×10^{-5} solution of **1** in ethanol was taken in the flask and photolyzed over a period of 24 h. Samples (5 ml) were withdrawn periodically by means of a syringe and the uv spectrum recorded for each sample. From the change in the absorbance at 2340–2350 Å, the rate of disappearance of **I** was evaluated to be $4.587 \pm 0.178 \times 10^{-3}$ min^{-1} corresponding to a half-life of 2.5 h.

The output of the lamp was determined with an uranyl oxalate actinometry according to the method of McLaren and Schugar.[22] The quantum yield was of the order of 0.45.

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Registry No.—**1**, 101-99-5; **2**, 87-25-2; **3**, 94-09-7; **4**, 62-53-3.

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(23) A referee suggested that a larger photoyield is to be expected at lower concentrations of **1** since more quanta of light are available for each molecule. However photolysis of **1** at the higher concentrations for extended periods of time (1 week) did not increase the photoyields over those obtained in 3 days.
(24) Care was taken to avoid loss of photoproducts during concentration.

Methylation of Nucleic Acid-Bases with Trimethyl Phosphate

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The action of trimethyl phosphate (TMP) on cytosine, thymine, uracil, adenine, and guanine has been examined in a homogeneous aqueous phase at 25–60 °C, pH 9–12. All these nucleic acid-bases underwent methylation reactions, showing the following reactivity order on the methylating site in each base: cytosine, N-1 > N-3; thymine and uracil, N-1 ~ N-3; adenine, N-9 ~ N-3 > N-7, N-1; guanine, N-1 ≳ N-7 > N-3 > N-9, O-6. These results and reactions of monomethylated bases with TMP suggested TMP as an useful modifying agent for nucleic acids. The use of TMP as additives for commercial products was also considered briefly.

The direct N-alkylation of basic moieties of nucleic acids has been the subject of considerable chemical and biological interest in recent years. Such reactions may be not only useful in a synthetic point of view but also relevant to the study of mutagenic and carcinogenic effects which occur in living systems caused by alkylating agent.

Various alkylating agents have been employed in such investigations such as nitrogen[1,2] and sulfur[3,4] mustards as well as diazoalkanes,[5,6] alkyl esters of sulfurous oxy acids,[7-13] alkyl halides,[14-16] and others.[17-20]

However, there have been no alkylation studies with trimethyl phosphate (TMP), although TMP has been shown recently to cause mutagenic effects in male mice[21] as well as in Neurospora.[22] In vivo, TMP has been reported to function as alkylating agent, degrading in the rat to dimethyl hydrogen phosphate with formation of *S*-methylcysteine as an urinary metabolite.[23] It would, therefore, be interesting to study the reactivity of TMP toward nucleic acids, their components, and other natural products.

With these aspects in mind, we have studied the reactivity of TMP, showing previously N-methylation of imidazoles, purines, and pyrimidines upon fusing these bases in TMP at 160–220 °C.[24,25] Aside from its synthetic utility, however, this procedure would be too vigorous for the study of the action

Table I. Product Distribution in the Reactions of Pyrimidines and Purines with Trimethyl Phosphate (TMP)[a]

Base	Product[b]	pH	R_f[c]	λ_{max} (log ϵ)[d] at pH 7	Spectroscopic yield, %[e] 25 °C 24 h	25 °C 48 h	37 °C 10 h	37 °C 24 h	60 °C 10 h	60 °C 24 h	Isolated[f] yield, %	Registry no.
Cytosine (1)	1-Methyl-C (4)	11–12	0.41	275.0 (4.02)	34	48	33	40	36	41	28	1122-47-0
	1,3-Dimethyl-C (5)		0.08	281.5 (3.98)	0	0	0	0	0	0	9	6749-87-7
	1,3-Dimethyl-U (11)		0.80	267.0 (3.92)	0	0	0	0	5	10	12	874-14-6
	(Cytosine)		0.19	267.0 (3.79)	61	46	66	57	55	40		
Thymine (2)	1-Methyl-T (6)	9–10	0.62	273.0 (3.99)	13	16	14	21	18	23	12	4160-72-9
	3-Methyl-T (8)		0.82	266.0 (3.85)	12	14	14	15	16	18	17	4160-77-4
	1,3-Dimethyl-T (10)		0.88	272.0 (3.97)	7	17	6	18	31	36	52	4401-71-2
	(Thymine)		0.20	265.0 (3.90)	55	41	63	42	32	20		
Uracil (3)	1-Methyl-U (7)	9–10	0.58	267.5 (3.93)	13	20	16	21	20	21	12	615-77-0
	3-Methyl-U (9)[g]		0.74	260.0 (3.87)	12	17	15	17	18	18	13	608-34-4
	1,3-Dimethyl-U (11)		0.88	267.0 (3.92)	7	17	6	18	31	36	5	
	(Uracil)		0.26	260.0 (3.91)	60	33	57	36	25	17		
Adenine (12)	3-Methyl-A (13)	9–10	0.51 0.28	274.0 (4.01)	27	34	20	25	29	23	6	5142-23-4
	7-Methyl-A (15)		0.18 0.09	269.0[h,n]	0	6	5	5	3	2		935-69-3
	9-Methyl-A (14)		0.74 0.46	263.0 (4.09)	28	34	24	30	32	28	27	700-00-5
	N^6,9-Dimethyl-A (16)		0.84 0.58	268.0 (4.10)	0	4	0	2	10	10	10	2009-52-1
	3,7-Dimethyl-A (17)		0.02 0.01	278.0[i,n]	0	0	0	0	6	14		60065-12-5
	Imidazole ring-opened N^6,7,9-trimethyl-A (18)		0.18 0.04	263.5[j]	0	3	4	5	4	6	1	49581-54-6
	(Adenine)		0.55 0.31	260.0 (4.13)	32	13	34	19	3	2		
Guanine (22)	1-Methyl-G (23)	11–12	0.08 0.33	250.0 (3.87) 274.5 (3.77)			27	30		20	1	938-85-2
	7-Methyl-G (24)		0.15 0.47	250.0[s] 283.5[k,n]			0	10		0		578-76-7
	1,7-Dimethyl-G (25)		0.23 0.65	253.0 (3.76) 284.0 (3.81)			10	8		15	2	26758-00-9
	3,7-Dimethyl-G (26)		0.10 0.53	270.0 (3.76)			11	12		16	10	19143-67-0
	Imidazole ring-opened 1,7,9-trimethyl-G (27)		0.23	269.0 (4.22)[l]			Tr	Tr		7	20	60065-13-6
	O^6,3,7-Trimethyl-G (28)		0.34	(3.82)[m] 269.0			Tr	Tr		5	4	60065-14-7
	(Guanine)			245.0 (4.04) 274.0 (3.92)			17	14		6		

[a] Reaction size: a base (0.90 mmol) + TMP (10.80 mmol) + H_2O (5 ml) at 25 °C; a base (1.80 mmol) + TMP (5.40 mmol) + H_2O (5 ml) at 37 and 60 °C. [b] C, T, U, A, and G refer to cytosine, thymine, uracil, adenine, and guanine rings, respectively. [c] Aluminum oxide TLC, solvent C for reaction mixtures of thymine and uracil; silica gel TLC, solvent D for the reaction mixture of cytosine; solvent D (left R_f) and solvent C (right R_f) for the reaction mixture of adenine; solvent B (left R_f) and solvent E (right R_f) for the reaction mixture of guanine. [d] Ultraviolet spectra in acidic (pH 1) and basic (pH 13) conditions were identical with those reported in literatures cited in the Experimental Section. [e] Tr refers to a trace yield. [f] Yields based on isolated amounts of products. Reactions were carried out using a large excess of TMP; see Experimental Section for details. [g] Mp 189.5–191 °C (EtOH–ether) (lit.[40] 174–175 °C). [h] λ_{max} 274.0 nm (pH 1), 269.0 (pH 13) [G. B. Elion, *J. Org. Chem.*, **27**, 2478 (1962): λ_{max} 274 nm (pH 1), 270 (pH 13)]. [i] λ_{max} 281.0 nm (pH 13) [lit.[27] λ_{max} 277 nm (pH 7) and 281 (pH 13)]. [j] λ_{max} 269.0 nm (pH 1), 261.0 (pH 13) [ref 12 reports λ_{max} 271 nm (pH 1) and 260 (pH 13) for the imidazole ring-opened N^6,7-dimethyladenosine]. [k] λ_{max} 251.5 and 272.0[s] nm (pH 1) [W. Pfleider, *Justus Liebigs Ann. Chem.*, **647**, 167 (1961), reports λ_{max} 250 and 270[s] nm (pH 1); 248,[s] 283 (pH 7)]. R_f of the authentic sample: 0.15 (solvent B) and 0.47 (solvent E). [l] λ_{max} 269.0 nm (4.33) (pH 1) and 269.0 (4.21) (pH 13). [m] λ_{max} 267.0 nm (3.90) (pH 1) and 291.0 (3.72) (pH 13). [n] Compound was not isolated. [s] Shoulder.

of TMP on many natural products, where milder conditions are required.

This paper presents reactions of TMP with nitrogen heterocycles of nucleic acids in an aqueous solution of pH 9–12 at 25–60 °C, revealing facile methylation of these bases. Whereas other alkylating agents such as mentioned above are little soluble in water, TMP is miscible freely with water and allowed alkylation reactions to be run in a homogeneous aqueous phase for the first time.

Following are the characterization of products from reactions of cytosine (1), thymine (2), uracil (3), adenine (12), and guanine (22). The reactivity of these nucleic acid–bases will be also compared qualitatively in the succeeding section and discussed in terms of selective alkylation by TMP.

Results and Discussion

Reactions were generally carried out at 25, 37, and 60 °C by mixing a base and TMP in water at an appropriate pH (pH 9–11 for **2**, **3**, and **12** and pH 11–12 for **1** and **22**). Although the relatively high pH was used for **1** and **22** to overcome the low solubility of these bases, hydrolysis of TMP was slow even under this condition. For example, when the same molar mixture of TMP and water as in the alkylation reaction was kept at 37 and 60 °C for 24 h at pH 11, the extent of hydrolysis of the ester was about 3 and 10%, respectively. The decomposition of the ester was virtually negligible between pH 9 and 10.

Products were separated by a combination of extraction and column chromatography. Alkylation sites were determined most conveniently by ultraviolet, NMR, and mass spectra. Other physical constants (R_f, melting point, elemental analysis, etc.) were also employed for the identification of products.

Cytosine (1), Thymine (2), and Uracil (3). Alkyl halides in dimethyl sulfoxide in the presence of potassium hydroxide[26] and dimethyl sulfate in dimethylformamide or dimethylacetamide[11] have been most frequently utilized for the direct alkylation of these pyrimidines. These reagents convert **1** to

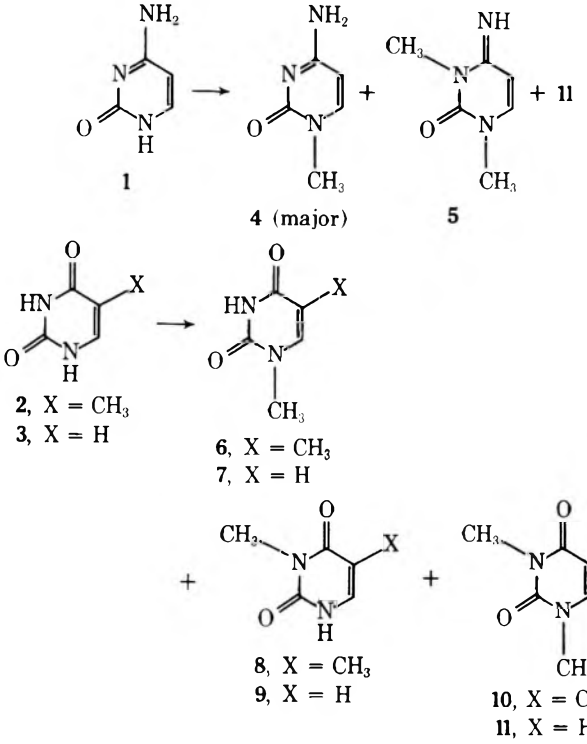
Table II. Reactions of Monomethylpyrimidines and -purines with Trimethyl Phosphate (TMP)[a]

Reactant	Product	Yield, %[b] 7 h	14 h	24 h
1-Methylcytosine (4)	1,3-Dimethyluracil (11)	Tr	Tr	4 (95)
1-Methyluracil (7)	11	15 (83)	23 (73)	37 (60)
3-Methyluracil (9)	11	12 (84)	24 (73)	40 (55)
3-Methyladenine (13)	3,7-Dimethyladenine (17)	8 (77)	11 (74)	14 (70)
9-Methyladenine (14)	N^1,9-Dimethyladenine (21)	Tr	Tr	2 (94)
	N^6,9-Dimethyladenine (16)	Tr	Tr	3

[a] Reaction size: 4, 7, 9, and 13 (0.127 mmol) + TMP (0.371 mmol) + H_2O (0.35 ml); 14 (0.127 mmol) + TMP (0.74 mmol) + H_2O (0.70 ml). pH used: 9.5–10.0 (NaOH). Reaction temperature: 37 °C for reactions of 4, 7, 9, and 14; and 60 °C for the reaction of 13. [b] Tr refers to a trace yield. The percentage of the starting monomethyl bases unreacted are shown in parentheses.

a mixture of 3-alkyl (major) and 1,3-dialkyl derivatives[10] and 2 and 3 generally to a mixture of 1-alkyl and 1,3-dialkyl derivatives.

The present method with TMP in a water phase gave results somewhat different from these reactions. Table I summarizes the distribution of products at various reaction times and temperature. Thus, cytosine (1) was substituted at the N-1 position mainly to produce 1-methylcytosine (4) with a small amount of 1,3-dimethyluracil (11). Upon using a large



excess of TMP, 1,3-dimethylcytosine (5) was isolated in addition to these products. 3-Methylcytosine was not formed in the present reaction. Methylation of the exocyclic 4-NH_2 and C^2O groups was not observed, either. The occurrence of a substantial amount of 11 may be attributed to the hydrolysis of 5. Indeed, an authentic sample of 5 was transformed to 11 under comparable conditions. The alternative formation of 11, e.g., the deamination of 1 or 4 and the subsequent methylation at the N-3 position of the resulting uracil derivatives (2 or 7), would be less likely as the source of 11 since both 1 and 4 are fairly stable under the present reaction condition, undergoing deamination to the extent of only 1–2%.

Thymine (2) and uracil (3), on the other hand, were substituted at both the N-1 and N-3 positions to give a mixture of 1-methyl (6 and 7), 3-methyl (8 and 9), and 1,3-dimethyl (10 and 11) derivatives. Methylation of the C^2O and C^4O groups was not observed at all. As depicted in Table I, the distribution of these products is similar in both 2 and 3.

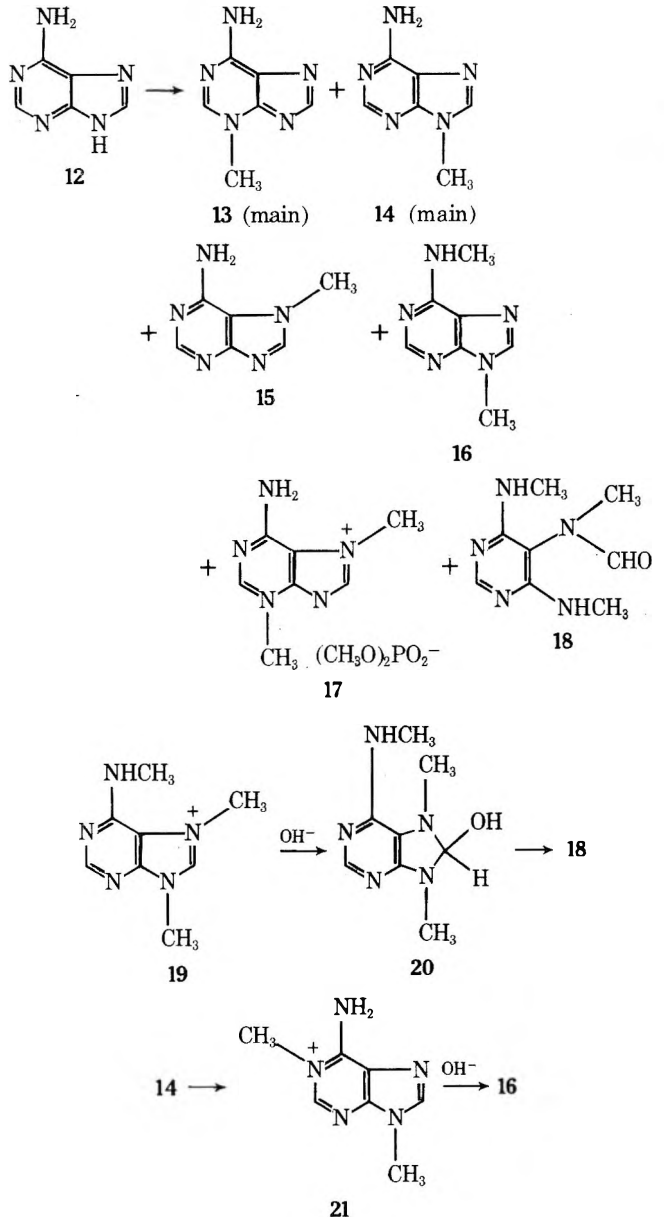
The controlled experiments revealed that the yield of 11 from methylation of 7 is approximately equal to that from 9 (see Table II). TMP, thus, appears to be attacked at the N-1 and N-3 positions of 2 and 3 equally to produce monomethyl derivatives (7 and 9), both of which are then remethylated to afford 1,3-dimethyl derivatives at similar rates. Upon using a large excess of TMP, 10 and 11 were isolated in semiquantitative yields. The synthetic utility of the facile methylation of 6 and 7 will be discussed later in General Remarks.

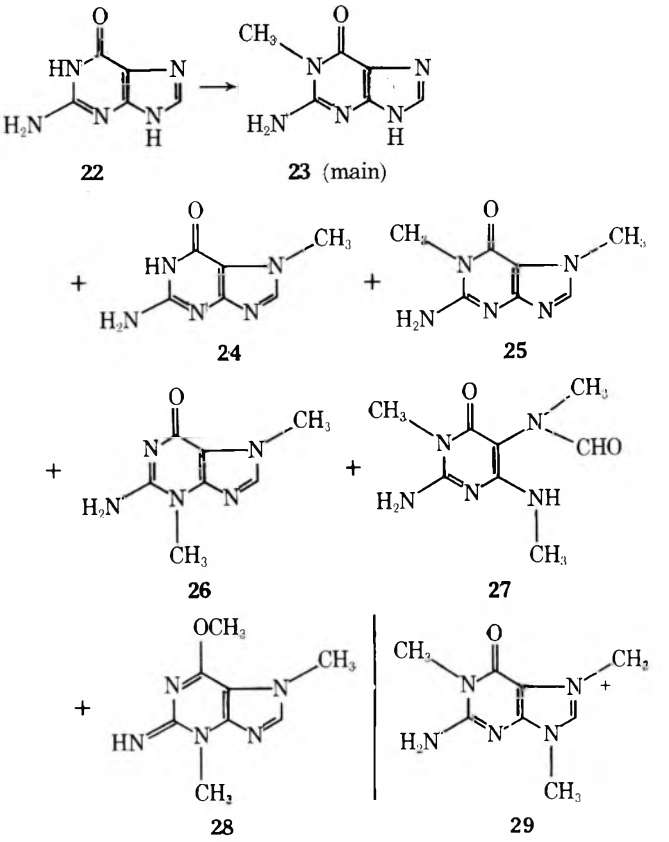
Adenine (12). Alkylation of 12 has been conducted with various alkylating agents such as dimethyl sulfate, diazomethane, alkyl halides, etc. Accumulating data show that the alkylation sites are influenced a great deal by solvent, pH, steric factors, temperature, etc. It, however, has been generally observed that the N-3 position is alkylated preferentially to the N-9 position under neutral conditions,[7,8,17,27] whereas under basic conditions the N-9-substituted product is formed mainly with the conformation of N-3-substituted adenine.[15,20,28]

The present reaction of adenine (12) with TMP took place smoothly to generate about six ultraviolet-absorbing products (13–18, see Table I). Compounds 13 and 14, which were major products obtained in comparable yields, and 16 were identified as 3-methyl-, 9-methyl-, and N^6,9-dimethyladenines, respectively, through their known physical constants. Products 15 and 17 could not be isolated but were identified tentatively as 7-methyl- and 3,7-dimethyladenines, respectively, based on their ultraviolet spectra which had close resemblances to those of the assigned compounds. At low temperatures the yields of these products were negligible as shown in Table I, but the formation of 17 increased considerably at 60 °C and appeared to accompany the consumption of 13 and 15. The reaction of 13 and TMP also afforded 17 as the chief product under comparable conditions. These results coincide with Leonard's observation that N-3-substituted adenine is alkylated mainly at the N-7 position and vice versa.[27]

Product (18) was generated in a small yield; it had an ultraviolet spectrum similar to that of imidazole ring-opened N^6-methyl-7-ethyladenosine.[12] The mass spectrum showed ion peaks at *m/e* 195 ($M^{\cdot+}$), 166 (M − $NHCH_2$), 137 [M − $N(CH_3)CHO$], etc. From these, 18 was identified as 4,6-di(methylamino)-5-methylformamidopyrimidine. Its precursor may be N^6,7,9-trimethyladenine (19), in which the electrophilic C-8 position would be attacked by hydroxyl ions to undergo imidazole ring-opening reaction via 20.

Although 1,9-dimethyladenine (21) was not detected in the reaction mixture, its formation via 14 would be expected from the very basic and nucleophilic nature of the N-1 position in 9-alkyladenine.[14,29,30] Actually, the reaction of 14 and TMP produced 21 and 16 in comparable yields (see Table II). The coproduct (16) may be derived from the Dimroth rearrangement of alkali-labile 21 rather than the direct methylation at the 6-NH_2 group.[31]





The above results thus show that adenine (**12**) is methylated with TMP at the N-3 and N-9 positions mainly. Methylation of the N-1 and N-7 positions provide relatively small contribution to the overall reactions but tend to increase with a rise of reaction temperature, generating di- and trimethylated derivatives.

Guanine (22). The guanine moiety has been established as a prime target in the alkylation of DNA by alkylating agents. However, the present knowledge of alkylation of **22** is limited. Pal reported four products in the reaction with ethyl methanesulfonate at pH 12 but identified only 7-ethylguanine.[7] Reiner and Zamenhof used dimethyl and diethyl sulfates at pH 10.8 and assigned one of the products as 7-methylguanine (**24**) on a spectrometric basis, but several other products were not identified.[9] Robins et al., on the other hand, found a quantitative formation of 7,9-dimethylguanine with dimethyl sulfate in dimethylacetamide.[8]

In the present reaction of **22** with TMP at pH 11–12, six ultraviolet-absorbing products were observed by thin layer chromatography of the reaction mixture (**23–28**, see Table I). One of the spots (compound **24**), which was seen when the reaction was carried out at 37 °C for 24 h as shown in Table I, was assigned as 7-methylguanine (**24**) based on the ultraviolet spectrum of the aqueous extract. 7-Methylguanine (**24**) is rather reactive and appears to undergo further methylation reaction (vide infra). The other products were all isolated to give 1-methylguanine (**23**, a major product) and 1,7-dimethyl- and 3,7-dimethylguanines (**25** and **26**) both in substantial yields. Here, the structure of **26** was determined from its NMR spectrum and conversion to 3,7-dimethylxanthine (theobromine) through nitrous acid treatment. The structure of a minor product (**27**) was established as 2-amino-1,6-dihydro-1-methyl-4-methylamino-5-*N*-methylformamido-6-oxopyrimidine from the NMR spectrum and its resemblance in the ultraviolet spectrum to that of imidazole ring-opened 1,7-dimethylguanosine.[13] 1,7,9-Trimethylguanine (**29**) may be considered as the precursor of **27**, being attacked by hydroxyl ion at the C-8 position in a similar way as the formation of **18**. Another minor product (**28**) was brightly fluorescent under ultraviolet light and was stable under alkaline conditions, suggesting a nonpolar O^6-methyl derivative. The NMR spectrum in deuteriochloroform showed three singlets each integrating as three protons at 2.40, 2.55, and 3.60 ppm, and a singlet integrating as one protone at 7.55 ppm, indicating attachment of two methyl groups on nitrogen atoms and one methyl group on an oxygen atom. The mass spectrum showed *m/e* 193 ($M^{\cdot+}$) and 136 ($M - CH_3OCN$), which may suggest the absence of a methyl group on the N-1 position. These considerations leave O^6,3,7-trimethylguanine as the most possible structure for **28**. The formation of O^6,3,9-trimethylguanine would be hindered sterically since the 3-methyl and 9-methyl groups are situated in peri position to each other.

The yield distributions of products mentioned above indicate that the N-1 position of guanine (**22**) is comparative to or more reactive than the N-7 position followed by the N-7 and N-3 positions in methylation with TMP, although the N-7 position was believed to be the most susceptible site with other alkylating agents even under alkaline medium.

General Remarks

The present procedure allowed us to carry out methylation reactions of nucleic acid–bases in homogeneous aqueous phase owing to water-soluble and stable properties of TMP. Most

other alkylating agents are relatively short lived under an aqueous environment or insoluble in water, and reactions are generally performed in an organic solvent or a mixture of water and an organic solvent. These characteristics of TMP would favor its use for the alkylation reactions of water-soluble compounds.

In the present reactions, TMP was found to alkylate the major heterocyclic moieties of nucleic acids. Inspection of Table I shows the reactivity of heterocycles in the following qualitative order based on the consumption of the starting materials: adenine (**12**) > guanine (**22**) > uracil (**3**) ~ thymine (**2**) > cytosine (**1**). In each of these bases, the first methylation occurs in the following order: adenine, N-9 ~ N-3 > N-7, N-1; guanine, N-1 ≳ N-7 > N-3 > N-9, O-6; uracil, N-1 ~ N-3; thymine, N-1 ~ N-3; cytosine, N-1 > N-3.

These results and distribution of products may indicate that (1) the successive methylation of 1-methyluracil and -thymine (**6** and **7**) to 1,3-dimethyl derivatives (**10** and **11**) takes place easily, but (2) that conversion of 1-methylcytosine (**4**) and of 9-methyladenine (**14**) to dimethyl derivatives occur very slowly; (3) guanine (**22**), on the other hand, appears to undergo a fast methylation to produce mono- and dimethyl derivatives. Aspects 1 and 2 were ascertained in control experiments (see Table II). Facile methylation of 9-alkylguanine with TMP was confirmed by the rapid formation of 1-methyl- and 1,7-dimethylguanosines from guanosine.[32] The above differences in the methylation of bases might be useful for the modification of nucleic acids and their components, allowing especially selective methylation of thymidine and uridine both at the N-3 position.

In addition to N-methylation, O-6-methylation of guanine (**22**), which is seen in the formation of **28**, might be noteworthy from the physiological point of view despite its low yield, because O-6-alkylation of guanine residues in nucleic acids has been considered to be the cause of powerful mutagenic effects through an atypical base pairing.[33] The present results of above-mentioned N- and O-methylations may, thus, emphasize the careful consideration for the employment of TMP as food additives and for other purposes.[34]

The kinetics and mechanisms of the present reactions have not been examined, but methylation may take place most likely in a bimolecular fashion between the anionic forms of the bases and TMP under the present conditions. Here, TMP reacts with the bases efficiently in an alkaline pH range and uses one of its three methyl groups for methylation, being converted to dimethyl hydrogen phosphate, which no longer exhibits alkylating properties.

Experimental Section

Melting points were uncorrected. Ultraviolet spectra were measured with a Hitachi 3T spectrometer. ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer R-20 spectrometer with a dilute solution in deuteriochloroform, deuterioxide, or dimethyl sulfoxide-d_6 and tetramethylsilane as an internal or an external standard. Mass spectra were obtained using Atlas CH-4B and JEOL 01SG-2 spectrometers.

Thin layer chromatography was performed on silica gel [GF_{254} (type 60), Merck] or aluminum oxide [PF_{254} (type 150), Merck] using a mixture of chloroform and methanol in the following volume ratio: solvent A, 9:1; B, 7:1; C, 5:1; and D, 5:2, or solvent E, 1-propanol–concentrated ammonium hydroxide, 5:1. Column chromatography was carried out using silica gel (Merck, art. 7734, 70–230 mesh) or aluminum oxide (Merck, art. 1097).

Commercially available cytosine, thymine, uracil, adenine, and guanine were used without further purification. Trimethyl phosphate (TMP) was distilled prior to use.

Determination of Product Distribution in the Reaction Mixture of a Base and TMP. The base (1.80 or 0.90 mmol) was dissolved in aqueous sodium hydroxide solution of pH 9–12 (5.0 ml) and the solution was treated with TMP (5.40 or 10.80 mmol) at a specified reaction temperature as shown in Table I. The pH of the solution was maintained in the same level with occasional addition of 1 N aqueous sodium hydroxide. Two or three aliquots of 3 μl of each of the reaction mixtures were spotted on a thin layer chromatogram after 10, 24, and 48 h. The plate was developed immediately after spotting, using solvent D for **1**, C for **2**, **3**, and **12**, and E for **22**. The product spots were then scraped individually from the plate in order to extract the substance from the spot with water (3 ml). Absorbancy of the solution was recorded at the respective λ_{max}. The yield of the product at each reaction time was calculated from the equation $100\epsilon_a A/\epsilon_p A^0$, where ϵ_a and ϵ_p are molecular absorbancies of the starting base and that of the product, and A^0 and A are the absorbancies of the starting base at zero time and that of the product at a suitable reaction time.

The products and their distributions in the reaction mixtures are summarized in Table I. Control experiments were performed for bases (**4**, **7**, **9**, **13**, and **14**) in a similar way as mentioned above. The reaction size, conditions, and results are described in Table II.

Isolation of Products. The reactions of bases and TMP were carried out in a manner similar to that mentioned above. Following are reaction sizes and isolation procedures. The mobilities (R_f) in thin layer chromatography are shown in Table I with references on the ultraviolet spectral peak at pH 7 used for identification. Ultraviolet spectra at pH 1 and 13 as well as the melting points of all known compounds agreed in most cases with literature values. The NMR spectra were obtained in all compounds and coincided with the assigned structures. Yields are calculated after recrystallization and are based on the isolated amounts of products.

Cytosine (1). The base (1.00 g, 9.01 mmol), TMP (3.75 g, 26.79 mmol), and water (15 ml) were mixed at pH 9–10, 60 °C for 24 h. The reaction mixture was extracted with chloroform (100 ml). The organic extract was concentrated and mixed with *n*-hexane (20 ml) to afford 1,3-dimethyluracil (**10**) as crystals: 0.15 g (12%); mp 123–125 °C (EtOH–water) (lit.[35] mp 120–121 °C). The water layer was concentrated and the residue was applied to a silica gel column (1.5 × 60 cm). Elution with chloroform–methanol (5:2 v/v) provided 1-methylcytosine and then 1,3-dimethylcytosine as the dimethyl hydrogen phosphate salts (0.55 and 0.17 g, respectively). The salts were subsequently treated with an anionic exchange resin (Dowex 1 × 8, 200–400 mesh, OH^- form). Elution with water gave the free form of 1-methylcytosine (**4**, 0.31 g, 28%); mp 298–300 °C (water) (lit.[36] 299–300 °C). 1,3-Dimethylcytosine (**5**) was obtained subsequently, 0.11 g (9%), mp 149–152 °C (sublimed) (lit.[11] 145 °C).

Thymine (2). The base (2.20 g, 17.46 mmol), TMP (7.50 g, 53.57 mmol) and water (30 ml) were mixed at pH 9.5–10.5, 60 °C for 24 h. The reaction mixture was neutralized with concentrated hydrochloric acid and the resulting solution was kept at 3 °C for 24 h to give 1-methylthymine (**6**, 0.12 g, 5%) as crystals, mp 282 °C (water) (lit.[37] 280–282 °C). The mother liquor was concentrated under reduced pressure to give the residue, which was then separated by aluminum oxide chromatography (2 × 40 cm), using chloroform–methanol (10:1 v/v) as a solvent. Twenty-five milliliters of the eluate was collected in each tube to give the following products. Fractions 1–2: 1,3-dimethylthymine (**10**, 1.39 g, 52%), mp 157–159 °C (EtOH–water) (lit.[37] 155 °C). Fractions 3–7: 3-methylthymine (**8**, 0.42 g, 17%), mp 211–212 °C (EtOH) (lit.[38] 209–210 °C). Fractions 10–19: 1-methylthymine (**6**, 0.17 g, 7%).

Uracil (3). After a mixture of uracil (1.00 g, 8.93 mmol) and TMP (7.50 g, 53.57 mmol) in water (11 ml) was warmed at pH 9–11, 60 °C for 48 h, the following products were obtained after treating the reaction mixture in a manner similar to that mentioned in thymine: 1-methyluracil (**7**), 0.13 g (12%), mp 232–234 °C (EtOH–water) (lit.[39] 233–234 °C); 3-methyluracil (**9**), 0.15 g (13%), mp 189.5–191 °C (EtOH–ether) (lit.[40] 174–175 °C); 1,3-dimethyluracil (**11**), 0.06 g (5%).

Adenine (12). The base (1.22 g, 9.04 mmol), TMP (3.75 g, 26.79 mmol), and water (10 ml) were mixed at pH 10–11, 60 °C for 24 h. The reaction mixture was adjusted to pH 14 by the addition of 4 N sodium hydroxide and allowed to stand at room temperature for 24 h, precipitating 9-methyladenine (**14**) as crystals, 0.31 g (23%), mp 307–313 °C dec (EtOH–water) (lit.[41] 310 °C). The mother liquor was concentrated to give a residue which was subsequently mixed with ethanol (50 ml) and separated from undissolved substances. The residue which was obtained after concentrating the alcoholic solution was then divided into a chloroform-soluble part (A) and -insoluble part (B).

Part A was treated by a silica gel column (1 × 60 cm). Elution with chloroform–methanol (7:1 v/v) provided first N^6,9-dimethyladenine (**16**, 0.15 g, 10%); mp 193–195 °C (benzene–EtOH) (lit.[41] 190–191 °C), then **14** (0.06 g, 4%). The subsequent elution with the same solvent afforded the imidazole ring-opened N^6,7,9-trimethyladenine (**18**, 0.02 g, 1%): mp 224–226 °C (chloroform); mass spectrum (75 eV) *m/e* 195 (molecular ion, 32), 181 (71), 163 (37), 153 (100), 137 (46), 123 (25),

109 (40), 95 (42), 82 (20), and 67 (19). The ultraviolet spectrum of **18** was almost identical with that of the imidazole ring-opened N^6,7-dimethyladenosine as footnoted in Table I.

Part B was treated similarly by a silica gel column (1 × 60 cm) using the same developing solvent to give **14** (0.02 g, 1%) followed by 3-methyladenine (**13**, 0.08 g, 6%), mp 295–301 °C dec (water) (lit.[42] 309–312 °C).

Guanine (22). The base (2.62 g, 17.35 mmol) was suspended in a solution of TMP (15.00 g, 107.14 mmol) and water (50 ml, pH 13). During stirring at 60 °C, a homogeneous solution was obtained, showing a pH of 11.5–12.0. After 24 h, the reaction mixture was neutralized with concentrated hydrochloric acid to give a precipitate. The mother liquor, after extracting out unreacted TMP with chloroform, was combined with the aqueous washings of the above precipitate with hot water. The solution was then concentrated as much as possible. The resulting residue was applied to a silica gel chromatography column (3 × 50 cm) and eluted using chloroform–methanol (10:1 v/v) as a developing solvent. Twenty-five milliliters of the eluate was collected in each tube to provide the following products.

Fraction 12–16: O^6,3,7-trimethylguanine (**28**); 0.14 g (4%); mp 201 °C (EtOH); mass spectrum (75 eV) *m/e* 193 (molecular ion, 100), 178 (9), 164 (28), 149 (13), 138 (23), 136 (18), 124 (19), 109 (31), 96 (15), 82 (29), and 67 (34); NMR δ ($CDCl_3$) 2.40 (s, N^3- or N^7-CH_3, 3), 2.55 (s, N^7- or N^3-CH_3, 3), 3.60 (s, OCH_3, 3), 7.53 (s, H^8, 1), 7.55 (broad s, NH, 1).

Anal. Calcd for $C_8H_{11}H_5O_1 \cdot 0.8H_2O$: C, 46.29; H, 6.08; N, 33.75. Found: C, 46.31; H, 5.54; N, 33.38.

Fractions 18–48: 1,7-dimethylguanine (**25**), 0.06 g (2%), mp 312–315 °C (EtOH–water) (lit.[36] 330–331 °C).

Fractions 54–60: imidazole ring-opened 1,7,9-trimethylguanine (**27**); 0.74 g (20%); mp 254.5–256.5 °C (EtOH–water); NMR (Me_2SO-d_6) δ 2.70 (d, 6-N-CH_3, J = 5 Hz), 3.11 (s, 1-N-CH_3, 3), 6.35 (q, 6-NH, 1, J = 5 Hz), 6.93 (broad s, NH_2, 2), 7.65 (s, CHO, 1).

Anal. Calcd for $C_8H_{13}N_5O_1 \cdot H_2O$: C, 41.91; H, 6.60; N, 30.55. Found: C, 41.70; H, 6.26; N, 30.52.

Fractions 63–84: 3,7-dimethylguanine (**26**), 0.33 g (10%), mp 327–333 °C dec (EtOH–water) (lit.[43] 328–330 °C).

Fractions 98–140: 1-methylguanine (**23**), 0.02 g (1%), mp 370 °C (water) (lit.[41] 350 °C).

The identification of **26** was also performed by converting it into the xanthine derivative; e.g., a mixture of **26** (0.01 g) and sodium nitrite (0.01 g in 3 ml of 4 N hydrochloric acid) was warmed at 60 °C for 30 min. The silica gel thin layer chromatogram of the reaction mixture showed a single spot which had the same mobility as that of 3,7-dimethylxanthine [0.54 with solvent A and 0.70 with a mixture of acetone and methanol (5:1)]. The ultraviolet spectra of the extracted aqueous solution of the spot were identical with those of the authentic sample at pH 1, 7, and 13.

Registry No.—**1**, 71-30-7; **2**, 65-71-4; **3**, 66-22-8; **12**, 73-24-5; **22**, 73-40-5.

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Pyrogenesis of Succinic Acid and Dimethylmaleic Anhydride from Aspartic Acid

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Aspartic acid has been pyrolyzed under a slow stream of nitrogen at temperatures ranging from 350 to 650 °C. Succinic acid was the major nonvolatile acid product observed, with maximum yield (12%) at 650 °C. Aspartic acid-*4*-^{13}C at 500 °C gave succinic acid with unchanged ^{13}C enrichment. Fumaric acid and maleic acid are possible intermediates in this transformation. Fumaric acid, mixed with alanine and pyrolyzed, was converted in part to succinic acid. A plausible reaction path for the formation of succinic acid in this work is proposed, and the possible relevance of the present work to certain other pyrolysis reactions is discussed. A minor product of the pyrolysis of aspartic acid at 400 °C and higher temperatures was dimethylmaleic anhydride; under the same conditions alanine gave negligible amounts of dimethylmaleic anhydride. Pyrolysis of mixtures of alanine and aspartic acid gave a sevenfold or better improvement in the yield of dimethylmaleic anhydride, and the yield of this product was essentially unchanged when aspartic acid was replaced by fumaric acid in the mixed pyrolysis. Carbon-13 tracer experiments were used to establish the stoichiometry of the mixed pyrolysis reaction leading to dimethylmaleic anhydride. These experiments showed also that the carboxyl carbon atoms of aspartic acid become equivalent at some stage of the reaction. Evidence is presented for a close relationship between the formation of dimethylmaleic anhydride from alanine and aspartic acid or fumaric acid and the reduction of fumaric acid to succinic acid by alanine at elevated temperatures. A reaction scheme is presented to account for the ^{13}C distribution in the products.

Succinic acid has been observed as a product of pyrolysis of ovalbumin at reduced pressure,[1] and as a product of pyrolysis of malic acid and of sodium lactate, using nitrogen as a carrier gas.[2] Further, succinic acid has been observed as a constituent of cigarette smoke[3] and cigar smoke[4] in quantities suggesting that it originates, in part, from pyrolysis reactions. As will be seen from the work reported here, likely precursors of the pyrolysis-generated succinic acid are malic acid and aspartic acid. We have found that succinic acid is the major nonvolatile acid product observed in the pyrolysis of aspartic acid.[5]

The diversity of starting materials leading to succinic acid in pyrolysis reactions suggests the possibility that succinic acid can be formed by recombination of $\cdot CH_2CO_2H$ fragments, following carbon–carbon bond dissociation at elevated temperature in appropriate starting materials. We have carried out some pyrolysis experiments with ^{13}C-labeled aspartic acid that were designed to show to what extent succinic acid may be formed by such reaction from aspartic acid.

Dimethylmaleic anhydride was noted as a minor product in the conversion of aspartic acid to succinic acid and also in the course of using our controlled pyrolysis apparatus[6] to study pyrolysis of soy protein and an amino acid mixture having the same amino acid composition. These findings stirred our interest because the material pyrolyzed contained no carbon skeletons corresponding to that of dimethylmaleic anhydride and also because of the possible relevance of this finding to food preparation at high temperature and to tobacco smoking. Further, the pyrogenesis of dimethylmaleic anhydride from aspartic acid, and from alanine mixed with aspartic acid or fumaric acid, might provide evidence on the mode of formation of succinic acid in these same reactions and in certain other reactions leading to succinic acid, such as the pyrolysis of malic acid,[7] the dry distillation of ovalbumin,[8] and in tobacco smoking.[9,10]

At 350 °C, DL-aspartic acid was converted mainly into brown, amorphous polyaspartic acid.[11] Pyrolysis with extensive decomposition and carbonization became pronounced by 400 °C in our apparatus, and at 650 °C, the carbonlike residue amounted to 25% of the weight of the starting material Succinic acid was the major nonvolatile acid product, observed as its dimethyl ester in gas–liquid chromatography (GLC). The yield of succinic acid increased with increasing temperature of pyrolysis up to our highest temperature, 650 °C (Table I). Fumaric acid and maleic acid were observed as very minor products in this work. Our methyl esterification procedure for GLC estimation of nonvolatile acids was inappropriate for oxalic acid and other acids whose esters are easily hydrolyzed, but dimethyl oxalate was observed in our product mixtures, usually in trace amount. The four identified dimethyl esters accounted for 97 ± 1% of the total area under product elution peaks.

Pyrolysis of aspartic acid-*4*-^{13}C, 13.4 ± 1.0% ^{13}C enrichment, at 500 °C gave succinic acid-^{13}C with ^{13}C enrichment unchanged within experimental error (Table II). To the extent that succinic acid was produced by recombination of $\cdot CH_2{}^{13}CO_2H$ fragments, ^{13}C enrichment would be increased and some succinic acid-*1,4*-$^{13}C_2$ would be formed. The results of measurements summarized in Table II show, to the contrary, that such a reaction path was negligible. Nor did fumaric acid or maleic acid from aspartic acid-*4*-^{13}C show any significant difference in ^{13}C enrichment from that of the parent compound. Pyrolysis at 500 °C of a mixture of alanine and aspartic acid-*4*-^{13}C (60/40 mol/mol) also gave succinic acid-^{13}C and fumaric acid-^{13}C without significant changes in ^{13}C enrichment from that of aspartic acid.

Some experiments were designed to test the possibility that fumaric acid and/or maleic acid were involved as intermediates in the conversion of aspartic acid to succinic acid. A mixture of aspartic acid and fumaric acid (86/14 mol/mol) was pyrolyzed at 500 °C. The yield of succinic acid from this reaction was 24% greater than that obtained from aspartic acid alone under the same conditions (Table III). In another experiment alanine containing 21 mol % fumaric acid on pyrolysis at 600 °C gave a 7% yield of succinic acid (based on starting fumaric acid), substantially better than that from a mixture of alanine and aspartic acid under the same conditions (Table IV). Since alanine alone gave no succinic acid or fumaric acid on pyrolysis, it can be seen from these experiments that fumaric acid can be reduced to succinic acid by an α-amino acid at elevated temperatures. Pyrolysis at 600 °C of a mixture of alanine and maleic anhydride gave a mixture of nonvolatile acids qualitatively similar to that from pyrolysis of aspartic acid, as judged by GLC examination of their trimethylsilyl esters.

In a control experiment, pyrolysis of fumaric acid at 600 °C gave fumaric acid (40% recovery as dimethyl ester) and maleic acid (46% yield as dimethyl ester).

Table I. Pyrolysis of Aspartic Acid

Temp, °C	Yields of dicarboxylic acid products, mmol[a]			
	Succinic	Fumaric	Maleic	Total
350	0.7[b]	0.3[b]	0.04[b]	1.0[b]
400	3.6	0.4	0.06	4.0
500	5.5	1.1	0.09	6.7
600	5.7	0.9	0.09	6.7
600	5.6[c]	0.1[c]	0.02[c]	5.7
650	6.2	0.4	0.05	6.7

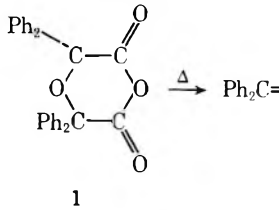
[a] Yields, mmol per 100 mmol of starting aspartic acid, were estimated by gas–liquid chromatography of dimethyl ester mixtures using an internal standard and comparing with known mixtures. [b] Based on unrecovered starting material. [c] Amorphous polyaspartic acid, obtained from the experiment at 350 °C, was employed in this experiment.

Table II. Mass Spectrometry Results for Aspartic-*4*-^{13}C Acid and for Succinic, Fumaric, and Maleic Acid Products from Pyrolysis at 500 °C, Examined as Dimethyl Esters

M/z	Assignment	Excess ^{13}C,[a] %
M^+ (not observed)	$CH_3O_2C^*CH_2CH_2CO_2CH_3^+$	
115, 116	$CH_3O_2C^*CH_2CH_2CO^+$	12.5 ± 0.8[b]
87, 88	$CH_3O_2C^*CH_2CH_2^+$	7.2 ± 0.8
M^+	$CH_3O_2C^*CH{=}CHCO_2CH_3^+$ (*trans*)	14.0 ± 0.3[b]
85, 86	$CH_3O_2C^*CH{=}CH^+$	6.5 ± 0.6
M^+ (not observed)	$CH_3O_2C^*CH{=}CHCO_2CH_3^+$ (*cis*)	
113, 114	$CH_3O_2C^*CH{=}CHCO^+$	13.3 ± 0.3
85, 86	$CH_3O_2C^*CH{=}CH^+$	6.5 ± 0.6
M^+ (not observed)	$CH_3O_2C^*CH_2CHNH_2CO_2CH_3^+$	
102, 103	$CH_3O_2C^*CH_2CH{=}NH_2^+$	14.7 ± 0.8
88, 89	$CH_3O_2CCH{=}NH_2^+$	1.1 ± 0.2

[a] Percentage ^{13}C together with standard deviation of five or more measurements, corrected for natural ^{13}C abundance and mass spectrometer background by comparison with corresponding unenriched materials. [b] Results for the product from pyrolysis of aspartic-*4*-^{13}C acid alone were indistinguishable from those obtained for the corresponding product from alanine mixed with aspartic-*4*-^{13}C acid, within experimental uncertainty. Both results are included here.

At elevated temperatures benzilic acid undergoes decomposition to diphenylacetic acid, benzophenone, and carbon dioxide.[12] Since carbon monoxide was not produced in this reaction, the benzophenone product could not have been formed by the familiar decarbonylation route. At somewhat lower temperatures, benzilic acid underwent dehydration to the cyclic ether anhydride **1**,[13,14] and when **1** was heated above 250 °C, it decomposed into carbon dioxide, benzophenone, and diphenylketene[13] (eq 1).



$$\xrightarrow{\Delta} Ph_2C{=}C{=}O + Ph_2C{=}O + CO_2 \quad (1)$$

1

The dehydration of benzilic acid to **1** followed by decomposition of **1** accounts very well for the overall decomposition of benzilic acid at elevated temperatures, since water produced in the first step can react with diphenylketene to give the observed diphenylacetic acid.

Mandelic acid undergoes decarbonylation to produce benzaldehyde and carbon monoxide.[15] Hurd[16,17] has shown that thermal decomposition of mandelic acid also produces phenylacetic acid and carbon dioxide. Further, Hurd and Raterink prepared an ether anhydride from mandelic acid, analogous to **1**, and showed that it decomposed at 250 °C in the manner of **1**, in part.[17]

Table III. Pyrolysis of Aspartic Acid Mixtures at 500 °C

Second component	Yields of dicarboxylic acids, mmol[a]		
	Succinic	Fumaric	Maleic
None	5.5	1.1	0.09
Fumaric acid, 14 mol %	6.8	2.8[b]	0.00
Alanine, 60 mol %	5.4	0.2	0.00

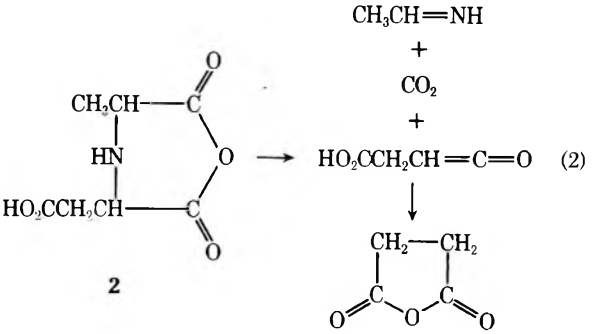
[a] See corresponding footnote, Table I. [b] Percentage recovery.

Table IV. Pyrolysis of Alanine Mixtures at 600 °C

Second component	Yields of dicarboxylic acids, mmol[a]		
	Succinic	Fumaric	Maleic
None	0.0	0.0	0.0
Aspartic acid, 40 mol %	4.7	0.1	0.0
Fumaric acid, 21 mol %	7.3[b]	1.7[c]	0.0
Succinic acid, 20 mol %	88[c]	0.0	0.0

[a] See corresponding footnote, Table I. [b] mmol per 100 mmol of unrecovered fumaric acid. [c] Percentage recovery.

The α-hydroxy acid to ether anhydride to ketene pathway established for the formation of diphenylacetic and phenylacetic acids (above) can be applied to the formation of succinic acid from malic acid by pyrolysis: reversible dehydration of malic acid to fumaric acid occurs at elevated temperature,[18] and the required cyclic ether anhydride intermediate is a plausible product resulting from addition of malic acid to the carbon–carbon double bond of fumaric acid (or maleic acid) followed by dehydration. An analogous pathway seems reasonable for the formation of succinic acid from aspartic acid (partial deamination of aspartic acid to fumaric acid followed by addition of aspartic acid to the fumaric acid produced) and from alanine plus fumaric acid. In the latter case, the hypothesized cyclic intermediate **2** is unsymmetrical and alternative modes of decomposition are possible (eq 2 and 3).



2

$$2 \longrightarrow CH_3CH{=}C{=}O + CO_2 + HO_2CCH_2CH{=}NH \quad (3)$$

In the present work the yield of succinic acid from amorphous polyaspartic acid was almost as good as that from aspartic acid itself under the same conditions (Table I). Consequently, it seems reasonable to extend the proposed reaction path, with slight modification, to account for the formation of fatty acids and succinic acid in the pyrolysis of ovalbumin.[1]

On the basis of the proposed reaction path, the overall re-

Table V. Dimethylmaleic Anhydride from Aspartic Acid by Pyrolysis

Temp, °C	Yield,[a,b] %
400	0.06
500	0.10
600	0.09
600	0.05[c]
650	0.06

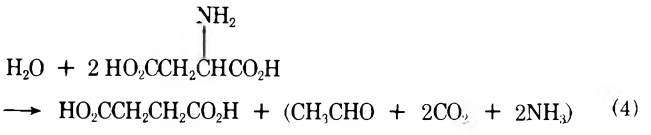
[a] Yields were estimated by means of gas–liquid chromatography, using an internal standard and comparison with known mixtures. [b] Calculated on the basis of the reaction, 2 aspartic acid → dimethylmaleic anhydride + $2NH_3$ + H_2O + $2CO_2$. [c] Amorphous polyaspartic acid was employed in this experiment.

Table VI. Dimethylmaleic Anhydride from Mixtures Containing Alanine

Temp, °C	Second component	Yield,[a] %
600	None	<0.04[b]
500	Aspartic acid (40 mol %)	0.67[c]
600	Aspartic acid (40 mol %)	0.67[c]
600	Fumaric acid (21 mol %)	0.63[d]

[a] See corresponding footnote of Table I. [b] This upper limit was calculated on the basis of the supposed reaction, 2 alanine → dimethylmaleic anhydride + $2NH_3$ + H_2O. [c] Basis: aspartic acid + alanine → dimethylmaleic anhydride. [d] Basis: fumaric acid + alanine → dimethylmaleic anhydride.

action leading to succinic acid from aspartic acid by pyrolysis is, after hydrolysis, as shown in eq 4.

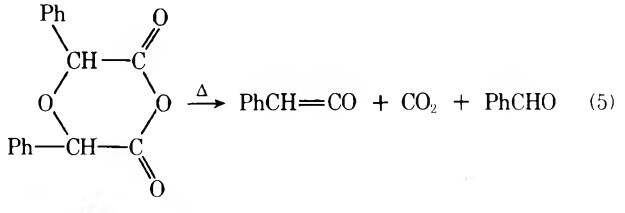


$$H_2O + 2\,HO_2CCH_2\underset{\displaystyle NH_2}{\underset{|}{C}}HCO_2H \longrightarrow HO_2CCH_2CH_2CO_2H + (CH_3CHO + 2CO_2 + 2NH_3) \quad (4)$$

Assuming the stoichiometry of eq 4, the yield of succinic acid from aspartic acid at 650 °C was 12.4%.

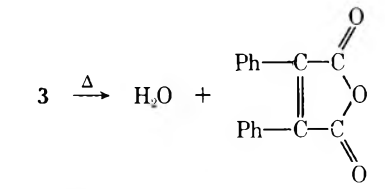
The yields of dimethylmaleic anhydride obtained at several temperatures from aspartic acid are given in Table V. Pyrolysis of alanine alone gave a negligible yield of dimethylmaleic anhydride but alanine exerted a remarkable effect on the yield of dimethylmaleic anhydride from aspartic acid (Table VI). Further, we observed that the yield of dimethylmaleic anhydride obtained from the pyrolysis of alanine mixed with fumaric acid was comparable to that obtained from the pyrolysis of alanine–aspartic acid mixture. There is a striking parallel between the yields of dimethylmaleic anhydride and yields of succinic acid for most of these reactions,[19] and we suspected a close relationship between the reaction paths leading to succinic acid and dimethylmaleic anhydride, involving one or more common intermediates.

A possible clue to the mode of formation of both succinic acid and dimethylmaleic anhydride in our pyrolysis reactions is furnished by results obtained by Hurd and Raterink[17] in the thermal decomposition of the cyclic ether anhydride **3**. The weight of evidence indicated strongly that most of the products formed from **3** arose from the two reactions, eq 5 and 6.[16,17]



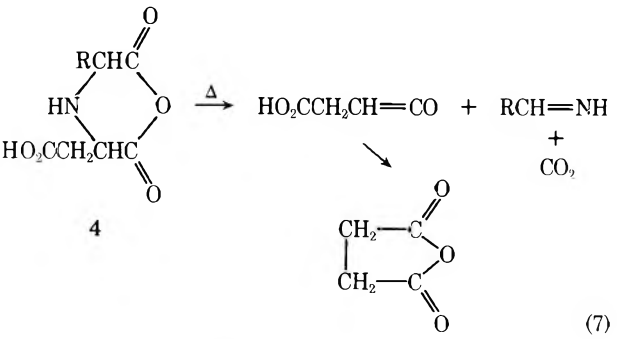
$$\mathbf{3} \xrightarrow{\Delta} PhCH{=}CO + CO_2 + PhCHO \quad (5)$$

3



$$\mathbf{3} \xrightarrow{\Delta} H_2O + \quad (6)$$

In the pyrolysis reactions reported herein, succinic acid and dimethylmaleic anhydride were produced together, or neither was produced (pyrolysis of alanine alone). In the reactions leading to both products, fumaric acid was either present in the mixture pyrolyzed or it could be produced from aspartic acid by loss of ammonia (Tables V and VI). In these reactions a cyclic imino anhydride (**4**) analogous to **3** could be produced as a transitory intermediate by addition of α-amino acid to the carbon–carbon double bond of fumaric acid (or, possibly, maleic acid). Thermal decomposition of **4** could produce both succinic anhydride, eq 7, and disubstituted maleic anhydride, eq 8.

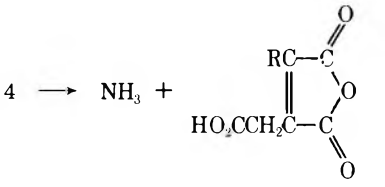


4

$$\xrightarrow{\Delta} HO_2CCH_2CH{=}CO + RCH{=}NH + CO_2 \quad (7)$$

a, R = HO_2CCH_2

b, R = CH_3



$$\mathbf{4} \longrightarrow NH_3 + \quad (8)$$

5

a, R = HO_2CCCH_2

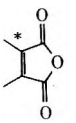
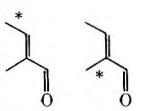
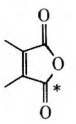
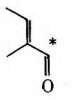
b, R = CH_3

Because **5** is a β,γ-unsaturated acid it would be expected to undergo decarboxylation readily and give rise to relatively volatile dimethylmaleic anhydride.

Added alanine increases the yield of dimethylmaleic anhydride from aspartic acid (Tables V and VI) but does not increase the yield of succinic acid from aspartic acid. This effect of added alanine on the yield of dimethylmaleic anhydride from aspartic acid suggests that the rate of reaction 8 relative to that of reaction 7 is more favorable for **4b** than for **4a**. Accordingly, our interpretation of the mode of formation of dimethylmaleic anhydride leads to the expectation that most of the dimethylmaleic anhydride produced in the pyrolysis of alanine–aspartic acid mixtures arises from the addition of alanine to fumaric acid and/or maleic acid derived from aspartic acid, followed by dehydration to **4b** and thermal decomposition of **4b** to **5b**.

Carbon-13 tracer experiments were designed to test the major points of the above interpretation of the formation of dimethylmaleic anhydride from alanine-aspartic acid mixtures: the correct reaction stoichiometry can be established; and it can be determined whether or not the carboxyl carbon atoms of aspartic acid actually become equivalent at some stage of reaction prior to decarboxylation.

Table VII. Carbon-13 Labeled Dimethylmaleic Anhydride from Labeled Mixtures of Amino Acids at 500 °C: (a) Alanine-3-^{13}C and Unenriched Aspartic Acid, 60/40 mol %; (b) Aspartic-4-^{13}C Acid and Unenriched Alanine, 40/60 mol %

	Labeled component of mixture	Dimethylmaleic anhydride	
		M/z 126, 127	*M/z* 82, 83
	$C^*H_3CHNH_2CO_2H$		
Excess ^{13}C[a]	18.6 ± 0.8%[b]	19.2 ± 0.4%	18.0 ± 0.3%
	$HO_2C^*CH_2CHNH_2CO_2H$		
Excess ^{13}C[a]	13.4 ± 1.0%	6.7 ± 0.7%	3.2 ± 0.6%

[a] Percentage ^{13}C together with the standard deviation of five or more measurements, corrected for natural ^{13}C abundance and mass spectrometer background by comparison with the corresponding unenriched material. [b] Measurements made on the methyl *N*-acetylester. [c] Measurements made on dimethyl esters of the starting amino acid and derived succinic, fumaric, and maleic acids.

Mass spectrometry results for two ^{13}C tracer experiments on the formation of dimethylmaleic anhydride from mixtures of alanine and aspartic acid are summarized in Table VII. Alanine-3-^{13}C mixed with unlabeled aspartic acid and pyrolyzed at 500 °C produced dimethylmaleic anhydride having the same excess ^{13}C as the starting alanine (reaction a, Table VII). This result shows that dimethylmaleic anhydride was produced exclusively from one molecule of alanine and one molecule of aspartic acid.

Aspartic-4-^{13}C acid was mixed with unlabeled alanine and pyrolyzed at 500 °C. The dimethylmaleic anhydride obtained from this reaction contained one-half the excess ^{13}C of the starting aspartic acid (Table VII, reaction b). This result confirmed the reaction stoichiometry found in the first tracer experiment, above, and also showed that the two carboxyl carbon atoms of aspartic acid do become equivalent at some stage of the reaction leading to dimethylmaleic anhydride, in agreement with the belief that fumaric acid and/or maleic acid is an intermediate.

It has been shown above that fumaric acid can be reduced to succinic acid by alanine at elevated temperatures, and fumaric acid and/or maleic acid has been implicated as an intermediate in the formation of succinic acid from aspartic acid by pyrolysis. The apparent close relationship, indicated by the present results, between succinic acid formation and formation of substituted maleic anhydride suggests that at least small amounts of substituted maleic anhydrides may be formed in certain other high-temperature reactions that have been reported to produce succinic acid.[10]

Experimental Section

Materials. DL-Aspartic acid, a commercial sample of good quality by ^1H NMR analysis, was further purified by recrystalliztion from water. DL-Alanine was similarly analyzed and purified. Maleic acid was obtained from maleic anhydride by recrystallization from water. Commercial 99+% fumaric acid was used without further purification. Dimethyl esters used for comparison purposes were prepared by standard methods and purified by distillation, except dimethyl oxalate, which was a commercial sample.

DL-Aspartic-4-^{13}C acid was obtained from Merck Sharp and Dohme Canada Ltd. and was diluted by recrystallization from water with added unlabeled aspartic acid.

L-Alanine-3-^{13}C was obtained from Merck Sharp and Dohme Canada Ltd. and was diluted with unlabeled DL-alanine. An aqueous solution of the diluted alanine-3-^{13}C, containing excess L isomer, was evaporated to dryness; the residue was ground in a mortar and stored over anhydrous calcium chloride.

Methyl DL-2-Acetaminopropionate. DL-Alanine (1.0 g, 11 mmol) was esterified, using absolute methanol and excess hydrogen chloride. Most of the solvent was removed by azeotropic distillation with benzene. The last of the solvent was removed at reduced pressure in a rotary evaporator, then the residue was dissolved in dilute sodium carbonate solution and treated with excess acetic anhydride, added in small portions with vigorous shaking. Water and acetic acid were removed at reduced pressure with a rotary evaporator and the residue was extracted with several small portions of chloroform. Chloroform was replaced by petroleum ether and the product was crystallized and recrystallized from ether–petroleum ether with cooling, and stored in a vacuum desiccator over anhydrous calcium chloride. The hygroscopic product melted at 40–43 °C, placed on the hot stage at 30 °C and heated rapidly, 0.71 g (45%): mass spectrum *m/e* 145, M^+; 114, $(M-31)^+$; 86, $(M-59)^+$. The ^1H NMR spectrum in Me_2SO-d_6 was appropriate for the expected structure.

δ, ppm	No. of protons	Assignment
1.3 doublet	3	CH_3CH
1.8 singlet	3	CH_3CO
3.6 singlet	3	CH_3O
4.4 quartet	1	CH_3CH

The L isomer of methyl 2-acetaminopropionate is reported to be an oil.[20]

Methyl 2-Acetaminopropionate-3-^{13}C. Carbon-13 labeled acetylalanine methyl ester, containing excess L isomer, was prepared from alanine-3-^{13}C as described for the corresponding unlabeled material, above. The chloroform extract of product was evaporated to give a slightly discolored oil which crystallized at room temperature in a vacuum desiccator over anhydrous calcium chloride.

Apparatus. The pyrolysis equipment used in this work has been described elsewhere.[6] The material to be pyrolyzed (2 g, powdered) was distributed as evenly as possible over a length of 100 cm in an 11-mm o.d. quartz tube. The tube was mounted on a rack, slightly declined from the horizontal. A small, ice-cooled trap was attached to the pyrolysis tube at the lower end, and a stream of nitrogen (60 ml/min) was passed through the tube to flush air and to serve as a carrier. Pyrolysis was accomplished by means of a mobile furnace which was motor driven along the rack at a rate of 1.35 cm/min.

Pyrolysis. The pyrolysis of aspartic acid and of alanine–aspartic acid mixtures at 400 °C and higher was accompanied by extensive carbonization and evolution of gases. Pyrolyzate preceded the furnace, being reheated by the furnace, and gradually moving down the pyrolysis tube. Very little condensate, mostly water droplets, collected in the cold trap. Pyrolyzate was washed from the tube with dilute aqueous sodium hydroxide, a little methanol, again with dilute alkali and, finally, with water.

Analysis. Methanol and most of the water were distilled from the trap and pyrolysis tube washings, above, and the concentrated alkaline solution was heated under reflux for a period of 24–48 h. This extended alkaline hydrolysis is designed to convert succinic acid derivatives to succinate for subsequent conversion to methyl succinate. Distillation was resumed and continued (with addition of water to the pot, if necessary) until the distillate was colorless, odorless, and neutral (discarded). The contents of the pot were acidified with hydrochloric acid and filtered and the acidic solution was submitted to continuous ether extraction (5–7 days). The residue obtained by

evaporation of ether from the extract was dried by azeotropic distillation of water with benzene, then esterified with absolute methanol (50 ml) and concentrated sulfuric acid (1 ml). Most of the methanol was removed from the reaction mixture by codistillation with benzene and the mixture was neutralized with cold aqueous sodium carbonate solution. The aqueous layer was saturated with salt and extracted repeatedly with benzene. The combined benzene extracts were washed with water, dried, and concentrated by distillation of most of the solvent. In GLC examination[21] of product mixtures from aspartic acid, the esters of oxalic, fumaric, succinic, and maleic acids accounted for 97 ± 1% of the area under product elution peaks. A measured amount of dimethyl citraconate was added as an internal standard to ester mixtures for quantitative estimation of products.

Dimethyl esters of oxalic, fumaric, and succinic acids accounted for 70 ± 1% of the area under elution peaks in GLC of product mixtures from alanine–aspartic acid pyrolysis; several unidentified minor and trace products from alanine accounted for the remaining area. Dimethyl fumarate was used as an internal standard for quantitative estimation of dimethyl succinate. Results of GLC examination of the product mixture obtained from pyrolysis of alanine–fumaric acid were similar to those described for alanine–aspartic acid mixtures.

The identities of dimethyl esters of nonvolatile acid products were confirmed by isolation in preparative GLC[21] and comparison of their mass spectra with those of authentic samples and, except for dimethyl maleate, by means of infrared spectra and melting points.

In actual-scale control experiments, mixtures of succinic and fumaric acids were carried through the analytical procedure described above. The amounts of succinic and fumaric acids observed as dimethyl esters in GLC were 84 ± 2 and 82 ± 9% and the yield data for succinic and fumaric acids given in Tables I, III, and IV have been corrected accordingly. In a similar control experiment, not to scale, only moderate loss of maleic acid occurred during the analytical procedure; yields of this trace product were corrected using the somewhat arbitrary correction factor of 1.2.

Dimethylmaleic anhydride was removed from the hydrolyzed pyrolyzate by distillation with steam prior to continuous ether extraction of the nonvolatile acid products of pyrolysis. Gas–liquid chromatography of the organic material extracted from the steam distillate gave several trace peaks and one major elution peak, which corresponded in retention time to that of a purified sample of dimethylmaleic anhydride obtained from Aldrich Chemical Co. Dimethylmaleic anhydride was isolated by means of preparative GLC and its identity was confirmed by comparison of its mass spectrum, infrared spectrum, and melting point with those of authentic material.

Carbon-13 assays were done by the Mass Spectroscopy Center of the University of Kentucky.

Acknowledgment. This study was carried out under Contract 12-14-100-7001 (63) with the Agricultural Research Service, U.S. Department of Agriculture, administered by Athens, Ga., area, Richard B. Russell Agricultural Research Center, Athens, Ga.

Registry No.—DL-Aspartic acid, 617-45-8; succinic acid, 110-15-6; dimethylmaleic anhydride, 766-39-2; methyl DL-2-acetamidopropionate, 26629-33-4; DL-alanine, 302-72-7.

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(21) The column packing used was Silar 5CP on Gas-Chrom Q, supplied by Applied Science Laboratories Inc.; 3% liquid phase for analytical column packing, and 10% liquid phase for preparative GLC.

Study of Benzhydrylamine-Type Polymers. Synthesis and Use of *p*-Methoxybenzhydrylamine Resin in the Solid-Phase Preparation of Peptides[1]

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Starting with the phenylketopolystyrene–1% divinylbenzene intermediate, two routes have been compared for the synthesis of phenylaminomethylpolystyrene–1% divinylbenzene (benzhydrylamine-type polymer), useful for the preparation of C-terminal amide peptides by solid-phase synthesis. The desired primary amine containing polymer can best be obtained via the Leuckart reaction, while reduction of the oxime intermediate with metal hydrides leads to a large percentage of secondary amine. The Demjanov reaction has been adapted for the analysis of primary and secondary amine content of the polymers. Anisylaminomethylpolystryrene–1% divinylbenzene has also been synthesized by the Leuckart reaction, characterized with respect to primary and secondary amine content, and its usefulness illustrated by the synthesis of the hypothalamic hormone, Thyroliberin (TRH), and a series of model peptides.

In 1970 Pietta and Marshall[2] introduced into solid-phase peptide synthesis[3] a resin based upon a phenylaminomethylpolystyrene–2% divinylbenzene structure (benzhydrylamine resin), which attaches the growing peptide chain via a C-terminal amide bond to the polymeric support. The advantage over the utilization of a benzyl ester type linkage[4] for the

synthesis of peptides terminating in a carboxamide are the elimination of transesterification[5-8] and the possibility for the direct synthesis of peptides with a C-terminal carboxamide moiety containing aspartic and/or glutamic acid residues in the peptide chain.

A literature survey indicates that most syntheses using benzhydrylamine resin deal with the preparation of TRH, LH-RH, calcitonin, oxytocin, and their respective analogues, all of which terminate in either glycinamide or prolinamide.[9-16] Fortunately, peptides terminating in these two residues are removed from the benzhydrylamine resin in high yield by treatment with HF. However, experiences in our tides with a C-terminal phenylalanine residue are removed from benzhydrylamine resins at a low yield of 25–30%, although Pietta et al.[18] report a yield of 57% with the crude C-terminal tetrapeptide of gastrin, Trp-Met-Asp-Phe-NH_2.

The reason for the low yields obtained resides in the method recommended for the preparation of the benzhydrylamine resin. Pietta et al.[9] favor the synthesis of the benzhydrylamine resin via an oxime derivative which is reduced by metal hydride, although two additional routes starting with the phenylketo derivative of polystyrene–1% (or 2%) divinylbenzene copolymer have been explored (Figure 1). The route

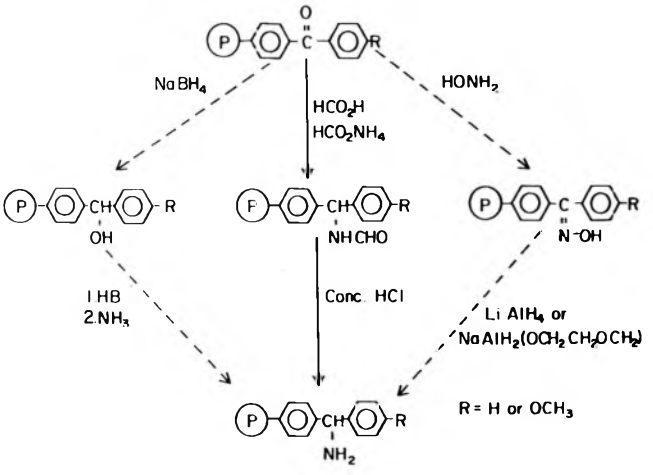


Figure 1. Synthetic routes to benzhydrylamine resin. The pathway indicated in solid lines was preferred in this study.

via the oxime may not have been the best choice, since it is a priori suspect to deleterious rearrangements. It has been reported[19,20] that the reduction of oximes can be accompanied by rearrangement involving a Curtius-type intermediate to give secondary amines, from which the final peptide cannot be removed by HF treatment.[21]

Another problem concerns the rate of acid-catalyzed cleavage of the peptide amide from the benzhydrylamine resin. The rate is directly proportional to the stability of the resultant carbonium ion on the polymer. Therefore, a *p*-anisyl-substituted resin—rather than a phenyl-substituted resin—would be expected to facilitate the release of the peptide amide.

In view of the above considerations the preparation and properties of benzhydrylamine resins, including the *p*-methoxy derivative,[2,18] were studied in some detail. The suitability of *p*-methoxybenzhydrylamine resin for the synthesis of peptides terminating in a carboxamide is investigated.

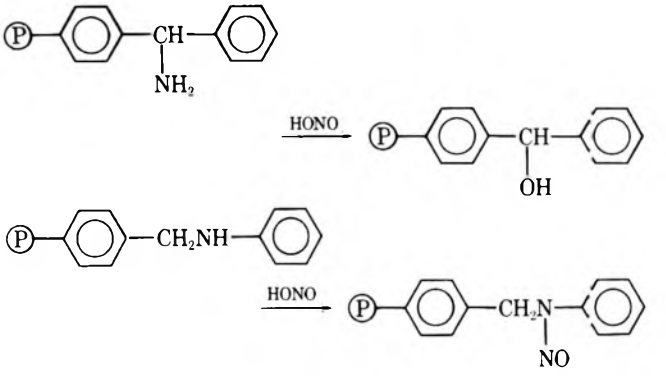
Results and Discussion

There are three synthetic routes to benzhydrylamine resin, starting from the common intermediate, phenylketo derivative, prepared by the Friedel–Crafts benzoylation of polystyrene–1% divinylbenzene copolymer (see Figure 1). For our work we have concentrated on the Leuckart and oxime reduction routes.

Three samples of benzhydrylamine resin were prepared from the same benzoylated polystyrene. One portion was converted to the oxime derivative and then reduced with Vitride according to the procedure described by Pietta et al.[9] Another sample of the oxime was subjected to Vitride reduction using a reversed sequence addition of reagents. A third portion of the benzoylated polystyrene was subjected to Leuckart reduction, followed by hydrolysis of the formylamine. The three products were analyzed for primary and secondary amine content by an adaptation of the Demjanov reaction.[22]

Primary amine will react with the nitrous acid to evolve N_2 and generate a secondary alcohol. Secondary amine will not diazotize but will nitrosate to yield a nitrosoamine derivative (Scheme I). Clearly, the nitrogen content of the polymer after

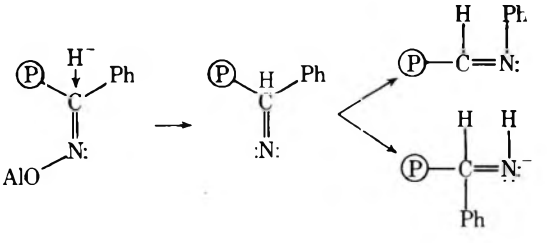
Scheme I



diazotization is a direct measure of the secondary amine content. Subtraction of the secondary amine value from the total amine yields the primary amine content of the resin.

The formation of secondary amine as a by-product of the hydride reduction of acetophenone oxime was first reported by Smith et al.[19] It was later suggested that hydroxylamines are intermediates in the hydride reduction of oximes.[20,23] We prefer the explanation of Graham and Williams[24] for the reduction of oximes with hydrides, which proceeds via the metal complex shown in Scheme II. In this case, the aluminate ion

Scheme II



is displaced either by attack of hydride ion (primary amine formation) or by phenyl migration (secondary amine formation). The results in Table I clearly indicate that the benzhydrylamine resin prepared via reduction of the oxime intermediate contains substantial amounts of secondary amine, while the resin with the highest primary amine content is obtained by the Leuckart reaction. For this reason, the *p*-methoxybenzhydrylamine polymer evaluated in this study for its usefulness in peptide synthesis was prepared via the Leuckart reduction of the *p*-anisoylated polystyrene–1% divinylbenzene copolymer. The resin obtained contained only 0.02 mequiv of secondary amine per gram of polymer and 0.6 mequiv/g of primary amine.

Table I. Comparison of Benzhydrylamine Resin Prepared by Leuckart Reaction or Oxime Reduction

Resin	Nitrogen, %	Total amine, mequiv/g	Nitrogen after diazotization, %	Secondary amine, mequiv/g	Primary amine, mequiv/g
Oxime I	1.33	0.95	1.40	0.50	0.45
Oxime II	1.36	0.97	1.70	0.61	0.36
Leuckart	1.22	0.87	0.06	0.02	0.85

Table II. Dipeptide Synthesis on *p*-Methoxybenzhydrylamine Resin

C-Terminal protected amino acid residue	Ninhydrin test after 1st coupling step	C-Terminal amino acid concn, μmol/mg	Ninhydrin test after second coupling step with Boc-Ala	Acid hydrolysis of dipeptide resin	
				C-terminal residue, μmol/mg	Ala concn, μmol/mg
Box-Gly	Negative	0.46	Negative	0.45	0.47
Boc-Pro	Negative	0.47	Negative	0.48	0.49
Boc-Phe	Negative	0.45	Negative	0.46	0.45
Boc-Val	Negative	0.53	Negative	0.51	0.49
Boc-Glu(OBzl)	Negative	0.47	Negative	0.51	0.46

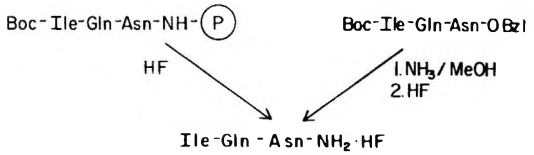


Figure 2. Methods of preparation of Ile-Gln-Asn-NH_2 by classical and solid-phase procedures.

A selected number of model dipeptides were synthesized on the *p*-methoxybenzhydrylamine resin in order to test for stability of the C-terminal amide bond during the removal of the *N-tert*-butyloxycarbonyl group with 33% v/v trifluoroacetic acid in methylene chloride. Samples of resin substituted with the first N-portected amino acid (X) were subjected to acid hydrolysis and amino acid analysis[25] as were the Boc-Ala-X-resin dipeptide products. From the results listed in Table II it is apparent that the C-terminal amide bond is stable to Boc-deprotection conditions. All of the five protected amino acids investigated substituted on the resin with ease and in high yields.

In view of the reported low recovery from benzhydrylamine resin[17,18] of peptides terminating in phenylalanine the Boc-Ala-Phe-*p*-methoxybenzhydrylamine polymer was subjected to treatment with anhydrous HF. The dipeptide Ala-Phe-NH_2·HF was recovered in 92% yield. The substitution level on the resin for Phe is 0.45 mequiv/g and for Ala 0.46 mequiv/g (Table II). After HF cleavage of the dipeptide, the residue resin was subjected to acid hydrolysis[25] and amino acid analysis. The amino acid levels found are Phe, 0.02 mequiv/g; Ala, 0.02 mequiv/g. This is indicative of at least a 95% cleavage of dipeptide from the resin.

To further demonstrate the usefulness of the *p*-methoxybenzhydrylamine resin, the synthesis of the hypothalamic hormone Thyroliberin (TRH)[26] was undertaken. The synthetic hormone was recovered in 78% yield after purification, and had a biological activity identical with that of the TRH standard when tested in the in vitro rat pituitary assay.[27]

The *p*-methoxybenzhydrylamine resin was further evaluated by introducing the first amino acid residue onto the resin via an activated ester condensation. The derivative synthesized was Boc-Ile-Gln-Asn-resin and the crude tripeptide was recovered in 94% yield, 65% after crystallization from water/2-propanol. Inasmuch as Ile-Gln-Asn-NH_2 is a possible candidate in our continued search for the MSH-releasing factor[28,29] it was deemed necessary to confirm the physical chemical properties of the tripeptide prepared by an independent method using classical peptide synthesis (Figure 2). The benzyl ester Boc-Ile-Gln-Asn-OBzl[30] was converted to the amide with ammonia in methanol and then deprotected with HF in the presence of anisole. Both classical and solid-phase products were identical.

Experimental Section

***p*-Anisoylation of Copolystyrene–1% Divinylbenzene.** To a stirred suspension of 50 g of polystyrene resin cross-linked with 1% divinylbenzene (Bio-Beads X-1, 200–400 mesh, Bio-Rad Corp., Richmond, Calif.) in 500 ml of nitrobenzene at 10 °C were added simultaneously solutions of anhydrous aluminum chloride (21.4 g, 0.16 mol) in 75 ml of nitrobenzene and *p*-anisoyl chloride (13.7 g, 0.086 mol) in 50 ml of nitrobenzene. The mixture was heated to 35 °C for 4 h and cooled to 10 °C. HCl (4 N, 250 ml) was added, and the mixture was then heated to 60 °C, diluted with 250 ml of water, and stirred for an additional 5 min. The solid was recovered by suction filtration. The resin was then washed with tetrahydrofuran (500 ml), tetrahydrofuran–water (1:1 v/v) (500 ml), water (500 ml), water–methanol (1:1 v/v) (500 ml), and methanol (500 ml) and dried in vacuo at 45 °C. Recovery was 58.5 g; the product exhibited a strong carbonyl absorption at 1675 cm^{-1} (KBr pellet).

Anisylformylaminomethylpolystyrene–1% Divinylbenzene (Leuckart Reaction). The *p*-anisoylated Bio-Beads (58.5 g), ammonium formate (165 g), formamide (200 ml), 88% formic acid (250 ml), and nitrobenzene (600 ml) were added to a 2-l., three-necked, round-bottomed flask, fitted with a mechanical stirrer, thermometer, and a Dean-Stark recovery trap. The reaction mixture was heated to 165–175 °C while stirring. After 2 h 50 ml of 88% formic acid was added and another 50 ml of 88% formic acid every hour. After a total of 5 h the reaction mixture was cooled to room temperature and the solid isolated by filtration, washed with tetrahydrofuran (750 ml), tetrahydrofuran–ethanol (1:1 v/v) (750 ml), and ethanol (750 ml).

Anisylaminomethylpolystyrene–1% Divinylbenzene. The Leuckart reaction product, still wet with ethanol, was suspended in 400 ml of ethanol. Concentrated HCl (175 ml) was added and the mixture was stirred under reflux for 2 h. After cooling to room temperature, the solid was collected by filtration and washed by suspension for several hours in ethanol (4 × 250 ml) until the wash gave a negative silver chloride test. The polymer was dried to a constant weight (59.9 g). The *p*-methoxybenzhydrylamine resin contains 0.87% nitrogen, which is equivalent to 0.62 mequiv amine/g resin.

Determination of Secondary Amine Content of *p*-Methoxybenzhydrylamine Resin (Demjanov Reaction). One gram of the above described resin was suspended in 200 ml of *p*-dioxane and 2 N HCl (60 ml) was added with stirring over 30 min. Sodium nitrite (0.69 g, 0.01 mol) in water (20 ml) was added and the reaction mixture was then stirred at room temperature for 2 h. The product was recovered by filtration and washed with chloroform (50 ml) and methanol (150

ml), and then air dried. The resin was ninhydrin negative (31). Elemental analysis for nitrogen gave a value of 0.07% N, which corresponds to 0.02 mequiv of secondary amine/g resin.

Comparison of Leuckart Reaction vs. Oxime Reduction in the Preparation of Benzhydrylamine Resins. Benzoylated copolystyrene–1% divinylbenzene was prepared as described for the *p*-anisoylated resin. Benzoylated resin (15g) was converted to the oxime by the method described by Pietta et al.[9] Two aliquots of the resulting oxime were then reduced with bis(2-methoxyethoxy)aluminum hydride (Vitride) in benzene using two modes of addition: (1) addition of oxime resin to a stirred excess Vitride solution in benzene, and (2) addition of Vitride solution to a stirred suspension of excess oxime resin in benzene. The third aliquot of benzoylated resin was converted to benzhydrylamine resin by the Leuckart reaction described above. The resulting products were analyzed for total amine content, subjected to the Demjanov reaction, and analyzed for secondary amine content (Table I).

Preparation of Dipeptides on *p*-Methoxybenzhydrylamine Resin. In a 100-ml solid-phase reaction vessel (Schwarz-Mann), 3 g of *p*-methoxybenzhydrylamine hydrochloride resin (0.62 mequiv amine/g polymer) was shaken with 35 ml of 10% v/v *N,N*-diisopropylethylamine in CH_2Cl_2 for 10 min. After removal of the base the resin was treated with 4.66 mequiv of the appropriate *tert*-butyloxycarbonyl amino acid (2.5-fold excess) in 20 ml of CH_2Cl_2 and 0.96 g (4.66 mequiv) of DCCI in 20 ml of the same solvent for 40 min at room temperature. The resin was washed with 35-ml portions each of 25% acetic acid in CH_2Cl_2, twice with $CHCl_3$, and twice with CH_2Cl_2. In the instances when the ninhydrin test was positive, the coupling was repeated using a 1.16-fold excess. In case of a negative ninhydrin test a 150-mg sample was withdrawn for amino acid analysis.

The Boc protecting group was removed by treatment of the resin with 35 ml of 33% (v/v) trifluoroacetic acid–methylene chloride for 45 min at room temperature. After treatment with two 35-ml portions of *N,N*-diisopropylethylamine–CH_2Cl_2 (8% by volume) for 10 min, the resin was washed with 35-ml portions each of $CHCl_3$ and CH_2Cl_2. The deprotected resin was treated with *tert*-butyloxycarbonylalanine (0.88 g, 4.66 mequiv) in 20 ml of CH_2Cl_2 and DCCI (0.96 g, 4.66 mequiv) in 20 ml of the same solvent for 40 min at room temperature. The resin was then washed as previously described, a small sample subjected to the ninhydrin test,[31] and recoupling was performed if necessary. A sample of dipeptide-substituted resin was hydrolyzed in 1:1 propionic acid–concentrated HCl at 135 °C for 4 h[25] and analyzed for amino acid content (see Table II).

Cleavage with HF of Alanylphenylalanine Amide from *p*-Methoxybenzhydrylamine Resin. Boc-Ala-Phe-resin (1.25 g) was placed in a Teflon cleavage vessel, 6.5 ml of anisole was added, and 20 ml of anhydrous HF was collected. The mixture was stirred for 45 min at room temperature. The HF was removed under reduced pressure and the resin dried in vacuo to remove the anisole. The dipeptide was extracted with 4% aqueous acetic acid (50 ml). Lyophilization of the extract yielded 111 mg (92%) of dipeptide amide hydrogen fluoride salt; TLC (*n*-BuOH–AcOH–H_2O, 4:1:1) shows one spot, R_f 0.37 as revealed by chloride tolidine reagent.[32] Anal. Calcd for $C_{12}H_{18}N_3O_2F \cdot H_2O$: C, 52.7; H, 7.38; N, 15.4. Found: C, 52.5; H, 7.20; N, 15.1. Amino acid analysis after 16 h of hydrolysis in 1:1 propionic acid–concentrated HCl at 135 °C gave the following molar ratios: Phe, 1.0; Ala, 0.98.

Z-L-Pyroglutamyl-N^{im}-tosyl-L-histidyl-L-prolyl-*p*-methoxybenzhydrylamine Resin. Boc-proline-substituted resin (5 g) prepared as described (Table I) was utilized for the preparation of the hormone. The following cycles of deprotection, neutralization, and coupling were carried out for the introduction of each of the other two residues (His, <Glu) in the peptide: (1) cleavage of the Boc group by two successive treatments with 40 ml of 33% trifluoroacetic acid in CH_2Cl_2 for 45 min at room temperature; (2) one wash with 40 ml of CH_2Cl_2; (3) treatment with three 40-ml portions of *N,N*-diisopropylethylamine in CH_2Cl_2 (8% by volume); (4) addition of 7.76 mequiv (2.5-fold excess) of Boc-N^{im}-tosyl-His in 20 ml of CH_2Cl_2 and 5 min of shaking; (5) addition of 7.76 mequiv of DCCI in 20 ml of CH_2Cl_2 followed by overnight reaction period; (6) one wash with 40 ml of 25% acetic acid in CH_2Cl_2; (7) one wash with 40 ml of $CHCl_3$; (8) ninhydrin test (if negative, go to step 9); (9) repetition of steps 1–8, this time coupling Z-<Glu, 7.76 mequiv; (10) one wash with 40 ml of anhydrous ethanol. After air drying 6.37 g of resin tripeptide was recovered.

L-Pyroglutamyl-L-histidyl-L-proline Amide (TRH). Z-<Glu-N^{im}-tosyl-His-Pro-NH_2 (1.29 g) was removed from the resin with HF as described above. The resin–peptide mixture was washed with anhydrous ethyl ether (3 × 25 ml) and the peptide extracted with 40 ml of MeOH. Evaporation of solvent yielded 189 mg of crude tripeptide. The hormone was purified on a silica gel column (13 g, 12 × 2 cm) by elution with MeOH–$CHCl_3$ (3:7 v/v). Yield of TRH was 132 mg (78%). The R_f on TLC was within experimental error when compared with an authentic sample in three different solvent systems: R_f 0.24 (*n*-BuOH–AcOH–EtOAc–H_2O, 1:1:1:1); R_f 0.63 ($CHCl_3$–MeOH–NH_4OH, 6:4.5:2); and R_f 0.40 (EtOH–H_2O, 7:3); $[\alpha]^{24}D$ −40° (c 1, MeOH). Amino acid analysis after 24 h of hydrolysis with 6 N HCl gave the following molar ratios: Pro, 1.0; Glu, 1.0; His, 0.99; and NH_3, 0.95.

Boc-L-Isoleucyl-L-glutaminyl-L-asparaginyl-*p*-methoxybenzyhydrylamine Resin. The *p*-methoxybenzhydrylamine hydrochloride resin (5 g) was shaken with 45 ml of 10% by volume *N,N*-diisopropylethylamine in CH_2Cl_2 for 10 min. After removal of the base the resin was treated with 4.6 g (fourfold excess) of Boc-Asn-ONp and 0.4 g of *N*-hydroxybenzotriazole in 75 ml of *N*-methyl-2-pyrrolidone for 16 h. The resin was washed with 70-ml portions each of CH_2Cl_2, absolute ethanol, 25% acetic acid in CH_2Cl_2, and CH_2Cl_2. The Boc protecting group was removed by treatment with 70 ml of 33% by volume trifluoroacetic acid in CH_2Cl_2 for 45 min at 23 °C. After treatment with two 70-ml portions of *N,N*-diisopropylethylamine–CH_2Cl_2 (8% by volume) for 10 min the resin was washed with two 70-ml portions of CH_2Cl_2. Next the peptide chain was elongated using Boc-Gln-ONp as acylating agent under the conditions described above. After 16 h the resin dipeptide gave a faint positive ninhydrin test. Hence, the resin dipeptide was acylated with acetic anhydride (1 ml) in the presence of *N,N*-diisopropylethylamine (1 ml) in *N*-methyl-2-pyrrolidone (75 ml) for 60 min. After acylation the resin dipeptide gave a negative ninhydrin test. The resin dipeptide was then carried through a deprotection and base treatment cycle. The following cycles were carried out for the coupling of Boc-Ile (at a 2.5-fold excess): a solution of Boc-Ile (7.75 mequiv, 1.86 g) and *N*-hydroxybenzotriazole (1.57 g, 11.6 mequiv) in 50 ml of *N*-methyl-2-pyrrolidone was added to the resin dipeptide and shaken for 10 min. At this point a solution of DCCI (1.60 g, 7.75 mequiv) in 20 ml of CH_2Cl_2 was added to the mixture while shaking was continued for 4 h. Since the ninhydrin test was positive a second coupling was carried out using Boc-Ile (1.20 g, 5 mequiv) and *N*-hydroxybenzotriazole (1 g, 7.5 mequiv) in 50 ml of *N*-methyl-2-pyrrolidone followed by DCCI (1 g, 5 mequiv) as described. Shaking continued for 4 h until the ninhydrin test was negative. The tripeptide resin was washed with 70-ml portions of *N*-methyl-2-pyrrolidone, $CHCl_3$, anhydrous ethanol, and twice with CH_2Cl_2. The resin tripeptide was then dried in vacuo (5.95 g, 93%).

L-Isoleucyl-L-glutaminyl-L-asparaginamide·HF. Boc-Ile-Gln-Asn-resin (1.3 g) was placed in a Teflon cleavage vessel and 4 ml of anisole was added. Treatment with 20 ml of anhydrous HF for 45 min with stirring at 0 °C liberated the peptide amide which was isolated as described above. Yield of crude product was 240 mg (94% based on the substitution level of the starting resin). Crystallization from water/2-propanol gave 164 mg (65%): R_f 0.19 (*n*-BuOH–AcOH–H_2O, 3:1:1); R_f 0.42 (*n*-BuOH–AcOH–Pyr–H_2O, 15:3:10:6); R_f 0.35 (EtOH–H_2O, 7:3); $[\alpha]^{23}D$ −40° (c 0.65, 1 N AcOH).

Amino acid analysis of a sample hydrolyzed for 22 h with 6 N HCl gave the following molar ratios: Asp, 1.0; Glu, 1.0; Ile, 0.93; and NH_3, 2.8.

Boc-L-Isoleucyl-L-glutaminyl-L-asparaginamide. Amidation of Boc-Ile-Gln-Asn-OBzl (375 mg, 0.67 mequiv) gave 300 mg (94.5%) of product: mp 232–234 °C; $[\alpha]^{24}D$ −10° (c 1, AcOH); R_f 0.39 (*n*-BuOH–AcOH–H_2O, 4:1:1). Anal. Calcd for $C_{20}H_{36}N_6O_7 \cdot \frac{1}{2}MeOH$: C, 50.4; H, 7.84; N, 17.2. Found: C, 50.6; H, 7.98; N, 17.1.

L-Isoleucyl-L-glutaminyl-L-asparaginamide HF. Boc-Ile-Gln-Asn-NH_2 (250 mg, 0.53 mequiv) was suspended in 2 ml of pure anisole and subjected to HF deprotection for 10 min at 0 °C by the method described above. After evaporation of the HF-anisole, the residue was dissolved in 20 ml of water, the aqueous solution washed with ethyl ether (2 × 20 ml), and the product recrystallized from water/2-propanol (190 mg, 91.9%): R_f 0.19 (*n*-BuOH–AcOH–H_2O, 3:1:1); R_f 0.42 (*n*-BuOH–AcOH–Pyr–H_2O, 15:3:10:6); R_f 0.35 (EtOH–H_2O, 7:3); $[\alpha]^{24}D$ −41° (c 0.75, 1 N AcOH). Amino acid analysis of a sample hydrolyzed for 22 h with 6 N HCl gave the following molar ratios: Asp, 1.0; Glu, 1.0; Ile, 0.98; and NH_3, 3.0.

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Registry No.—Copolystyrene-divinylbenzene, 9003-70-7; *p*-anisoyl chloride, 100-07-2; anisylformylaminomethane, 3400-22-4; anisylaminomethane, 5961-59-1; *p*-methoxybenzhydrylamine, 2538-34-3; *p*-methoxybenzhydrylamine HCl, 5267-46-9; *tert*-butyloxycarbonylalanine, 15761-38-3; alanylphenylalaninamide HF, 60195-80-4; Boc-Ala-Phe, 2448-58-0; Z-L-pyroglutamyl-N^{im}-tosyl-L-histidyl-L-prolyl, 60195-81-5; Boc-proline, 15761-39-4; Boc-N^{im}-tosyl-His, 35899-43-5; Z-<Glu, 32159-21-0; L-pyroglutamyl-L-histidyl-L-proline amide, 24305-27-9; Z-<Glu-N^{im}-tosyl-His-Pro-NH_2, 35899-45-7; Boc-L-isoleucyl-L-glutaminyl-L-asparagine, 52574-14-8; Boc-Asn-ONp, 4587-33-1; Boc-Gln-ONp, 15387-45-8; Boc-Gln-Asn-ONp, 60195-82-6; Boc-Ile, 13139-16-7; L-iscleucyl-L-glutaminyl-L-asparaginamide HF, 60195-83-7; Boc-L-iscleucyl-L-glutaminyl-L-asparaginamide, 60209-57-6; Boc-Ile-Gln-Asn-O-Bzl, 60209-58-7; Boc-Gly, 4530-20-5; Boc-Phe, 13734-34-4; Boc-Val, 13734-41-3; Boc-Glu(OBzl), 30924-93-7; Boc-Ala-Gly, 28782-78-7; Boc-Ala-Pro, 33300-72-0; Boc-Ala-Phe, 2448-58-0; Boc-Ala-Val, 60209-59-8; Boc-Ala-Glu(OBzl), 60209-60-1.

References and Notes

(1) This work was supported in part by USPHS Grant AM-18399. Nomenclature follows the tentative rules of the IUPAC-IUB Commission on Biochemical Nomenclature, *J. Biol. Chem.*, **247**, 977 (1972); **250**, 3215 (1975). Additional abbreviations used: Boc, *tert*-butyloxycarbonyl; Bzl, benzyl; DCCI, dicyclohexylcarbodiimide; ONp, *p*-nitrophenyl ester.
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Synthetic Approaches to 10-Epieudesmane Sesquiterpenes. A Synthesis of Intermedeol

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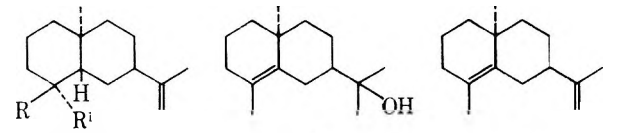
A number of synthetic approaches to the biosynthetically important 10-epieudesmane sesquiterpene intermedeol (1) have been explored. Reduction of epi-α-cyperone (6) with lithium–ammonia and oxidation of the intermediate enolate gave acetoxy ketone **9** as the major product. However, **9** could not be deoxygenated to intermedeol. Reduction of **6** with lithium in ammonia followed by trapping of the derived enolate with diethyl chlorophosphate gave enol phosphate ester **11**. Hydrogenolysis of **11** gave a mixture of three hydrocarbons, **3**, **4**, and **12**, while hydrogenolysis of the related enol phosphate **13** gave only one olefin (**15**) on reduction. The synthesis of **1** from α-agarofuran (**18**) was accomplished by the sequence conversion to the 3,4-oxide (**19**), reduction of **19** to 4β-hydroxydihydroagarofuran (**20**), and lithium–ethylenediamine reduction of **20** to diol **23**, which on partial dehydration afforded intermedeol (**1**). The C-4 epimer of intermedeol, **5**, was synthesized from 10-epieudesma-4,11-diene (**3**) by epoxidation to **24**, dissolving metal reduction of which gave **5**. The structure of **24** was confirmed by its conversion to 4α-hydroxydihydroagarofuran and that of **5** by reduction to the dihydro compound (**26**), which was synthesized by an alternate route.

In the generally accepted biosynthetic scheme[1] for the nonisoprenoid nootkatone–valencene group of sesquiterpenes, 10-epieudesmanes, such as intermedeol (**1**),[2] 10-epi-γ-eudesmol (10-epieudesm-4-en-11-ol, **2**),[3] and the isomeric 10-epieudesmadienes (**3** and **4**)[4] play a key role. These compounds can all, at least in principle, undergo the carbonium ion type rearrangement suggested many years ago by Robinson for the biosynthesis of eremophilone from a eudesmane precursor.[5] In addition, at the time when this work was initiated, an additional sesquiterpenoid alcohol, "paradisiol" (**5**), the C-4 epimer of intermedeol, had been reported.[6] However, the infrared spectrum of "paradisiol" and intermedeol indicated that these compounds were identical, and subsequent synthetic and NMR studies showed that intermedeol was correctly represented by structure **1**,[2c] as originally suggested by Zalkow.[2a] Subsequent direct comparison showed that these compounds are in fact identical.[7]

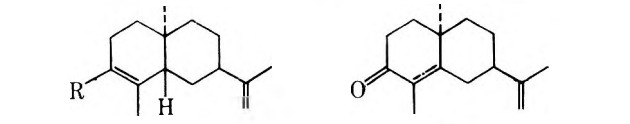
The obvious starting point for a synthesis of either inter-

medeol (1) or "paradisiol" (5) is epi-α-cyperone (10-epieudesma-4,11-dien-3-one, 6), the well-known annelation product of dihydrocarvone and ethyl vinyl ketone.[8] This molecule contains all 15 carbon atoms present in the desired products, has the requisite stereochemistry at C-7 and C-10, and is functionalized in a manner which should facilitate the stereoselective synthesis of 1 and/or 5.



1, R = OH; R¹ = CH₃
5, R = CH₃; R¹ = OH

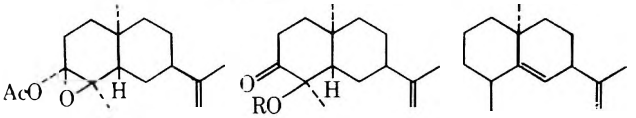
2



3

4, R = H
7, R = OAc
11, R = O₂P(OC₂H₅)₂

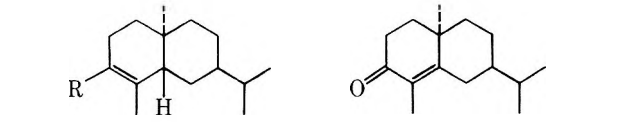
6



8

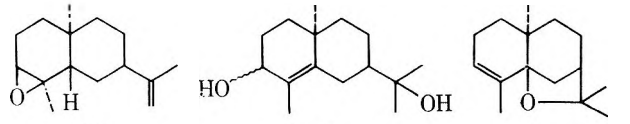
9, R = Ac
10, R = H

12



13, R = O₂P(OC₂H₅)₂
15, R = H

14



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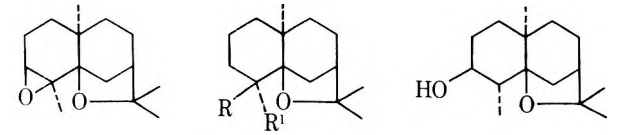
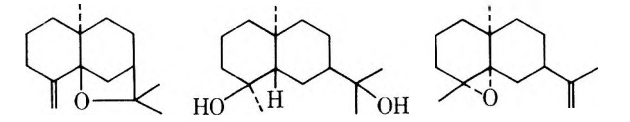
18



19

20, R = OH; R¹ = CH₃
25, R = CH₃; R¹ = OH

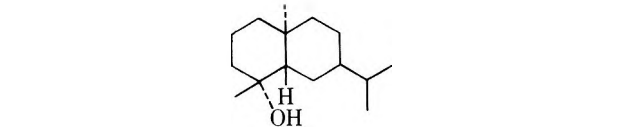
21



22

23

24



26

The initial approach to these sesquiterpenes introduced the correct stereochemistry at C-5 by lithium–ammonia reduction of enone 6 to the enolate anion. In an effort to effect oxygenation at C-4, the enolate was oxidized with lead tetraacetate[9] to give a mixture of products. Repeated chromatography of this mixture gave, in poor yield, a crystalline acetoxy ketone and a hydroxy ketone. The presence of relatively low field methyl singlets in their NMR spectra indicated that both compounds were oxygenated at C-4. They did not, however, have the same stereochemistry at this center since alkaline hydrolysis of the acetoxy ketone gave a ketol different from that obtained from the original reaction mixture. The stereochemistry of these compounds was resolved as follows: first, the same acetoxy ketone could be obtained in a three-step sequence by lithium–ammonia reduction of ketone 6 to the enolate and trapping this anion with acetic anhydride to give enol acetate 7. Treatment of 7 with *m*-chloroperbenzoic acid in ether[10] gave an unstable epoxy acetate, which on mild acid treatment gave the acetoxy ketone. By analogy with the acid-catalyzed rearrangement of the epoxy acetate derived from 3-acetoxy-2-cholestene,[11] the configuration of the C-4 acetate group in the acetoxy ketone should be opposite to that of the C-3 acetate in the precursor epoxide. Normal steric arguments lead to the conclusion that attack of peracid should occur from the less hindered β face of 7 leading to structure 8 for the epoxy acetate, and 9, 4β-acetoxy-5-epi-10-epieudesm-11-en-3-one, for the derived ketone.

A second factor indicating that 9 has the indicated stereochemistry follows from the observation that basic hydrolysis of the acetate gives a hydroxy ketone (10) in which the NMR signal for the angular methyl group appears at very slightly higher field (0.03 ppm) than that of the corresponding acetate (9). This is expected if the oxygen functionalities are both equatorial as they are in 9 and 10.[12] The hydroxy ketone obtained from the original lead tetracetate oxidation was different from 10, and on the basis of its spectral properties is probably the C-4 epimer of 10.

A number of attempts were made to remove the oxygen atom at C-3 in 9 and 10, including attempted formation of the ethylene thioketal of 9 and reduction of 9 and 10 to mixtures of diols followed by formation of the 3-tosylate or -mesylate. In all cases either no reaction occurred or gross mixtures were obtained.

In a second approach to intermedeol, enone 6 was converted to enol phosphate ester 11 in an attempt to prepare diene 4.[13] Hydrogenolysis of 11 with lithium–ethylamine led to partial reduction of the isolated double bond, while the use of lithium–ammonia gave a mixture of three dienes. The best results from the latter reductions were obtained using sodium–ammonia–*tert*-butyl alcohol for a short period of time, giving a mixture containing 42% of 4. Repeated preparative GLC gave pure 4, the properties of which agree with those reported for the natural product.[4] The major component of this mixture (46%) had spectral properties consistent with those reported for 10-epieudesma-4,11-diene (3).[4] The minor component of the mixture (12%) was assigned the structure 4-epi-10-epieudesma-5,11-diene (12) on the basis of its NMR spectrum, which shows a methyl doublet (J = 6 Hz) at δ 0.92, a methyl singlet at δ 1.00, the doubly allylic proton at C-7 as a multiplet at δ 2.52, and a one-proton vinyl quartet at δ 4.90. The stereochemistry at C-4 (equatorial methyl) is assigned on the basis of thermodynamic stability and the relatively small (6 Hz) coupling constant for the secondary methyl group.[14]

Although the lithium–ethylamine reduction of enol phosphate esters has been reported to proceed with virtually complete regiospecificity,[13] apparently the use of ammonia as a medium for these reactions leads to the equilibration of an intermediate carbanion. That the reduction is regiospecific in ethylamine was confirmed when it was found that the enol phosphate ester (13) derived from 10-epieudesm-4-en-3-one (14) was reduced cleanly with lithium–*tert*-butyl alcohol in this medium to give 5-epi-10-epieudesm-3-one (15).

Controlled oxidation of diene 4 gave 3β,4β-oxido-5-epi-10-epieudesm-11-ene (16) in good yield and greater than 70% purity;[15] however, following the disclosure by Zalkow[16] that a synthesis of intermedeol had been accomplished by the

lithium aluminum hydride reduction of epoxide **16**, this synthetic approach was abandoned.

In connection with some other work, the oxidation of 10-epieudesm-4-ene-3,11-diol (**17**)[17] with Jones reagent was attempted. However, rather than the expected ketone, the major product of this reaction was α-agarofuran (**18**).[17,18] Although the conversion of **17** and **18** by mild acid treatment has been reported,[18] the use of Jones reagent gives a product which is considerably cleaner than that obtained by the Canadian group.[19] Conversion of α-agarofuran to the 3β,4β-oxide (**19**),[20] followed by lithium aluminum hydride reduction, gave a 5:1 mixture of isomeric alcohols. The major product of the reduction was assigned the structure 4β-hydroxydihydroagarofuran (**20**) on the basis of its NMR spectrum (see Experimental Section), while the minor component of the mixture was assumed to be the 3β-hydroxy isomer (**21**) from similar considerations and its oxidation to the known 3-ketone.[18] The equatorial nature of the hydroxyl group in alcohol **20** was confirmed through its dehydration with thionyl chloride in pyridine to give β-agarofuran (**22**)[21] as the major product. It is noteworthy that reduction of epoxide **19** gives less than 20% of the product arising from normal trans diaxial opening of the oxide, while the epoxide which is a precursor to intermedeol gives ca. 60% of the axial secondary alcohol under similar conditions.[15]

Following the conditions used for the cleavage of the tetrahydrofuran ring of α-agarofuran,[20] reduction of alcohol **20** with lithium–ethylenediamine afforded as the major product a diol, assigned the structure 5-epi-10-epieudesma-4β,11-diol (**23**) on the basis of its NMR spectrum (see Experimental Section) and its preparation from natural intermedeol[2a,b,22] by oxidation with *m*-chloroperbenzoic acid and reduction of the resulting mixture of epimeric 11,12-epoxides with lithium aluminum hydride.

A number of attempts were made to selectively functionalize diol **23** in order to achieve a regioselective synthesis of intermedeol; unfortunately, this goal could not be achieved. However, dehydration of **23** using von Rudloff's procedure[23] gave a mixture of five compounds, of which intermedeol was the principal component. Pure intermedeol, identical in all respects with natural material, could be isolated from this mixture by careful chromatography.

As noted above, at the time these studies were initiated, the C-4 epimer of intermedeol, 5-epi-10-epieudesm-11-en-4α-ol (**5**), was considered to be a naturally occurring sesquiterpene.[6] Although this compound has subsequently been shown to be intermedeol,[2c,7] its synthesis remains of interest since a compound of this structure is a plausible natural product, because it is a substance having the structural and stereochemical features of a compound which could be found in nature. Also samples of **5** were needed for reference in connection with other work. Since alcohol **5** has an axial hydroxyl group, the obvious method of synthesis would involve reductive cleavage of an epoxide, either the 3α,4α-epoxide derived from diene **4**, or the 4α,5α-epoxide derived from diene **3**. In view of the problems encountered in preparing quantities of pure **4**, the latter approach was chosen.

10-Epieudesma-4,11-diene (**3**) occurs naturally and has been synthesized by desulfurization of the thioketal of enone **6**.[4] In an alternative approach, the mixture of epimeric alcohols obtained by reduction of enone **6**[17] was converted to the mixed acetates, which were then reduced to **3** by lithium in ammonia in an overall yield of 84% from enone **6**. Treatment of diene **3** with 1 equiv of *m*-chloroperbenzoic acid gave the desired epoxide (**24**). The α orentation of the oxirane ring is based on analogy with the reported epoxidation of the dihydro derivative of **3**,[24] and the conversion of **24** to 4α-hydroxydihydroagarofuran (**25**). This conversion was effected by reaction of epoxide **29** with *m*-chloroperbenzoic acid to give the bis epoxide and reduction under mild conditions to the 4α,5α-oxido-11-ol which on treatment with toluenesulfonic acid gave **25**.

Reduction of epoxide **24** with lithium–ammonia gave a single tertiary alcohol which on the basis of its NMR spectrum was either **5** or its C-5 epimer. That this alcohol was in fact **5** was confirmed by hydrogenation to 5-epi-10-epieudesman-4α-ol (**26**), a compound which had been synthesized earlier during the work leading to the confirmation of the identity of "paradisiol" and intermedeol.[2c] Alcohol **26** of known stereochemistry at both C-4 and C-5 was prepared from olefin **15** by conversion to the bromohydrin, a reaction known to occur by trans-diaxial addition of bromine and hydroxyl, and subsequent reduction with lithium aluminum hydride.[2c]

Experimental Section[25]

3-Acetoxy-5-epi-10-epieudesma-3,11-diene (7). A solution of 1.55 g of 10-epieudesma-4,11-dien-3-one (**6**)[8] in 20 ml of dry ether and 100 ml of liquid ammonia was reduced with lithium to the enolate of 5-epi-10-epieudesm-11-en-3-one as described below. The ammonia was replaced by 75 ml of dry benzene, and 30 ml of acetic anhydride was added slowly. The reaction mixture was stirred under nitrogen at room temperature for 1 h and poured into aqueous sodium bicarbonate, the aqueous layer was drawn off, washed with water and brine, and dried, and the solvent was removed at reduced pressure to give 1.343 g of yellow oil. This oil was dissolved in hexane-benzene (2:1) and chromatographed on Woelm silica gel. Elution with benzene gave 0.577 g of enol acetate **7** as a colorless liquid: ir 1755, 1687 cm^{-1}; NMR δ 0.91 (s, 3 H, CH_3), 1.45 (s, 3 H, $CH_3C=$), 1.72 (s, 3 H, $CH_3C=$), 2.10 (s, 3 H, CH_3CO), 4.84 (m, 2 H, $CH_2=$). For analysis, a small sample of this material was distilled at 130–140 °C (bath temperature, 0.1 mm).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.93; H, 9.85.

4β-Acetoxy-5-epi-10-epieudesm-11-en-3-one (9). A. A solution of 0.725 g of 10-epieudesma-4,11-dien-3-one (**6**) in 15 ml of dry ether was added to ca. 50 ml of dry distilled liquid ammonia. Lithium ribbon, just sufficient to impart a permanent blue color, was added and the reaction mixture was stirred at reflux for 50 min. The ammonia was evaporated in a stream of dry nitrogen while 50 ml of dry benzene was added. Following the removal of the ammonia, 5.10 g of freshly dried lead tetraacetate was added in portions and the reaction mixture was stirred at room temperature in a nitrogen atmosphere for 1.5 h. The reaction mixture was filtered through Celite, washed with water and brine, and dried and the solvent was removed at reduced pressure to give 0.541 g of yellow oil. The crude product was dissolved in hexane–benzene (1:1) and chromatographed on 35 g of Woelm activity III neutral alumina. Elution with these solvents gave 0.173 g of a mixture of 4-epi-5-epi-10-epieudesm-11-en-3-one and the starting dienone, while elution with benzene afforded 0.106 g of crude acetoxy ketone. A total of 1.704 g of material obtained in this manner from three runs was combined, dissolved in benzene, and chromatographed on 75 g of Woelm activity I silica gel. Elution with benzene–ethyl acetate (9:1) gave 1.345 g of an oil, which although homogeneous to TLC (silica gel G, benzene–ethyl acetate, 8:1) was obviously a mixture from the NMR spectrum. This mixture was distilled, bp 150–160 °C (bath temperature, 0.15 mm) to give 0.661 g of a mixture of essentially the same composition, which was taken up in benzene–hexane (1:1) and chromatographed on 30 g of Woelm activity II neutral alumina. The first fractions eluted with these solvents gave mixtures of unreacted ketone and the desired acetoxy ketone, while later fractions afforded 0.065 g of pure material as a crystalline solid. Recrystallization from aqueous methanol gave the analytical sample: mp 90–91 °C; mass spectrum *m/e* (rel intensity) 278 (7), 236 (29), 235 (38), 219 (30), 218 (100); ir 1735, 1640, 879 cm^{-1}; NMR δ 1.22 (s, 3 H, CH_3), 1.40 [s, 3 H, $C(OCOCH_3)CH_3$], 1.72 (br s, 3 H, $CH_3C=$), 2.01 (s, 3 H, CH_3CO_2), 4.62, 4.72 (m, 1 H each, $C=CH_2$).

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.51; H, 9.52.

The later benzene fractions and benzene–methylene chloride (4:1) gave 0.047 g of an oil, which on the basis of its spectral properties was identified as **4α-hydroxy-5-epi-10-epieudesm-11-en-3-one:** mass spectrum *m/e* (rel intensity) 236 (7), 219 (18), 218 (75), 203 (55), 193 (15), 190 (15), 179 (21), 175 (100), 162 (23), 161 (29), 149 (23), 148 (29), 147 (28); ir 3520, 1701, 1638 cm^{-1}; NMR δ 1.20 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3CO), 1.72 (br s, $CH_3C=$), 4.90 (br s, 2 H, $CH_2=$).

B. To a stirred solution of 0.538 g of 3-acetoxy-5-epi-10-epieudesma-3,11-diene (**7**) in 15 ml of ether at 0°C was added slowly a so-

lution of 0.496 g of *m*-chloroperbenzoic acid (72%) in 10 ml of ether. The reaction mixture was stirred at ambient temperature for 24 h, then shaken with successive portions of 10% aqueous sodium bisulfite, saturated sodium bicarbonate, water, and brine, and dried, and the solvent was removed at reduced pressure with gentle warming. The resulting yellow oil showed a carbonyl peak in the ir at 1755 cm^{-1}, and was, without purification, taken up in 15 ml of chloroform, treated with 0.025 g of toluenesulfonic acid, and stirred at room temperature for 18 h. The reaction mixture was washed with successive portions of saturated aqueous sodium bicarbonate and brine and dried and the solvent was removed to give 0.379 g of yellow oil, which was dissolved in benzene and chromatographed on Woelm silica gel. Elution with benzene–ethyl acetate (9:1) gave 0.140 g of acetoxy ketone **9**.

4β-Hydroxy-5-epi-10-epieudesm-11-en-3-one (10). A solution of 0.157 g of acetoxy ketone **9** in 10 ml of 1% methanolic potassium hydroxide was heated at reflux in a nitrogen atmosphere for 18 h. The reaction mixture was cooled, diluted with water, and extracted with methylene chloride. The extract was washed with water and brine and dried, and the solvent was removed to give 0.100 g of a yellow oil. TLC (silica gel G, benzene–ethyl acetate, 8:1) indicated that this material was almost exclusively one compound and it was purified by dissolving it in benzene–ethyl acetate (8:1) and filtering it through 3 g of Woelm silica gel to give 0.059 g of a pale yellow oil: ir 3636, 1712 cm^{-1}; mass spectrum *m/e* (rel intensity) 236 (17), 219 (58), 218 (75), 204 (25), 193 (100), 175 (75); NMR δ 1.22 (s, 6 H, CH_3), 1.75 (m, 3 H, CH_3C=), 4.82 (m, 2 H, CH_2=).

Deoxygenation of 10-Epieudesma-4,11-dien-3-one. To 125 ml of redistilled liquid ammonia was added a solution of 5.21 g of 10-epieudesma-4,11-dien-3-one (**6**) in 40 ml of dry ether. Sufficient lithium ribbon to impart a permanent blue color was added and the mixture stirred at reflux for 0.5 h. An additional 75 ml of dry ether was added and the ammonia was evaporated with gentle warming using a stream of dry nitrogen. During the evaporation of ammonia, sufficient ether was added to maintain a volume of ca. 100 ml. A solution of 10 ml of diethyl chlorophosphate in 75 ml of dry ether was added and the reaction mixture stirred at room temperature for 1 h. The phosphate ester was isolated by pouring the reaction mixture into water, drawing off the aqueous layer, washing the ethereal solution with successive portions of saturated aqueous sodium bicarbonate and brine, drying, and removing the solvent in vacuo with gentle warming. The crude phosphate ester showed characteristic infrared absorption at 1070 cm^{-1}; TLC indicated the presence of 5-epi-10-epieudesm-11-en-3-one as the only major impurity and this material was reduced without additional purification.

The crude phosphate ester was dissolved in a mixture of 75 ml of dry ether and 75 ml of dry *tert*-butyl alcohol and added to ca. 500 ml of redistilled liquid ammonia. To this solution was added 2.30 g of sodium and the reaction mixture stirred at reflux 8 min. The reaction was quenched by the addition of 100 ml of ethanol and the ammonia was removed in a stream of nitrogen. The residue was taken up in hexane and water, the aqueous phase drawn off, the hexane extracts washed with water and 10% hydrochloric acid and dried, and the solvent removed to give 3.66 g of yellow oil, which was dissolved in hexane and chromatographed on 110 g of Merck basic alumina. Elution with hexane gave 1.15 g of a mixture of hydrocarbons which upon GLC (OV-17, 200 °C) showed the presence of three compounds, in a ratio of 12:46:42 in order of increasing retention time. A small quantity of the mixture was separated by preparative GLC for characterization to give respectively **4-epi-10-epieudesma-5,11-diene (12)**, NMR δ 0.92 (d, 3 H, *J* = 6 Hz, CH_3CH), 1.00 (s, 3 H, CH_3), 1.78 (d, 3 H, *J* = 1 Hz, CH_3C=), 2.52 (m, 1 H, H-7), 4.45 (m, 2 H, CH_2=), 4.90 (q, *J* = 4 Hz, H-6);[26] **10-epieudesma-4,11-diene (3)**, identical with the material described below and the properties of which agree with those reported;[4] and **5-epi-10-epieudesma-3,11-diene (4)**, the ir and NMR spectra of which agree with those reported by Klein,[4] mass spectrum *m/e* (rel intensity) 204 (47), 189 (67), 161 (100).

5-Epi-10-epieudesm-3-ene (15). 10-Epieudesm-4-en-3-one (**14**) was treated with lithium and liquid ammonia followed by diethyl chlorophosphate as described in the deoxygenation of 10-epieudesma-4,11-dien-3-one (vide supra). The crude enol phosphate ester derived from 4.51 g of ketone was taken up in 20 ml of dry ether and 40 ml of dry *tert*-butyl alcohol and added to ca. 150 ml of redistilled ethylamine. Sufficient lithium ribbon was added to impart a permanent blue color and the reaction mixture stirred at reflux for an additional 10 min. The reaction was quenched with ethanol and the ethylamine evaporated in a stream of nitrogen. The residue was taken up in hexane, washed with successive portions of water, 10% hydrochloric acid, and 10% sodium carbonate, and dried and the solvent was removed at reduced pressure to give 2.80 g of pale yellow oil. The crude reaction product was taken up in hexane and chromatographed on 90 g of Merck alumina. Elution with hexane gave 1.13 of olefin **15** as a colorless oil: mass spectrum *m/e* (rel intensity) 206 (50), 191 (100), 177 (17), 163 (29), 151 (12); NMR δ 0.85 (s, 3 H, CH_3), 0.90 (d, 6 H, *J* = 7 Hz, isopropyl), 1.60 (br s, 3 H, CH_3C=CH), 5.30 (m, 1 H, CH_3C=C**H**). GLC (OV-17, 190 °C) indicated that this material was contaminated with a small amount (total, 17%) of three other compounds. For analysis a small quantity of the olefin was rechromatographed on Merck alumina.

Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.27; H, 12.68.

Further elution with hexane gave 0.35 g of 4-epi-5-epi-10-epieudesman-3-one as a waxy solid, mp 66–69 °C, after recrystallization from petroleum ether. The enantiomer is reported to melt at 66–67 °C.[27] The 2,4-dinitrophenylhydrazone had mp 224–226 °C after recrystallization from ethanol–ethyl acetate (lit. mp 222 °C for the enantiomer[27]).

3β,4β-Oxido-5-epi-10-epieudesm-11-ene (16). To a solution of 0.047 g of diene **4** in 3 ml of methylene chloride at 0 °C was added dropwise a solution of 0.049 g of *m*-chloroperbenzoic acid in 5 ml of the same solvent. The reaction mixture was stirred at 0 °C for 0.75 h and the excess peracid destroyed with 10% aqueous sodium bisulfite. The organic layer was drawn off and washed with successive portions of 5% aqueous sodium bicarbonate, water, and brine. After drying and removing the solvent at reduced pressure there was obtained 0.44 g of an oil which TLC (silica gel G, benzene–hexane, 1:1) showed to be contaminated with traces of another compound. No effort was made to purify this material. However, it had the expected spectral properties: mass spectrum *m/e* (rel intensity) 220 (10), 219 (52), 205 (100); NMR δ 0.80 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3CO), 1.68 (br s, CH_3C=), 2.77 (t, 1 H, *J* = 2 Hz, CHO), 4.55 (m, 2 H, CH_2=).

α-Agarofuran (18). To a solution of 10.6 g of 10-epieudesm-4-ene-3,11-diol[17] in 100 ml of permanganate stable acetone was added dropwise during 4 h 12 ml of Jones reagent. Dilution with water and extraction with ether gave 7.60 g of α-agarofuran, bp 69–72 °C (0.05 mm), the spectral properties of which were identical with those reported by Marshall.[17]

Lithium Aluminum Hydride Reduction of 3β,4β-Epoxydihydro-α-agarofuran. A solution of 4.80 g of epoxide **19**[20] in 100 ml of dry ether was added dropwise during 30 min to a stirred slurry of 1.20 g of lithium aluminum hydride in 100 ml of dry ether at −18 °C. The mixture was stirred for a further 4 h at this temperature and the product isolated in the usual manner. The oily crude material was found to be a 5:1 mixture of isomeric alcohols by GLC and was chromatographed on 50 g of neutral alumina. Elution with 5% benzene in pentane gave 3.0 g of **4β-hydroxydihydroagarofuran (20)**, bp 90 °C (0.05 mm), as the major product: ir 3575 cm^{-1}; NMR δ 1.10 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.24 (3 H, CH_3), 1.38 (s, 3 H, CH_3).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.59; H, 10.98. Found: C, 75.82; H, 10.90.

Continued elution with benzene–pentane mixtures containing increasing proportions of benzene yielded eventually **3β-hydroxydihydroagarofuran (21)**: bp 100 °C (0.05 mm); ir 3520 cm^{-1}; NMR δ 0.95 (d, 3 H, *J* = 5 Hz, CH_3CH), 1.05 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 3.58 (m, $W_{1/2}$ = 8 Hz, CHOH).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.59; H, 10.98. Found: C, 75.82; H, 10.90.

Oxidation of 0.025 g of alcohol **21** with Jones reagent and isolation of the product in the usual manner gave 0.014 g of 3-ketoagarofuran, mp 120–121 °C (lit. mp 124 °C[18]). The spectral properties are in agreement with those reported for this compound.[18]

β-Agarofuran (22). A solution of 0.240 g of 4β-hydroxydihydroagarofuran (**20**) in 5 ml of dry pyridine at 0 °C was treated with 0.65 ml of thionyl chloride. After 1.5 h the mixture was poured into ice–water and extracted with ether, and the product was isolated in the usual manner. The material so obtained was a mixture of β- and α-agarofuran in an 8:1 ratio by GLC. Chromatography on neutral alumina and elution with pentane gave β-agarofuran, bp 90 °C (0.05 mm), the spectral properties of which are consonant with those of authentic material.[20]

5-Epi-10-epieudesma-4β,11-diol (23). A. To a stirred solution of 0.300 g of 4β-alcohol **20** in 25 ml of dry, distilled ethylenediamine at 100 °C was added in portions, under nitrogen, 0.300 g of lithium metal. The mixture was heated at reflux for 1 h, cooled, poured into water, and extracted with ether. The residue was chromatographed on 30 g of neutral alumina. Elution with benzene gave a small amount of 10-epi-γ-eudesmol. Elution with ether gave a compound, presumably the 4β,5β-diol, which reacted readily with periodic acid: ir 3425 cm^{-1}; NMR δ 0.87 (d, 3 H, *J* = 6 Hz), 0.90 (d, 3 H, *J* = 6 Hz, isopropyl), 1.08 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3).

Finally, elution with ethyl acetate yielded 0.150 g of the desired

4β,11-diol (**23**) which crystallized from pentane in plates: mp 110–111 °C; ir (Nujol) 3455 cm^{-1}; NMR δ 0.90 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.29 [s, 6 H, $(CH_3)_2COH$]; (pyr) δ 0.93 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.40 [s, 6 H, $(CH_3)_2COH$].

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.94; H, 11.76. Found: C, 75.10; H, 11.54.

B. A solution of 0.050 g of intermedeol (**1**), isolated from "I" strain *Bothriochloa intermedia*,[22] was stirred with 1 equiv of *m*-chloroperbenzoic acid in 10 ml of chloroform for 18 h at 0 °C. The reaction mixture was washed with cold 5% aqueous sodium hydroxide, water, and brine, dried, and concentrated under reduced pressure to give 0.040 g of crude epoxy alcohol: ir 3460 cm^{-1}; no olefinic absorbance. This material was dissolved in 5 ml of ether and added to a slurry of 0.075 g of lithium aluminum hydride in 10 ml of ether and added to a slurry of 0.075 g of lithium aluminum hydride in 10 ml of ether and stirred at room temperature for 18 h. The excess hydride was decomposed with water and the residue thoroughly extracted with ether. The combined ether extracts were dried and concentrated under reduced pressure to give 0.035 g of diol **23**. The spectral and chromatographic (GL, TLC) properties of this material were identical with those described in A above.

5-Epi-10-epieudesm-11-en-4β-ol (Intermedeol, 1). A mixture of 0.800 g of diol **23** and 3.2 g of 2% quinoline on alumina[23] was heated at a bath temperature of 192 °C for 2 h. Isolation of the products with ether gave 0.710 g of a viscous oil which GLC showed to be a mixture of five compounds. The retention time of the principal component (33%) of this mixture corresponded to that of intermedeol. The mixture was chromatographed on 25 g of activity I basic alumina and elution with benzene gave 0.160 g of a mixture enriched in intermedeol. Rechromatography of this mixture on 2.5 g of Woelm silica gel and elution with hexane–benzene (4:1) gave 0.045 g of intermedeol of ca. 90% purity. Evaporative distillation followed by chromatography on 1.0 g of Woelm silica gel (elution with hexane–benzene, 9:1) gave 0.020 g of material, homogeneous to GLC and TLC, and which had spectral and chromatographic properties identical with those of natural intermedeol (**1**).

3-Acetoxy-10-epieudesma-4,11-diene. A solution of 2.65 g of 10-epieudesma-4,11-dien-3-ol[17] in 25 ml of dry pyridine was treated with 3.4 ml of acetic anhydride and kept at ambient temperature under nitrogen for 18 h. Dilution with water and extraction with ether gave 2.90 g of acetate: bp 120 °C (bath, 0.05 mm); ir 1735, 1645, 1275, 885 cm^{-1}; NMR δ 1.10 (s, 3 H, CH_3), 1.57 (s, 3 H, $CH_3C{=}C$), 1.67 (s, 3 H, $CH_3C{=}C$), 2.20 (s, 3 H, CH_3CO), 4.70 (s, 2 H, $=CH_2$).

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.67; H, 10.06.

10-Epieudesma-4,11-diene (3). A solution of 1.84 g of the acetate mixture described above in 70 ml of dry ether was added dropwise during 10 min to a stirred solution of 0.35 g of lithium metal in 150 ml of liquid ammonia. After a further 20 min, ammonium chloride was added and the ammonia allowed to evaporate. Water was added and the diene isolated with ether. Distillation, bp 100 °C (bath, 0.05 mm), gave 1.29 g of material, the spectral data for which are in agreement with those reported.[4]

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.14; H, 11.87.

4α,5α-Oxido-10-epieudesm-11-ene (24). *m*-Chloroperbenzoic acid (1 equiv) was added portionwise during 15 min to a stirred solution of 0.240 g of diene **3** in 20 ml of methylene chloride at 0 °C. Stirring was continued at room temperature for a further 45 min, and the solution was washed with cold 5% aqueous sodium hydroxide, water, and brine, dried, and concentrated. The oil residue was chromatographed on 8.0 g of Woelm activity III neutral alumina. Elution with hexane–benzene (9:1) gave 0.175 g of epoxide **24**: bp 95 °C (bath, 0.05 mm); ir 1641, 882 cm^{-1}; NMR δ 1.02 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3CO), 1.70 (s, 3 H, $CH_3C{=}$), 4.97 (s, 2 H, $CH_2{=}C$).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.83; H, 11.07.

4α-Hydroxydihydroagarofuran (25). To a solution of 0.220 g of epoxide **24** in 20 ml of methylene chloride was added a solution of 0.240 g of *m*-chloroperbenzoic acid in 20 ml of the same solvent and the mixture kept at room temperature for 18 h. The solution was washed with dilute alkali, brine, and water, then dried and concentrated to yield 0.225 g of diepoxide: NMR δ 1.00 (s, 3 H, CH_3), 1.27 [m, 6 H, $(CH_3)_2CO$]. The crude product in 5 ml of dry ether was treated with 0.100 g of lithium aluminum hydride in 10 ml of ether for 6 h at room temperature. Isolation of the product in the usual manner gave an oil which was dissolved in 10 ml of benzene, treated with a crystal of *p*-toluenesulfonic acid monohydrate, and stirred at room temperature for 5 days. Evaporation of the benzene in vacuo gave a semicrystalline mass which crystallized from hexane to give 0.075 g of material, mp 125–126 °C (lit. mp 130–131 °C[21]), alone or mixed with an authentic sample of 4α-hydroxydihydroagarofuran.

5-Epi-10-epieudesm-11-en-4α-ol (5). A solution of 0.300 g of epoxide **24** in 30 ml of dry ether was added during 10 min to a solution of 0.300 g of lithium metal in 100 ml of liquid ammonia and the mixture stirred for 2 h at reflux. Ammonium chloride was added and the ammonia allowed to evaporate. The residue was leached several times with ether and the extracts evaporated to yield 0.300 g of an oily residue which was chromatographed on 20 g of Woelm activity III neutral alumina. Elution with benzene afforded 0.175 g of alcohol **5**: bp 110 °C (bath, 0.05 mm); ir 3590, 1640, 885 cm^{-1}; NMR δ 1.05 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3COH), 1.72 (s, 3 H, $CH_3C{=}$), 4.90 (m, 2 H, $CH_2{=}$); NMR (pyr) δ 1.25 (s, 3 H), 1.73 (s, 3 H).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.07; H, 11.83.

5-Epi-10-epieudesman-4α-ol (26). A. A solution of 0.22 g of alcohol **5** in 50 ml of ethanol was shaken in hydrogen with 0.040 g of Adams catalyst at room temperature and pressure until absorption of hydrogen ceased. The suspension was filtered and the filtrate concentrated to leave 0.165 g of alcohol **26**: bp 100 °C (bath, 0.05 mm); mass spectrum *m/e* (rel intensity) 109 (100), 121 (59), 123 (36), 135 (44), 138 (69), 139 (62), 150 (33), 163 (79), 181 (95), 191 (72), 206 (23), 209 (72), 224 (10); NMR δ 0.85 (d, 6 H, J = 5.5 Hz, isopropyl), 1.10 (s, 3 H, CH_3COH); (pyr) δ 0.87 (d, J = 5.5 Hz), 1.25 (s, 3 H), 1.30 (s, 3 H).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.31; H, 12.83.

B. To a chilled (0 °C) solution of 0.717 g of 5-epi-10-epieudesm-3-ene (**15**) in 25 ml of tetrahydrofuran containing 5 ml of water and 2.5 ml of 8% aqueous perchloric acid was added, with stirring, 1.40 g of *N*-bromosuccinimide. The reaction mixture was allowed to warm to room temperature, stirred for 3 h, and poured into water. The resulting suspension was extracted with ether, and the extracts were washed with successive portions of 10% aqueous sodium bisulfite, sodium carbonate, and brine. After drying, the solvent was removed at reduced pressure and 40 °C to give a yellow oil. TLC, IR, and NMR indicated the presence of unreacted olefin as well as bromohydrin, and the crude reaction mixture was reduced directly by dissolving it in 100 ml of dry ether, adding 0.7 g of lithium aluminum hydride, and stirring at room temperature for 18 h. The reaction mixture was cooled to 0 °C and the excess hydride was decomposed with ice water. The ethereal solution was decanted from the precipitated aluminum salts, washed with brine, and dried and the solvent removed at reduced pressure to give 0.763 g of an oil, which was dissolved in hexane and chromatographed on Merck alumina. Elution with hexane–benzene (7:2) gave 0.169 g of dihydroparadisiol as a colorless oil. Although this material was homogeneous to TLC and GLC (SE-30, 200 °C), the mass spectrum indicated that it was contaminated with unreduced bromohydrin. Pure material, identical with that described in part A above, was obtained by distillation at 130 °C (bath, 0.2 mm) and rechromatography.

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Registry No.—**1**, 6168-59-8; **3**, 28290-20-2; **4**, 60132-29-8; **5**, 29969-75-3; **6**, 2303-31-3; **7**, 60064-80-4; **9**, 60064-91-7; **10**, 60064-92-8; **10** 4α enantiomer, 60064-93-9; **12**, 60064-94-0; **14**, 22555-76-6; **15**, 41703-44-0; **16**, 28290-25-7; **17**, 15051-79-3; **18**, 5956-12-7; **19**, 60064-95-1; **20**, 60132-34-5; **21**, 60064-96-2; **22**, 6040-08-0; **23**, 60132-35-6; **24**, 60064-97-3; **25**, 15052-76-3; **26**, 29868-51-7; 4-epi-5-epi-10-epieudesma-3-one, 54030-91-0; 10-epieudesma-4β,5β-diol, 60064-98-4; 3-acetoxy-10-epieudesma-4,11-diene, 60064-99-5; 10-epieudesma-4,11-dien-3-ol, 17023-63-1.

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Synthesis of Intermedeol and Related Sesquiterpenoid Studies[1]

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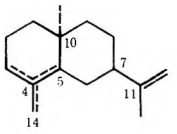
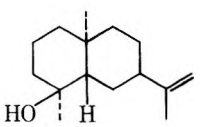
The 10-epieudesmanes (−)-7β,10α-selina-4,11-diene (I) and (+)-5βH,10α-selina-3,11-diene (II) were synthesized from 10α-selina-4,11-dien-3-one (VI) and natural (−)-7β,10β-selina-4,11-diene (I) was further converted into intermedeol (IV). Intermedeol (IV) was transformed into 5βH,10α-eudesmol (XI). On treatment with boron trifluoride etherate, neointermedeol (XV), a close relative of intermedeol, gave δ-selinene, while with thionyl chloride in benzene selina-4,11-diene was obtained.

The recent isolation of the dienes (−)-7β,10α-selina-4,11-diene (I) and (+)-5βH,7β,10α-selina-3,11-diene (II) from *Dipterocarpus alatus* Roxb.[3] and (−)-5β,7β,10α-selina-4(14),11-diene (III) from *Aristolochia indica* Linn.[4] are of particular interest since they can be visualized as arising biogenetically simply by dehydration of intermedeol (IV), the

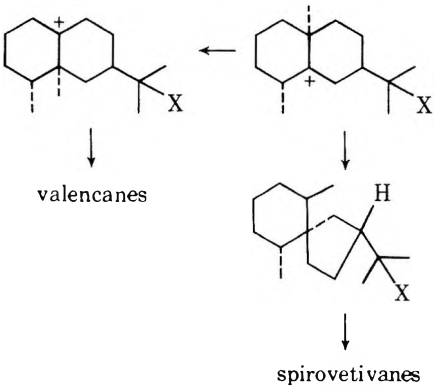


I, $\Delta^{4(5)}$
II, $\Delta^{3(4)}$, 5βH
III, $\Delta^{4(14)}$, 5βH



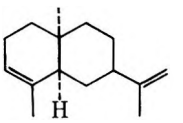
IV

first member of this family to be reported.[5] In fact, diene III was first prepared in 1962,[5b,6] by pyrolysis of intermedeol acetate, but was not recognized as such since, at that time, the configuration at C-7 was thought to be 7βH.[5a] The grapefruit constituent paradisol[7] is now known to be identical with intermedeol[8] and a direct comparison of the dehydration product of paradisol[7] with natural III has shown their identity.[4] Only a few other related 10-epieudesmanes have been reported,[9,10] but this group of sesquiterpenes appears to play an important role as biogenetic precursors to the valencanes and spirovetivanes.[11,12] Marshall and Andersen[12] have concluded from the literature on constituents of eudalene-yielding essential oils that (1) 10-epieudesmanes are more prone to rearrangement and (2) rearrangements always occur from a eudesmane with cis related methyl groupings. These observations were

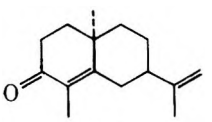


explained by postulating that relief of the strain associated with an axial isopropyl grouping and a 1,3-diaxial methyl interaction provides substantial driving force for the rearrangements.[12]

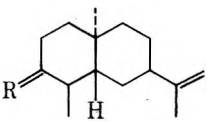
We now report the synthesis of I (21%) and II (13%) together with isomer V (37%) by a modified Wolff–Kishner reduction[13] of the previously reported dienone VI[14] and the further con-



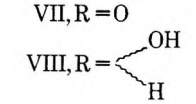
V



VI



VII, R = O

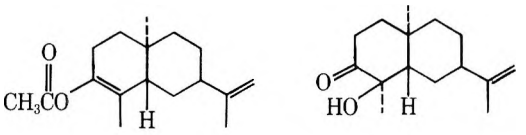
VIII, R = 

version of natural II into intermedeol (IV). The reaction conditions were selected to give the maximum amount of double bond migration. I and II were identical by ir and NMR spectra and by gas chromatography on three columns with authentic samples.[15] Diene V was characterized by its elemental analysis, mass spectrum, and by its ir (ν 1635, 880 cm^{-1}) and NMR [δ 0.87 (3 H), 1.65–1.73 (6 H), 4.72 (2 H), 5.30 (1 H)] spectra. The preference for protonation of the intermediate anion of the hydrazone at C-5 to give cis fused V may be explained as follows. If it is assumed that the orbital at C-5 is sp^3, presumed in the case of metal ammonia reductions of α,β-unsaturated ketones,[16] then continuous overlap with the C-4 sp^2 orbital can be maintained by an α-oriented (cis to C-10 methyl) C-5 orbital. This orientation would be expected to be preferred over the β orientation (leading to II) since the former intermediate, after protonation at C-5, would lead to an all-chair arrangement with an equatorial C-7 isopropenyl group whereas the latter case would lead to the less favorable B-ring twist-boat conformation. Grundon, Henbest, and Scott[17] showed that by using a modification of the Wolff–Kishner reduction procedure involving potassium *tert*-butoxide in refluxing toluene, double bond migration in α,β-unsaturated ketones could be minimized and, in particular, by using the preformed semicarbazone of cholest-4-en-3-one, essentially pure cholest-4-ene was obtained in high yield. When the semicarbazone of VI was subjected to these conditions, the only product detected by gas chromatography and isolation was I, the unrearranged diene.

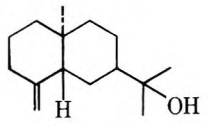
Epoxidation of natural II[15] with *m*-chloroperbenzoic acid (1 molar equiv) in methylene chloride gave a mixture in which a single epoxide predominated (~80% of products).[18] Attempted separation of this epoxide mixture by chromatography on silica gel led to disappearance of epoxides and formation of a ketone, presumably VII, as the major product. Therefore, the epoxide mixture was reduced with $LiAlH_4$ in THF at 60 °C and only after 16 h were the epoxides consumed. Gas chromatographic analysis indicated the presence of three products in the approximate ratio of 1.5:4.3:1.0. The most abundant product was eluted with benzene/hexane (~1:1) from an alumina column and was shown to be alcohol VIII by its spectral properties and its conversion to the known ketone VII[3,14] by Jones oxidation. The second most abundant reduction product was eluted from the alumina column prior to alcohol VIII, but repeated chromatography over alumina failed to provide it in completely pure form. An analytically pure sample was obtained by preparative gas chromatography and it was found to be identical by ir, NMR, and gas chromatography with natural intermedeol (IV).[5] This represents the first reported synthesis of intermedeol.[19] When intermedeol was first isolated[5b] we were surprised that it showed two bands of equal strength in its ir spectrum at 890 and 910 cm^{-1}; the presence of both these bands has been verified in the spectrum of pure synthetic intermedeol.

Regiospecific epoxidation of II at the more nucleophilic C-3, C-4 double bond was to be expected,[20] and an examination of Dreiding models clearly indicated that the β face (trans to C-10 Me) is less sterically encumbered. Thus, it is assumed that the major epoxide of II is the β-epoxide. However, this epoxide has no low-energy pathway available to it for reduction by lithium aluminum hydride, and indeed this reaction proceeded at a surprisingly slow rate as indicated above. Alcohol VIII must arise either by axial nucleophilic attack from the α side at the highly hindered C-4 tertiary position, or the epoxide undergoes prior rearrangement to the C-3 ketone, catalyzed by a Lewis acid impurity, which in turn is reduced.[21] Indeed, addition of $AlCl_3$ to the solution enhanced the rate of formation of alcohol VIII. Intermedeol is produced by hydride attack at the secondary C-3 position, but in order for there to be axial epoxide opening an A-ring boat conformation would be involved (presumably the B ring is also in a boat conformation).

An attempt was made to synthesize intermedeol from VI by reductive acylation with lithium/ammonia/*tert*-butyl alcohol and trapping with acetic anhydride to give enol acetate IX, followed by epoxidation with *m*-chloroperbenzoic acid and



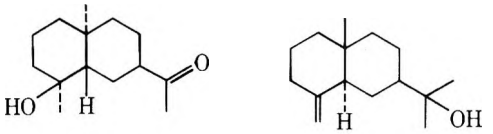
IX X



XI

alkaline hydrolysis to give X and finally conversion of X to intermedeol. Enol acetate IX was obtained, as expected, in a yield of about 65% and its NMR spectrum showed the characteristic C-4 methyl group at δ 1.43.[22] The ir spectrum of IX was analogous to that reported for its Δ^2 isomer.[23] Epoxidation of IX appeared to proceed without difficulty and the crude epoxide was hydrolyzed with aqueous ethanolic potassium hydroxide[24] to give X, in poor yield, after chromatography on alumina.[25] However, no means was found to efficiently remove the C-3 carbonyl group without disturbing the C-4 hydroxyl group or C-11 double bond.

Intermedeol has been converted into 5βH,10α-eudesmol (XI), a material not yet found in nature but presumably an important biogenetic precursor,[11] as follows. Oxidation with potassium permanganate–sodium periodate gave XII as previously described.[5a] Ketol XII was dehydrated to the exocyclic olefin with phosphorus oxychloride in pyridine, then addition of methylmagnesium iodide and the usual workup gave, after chromatography, 5βH,10α-eudesmol (XI), which was similar to but distinguishable from the natural product β-eudesmol (XIII) by thin layer and gas chromatography.[26]

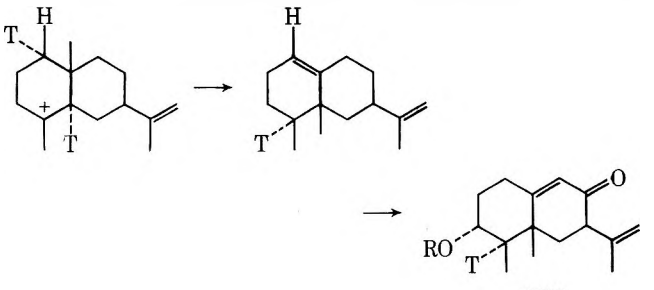


XII XIII

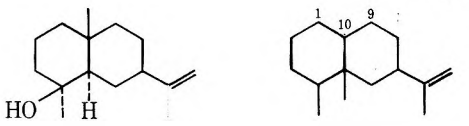
Insufficient quantities of intermedeol (IV) and XI have thus far been available to study their in vitro conversion to spirovetivanes and valencanes, as postulated in the biogenesis of these substances.[11,12]

Recently Brooks and Keates[27] provided in vivo support for the original Robinson postulation[28] that the C-5 methyl group in eremophilane sesquiterpenes arises by migration from C-10 in a precursor of the eudesmanoid skeletal type as outlined for petasin (XIV). Therefore, we attempted an in vitro simulation of this biogenetic pathway using neointermedeol (XV), a close relative of intermedeol, previously isolated by us from a different race of the same plant species that yielded intermedeol.[29] As mentioned above, Marshall and Andersen[12] postulated that in vivo a C-10 → C-5 methyl migration always occurs from a eudesmane with cis related methyl groups. However, in neointermedeol where the C-4 hydroxyl group is instead cis to the C-10 methyl group, the concerted sequence of trans anti parallel shifts (−) α C-1 H; β C-10 Me → β C-5 Me; α C-5 H → α C-4 H; (−) β C-4 OH are possible. In the event, exposure to boron trifluoride etherate for 3 min resulted in the conversion of neointermedeol into δ-selinene (selina-4,6-diene) in excellent yield while treatment with thionyl

chloride in benzene gave selina-4,11-diene as the major product. The latter was identified by the similarity of its ir and NMR spectra to those previously reported[30] and the almost identity of its NMR spectrum with that of its 10 epimer I. However, in the latter case there was indication that a "biogenetic type" rearrangement did occur to a small extent, involving either a C-10 → C-5 methyl migration to give either eremophilene (XVI) or its isomer 7αH-eremophila-9,11-diene (XVII)[31] or rearrangement to a spirovetivane. While

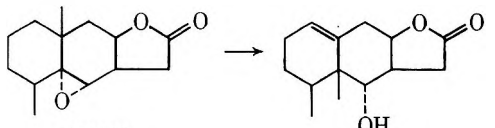


XIV



XV XVI, $\Delta^{1(10)}$
XVII, $\Delta^{9(10)}$

chromatography failed to yield the minor "biogenetic type" product in pure form, fractions enriched in this product were obtained in which the NMR spectra showed high-field methyl doublets and broad olefinic signals at about δ 5.3.[31,32] A number of unsuccessful attempts to effect the in vitro conversion of an eudesmanoid type precursor into an eremophilane type sesquiterpene have been recorded.[33] The only reported successful example of a C-10 → C-5 methyl migration in an eudesmanoid precursor involved the formic acid–acetone treatment of epoxydihydroalantolactone (XVIII).[34] More



XVIII

recently, Hochstetler[35] has shown that 2,2,8,8,10-pentamethyl-1(9)-octalin undergoes acid-catalyzed rearrangement via both a spiro[4.5]decalyl cation system and an angular methyl migration. Thus, in vitro "biogenetic type" rearrangements of simple eudesmanes (or 10-epieudesmanes) to eremophilanes (or valencanes) or spirovetivanes are not readily accomplished and may, in fact, require very rigid conformation features as present in the more highly substituted derivatives. In vivo this conformational rigidity could be enzyme controlled.

Experimental Section[36]

7β,10α-Selina-4,11-diene, 5βH,7β,10α-Selina-3,11-diene, and 5αH,7β,10α-Selina-3,11-diene (V). Ketone VI (4.8 g)[14] and 8 ml of hydrazine hydrate (64% in water) were dissolved in 350 ml of freshly distilled triethylene glycol. To this was added a solution prepared by dissolving 7.6 g of potassium hydroxide in 100 ml of triethylene glycol. The combined solution was heated at 100 °C for 30 min, then the temperature raised to 210 °C over a period of 30 min, where it was maintained for 1 h, during which time hydrazine and water distilled out of the solution.[13] Extraction with petroleum ether (bp 30–60 °C), washing with water, drying ($MgSO_4$), and concentration gave 4.24 g of product which by gas chromatography (Carbowax 20M column) was shown to be composed of, in order of elution, 37% V, 21% I, and 13% II. Repeated column chromatography on 10% silver nitrate–silica gel columns provided analytically pure samples of the three dienes which were eluted with 10% benzene in petroleum ether in the order II, V, and finally I. I and II were identical with authentic samples[3,15] of I and II by gas chromatography (Carbowax 20M column) alone and on admixture, and by superposition of their ir, NMR, and mass spectra. Infrared and NMR spectra of I and II have been previously reported.[3]

Wolff–Kishner reduction of the semicarbazone of VI under the conditions of Grunwald et al.[17] gave only I. Thus, 1.0 g of semicarbazone VI (mp 177–180 °C, lit.[14] mp 177 °C) and 0.8 g of potassium *tert*-butoxide were added to 15 ml of toluene and the solution was refluxed for 90 h. Nitrogen evolution (~89% theoretical) appeared to cease after 68 h. The solution was neutralized with hydrochloric acid and extracted with ether. After the usual workup, gas chromatography and NMR analysis of the crude product indicated the presence of only I. As previously, an analytically pure sample of I was prepared and was identical with I prepared as described above.

Diene V, which showed a single peak by gas chromatography, exhibited the following properties: bp 70 °C (0.1 mm) (bath); mass spectrum 204.1889 (calcd, 204.1878); ir ν_{max} (neat) 1645 and 890 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.88 (3 H, s), 1.66–1.75 (6 H, m), 4.72 (2 H, m), 5.30 (1 H, m).

Synthesis of Intermedeol (IV). To a solution containing 0.994 g of II[15] (88.5% purity by gas chromatography) in 25 ml of methylene chloride at −10 °C was added dropwise a solution containing 0.944 g of *m*-chloroperbenzoic acid in 25 ml of methylene chloride at 0 to −10 °C over a period of 5 min. Gas chromatography indicated reaction to be complete after an additional 20 min of stirring. The methylene chloride solution was then washed successively with a saturated sodium sulfite solution, a sodium bicarbonate solution, then a saturated brine solution. Drying ($MgSO_4$) and concentration with a rotary evaporator gave 0.997 g of the crude epoxide product, gas chromatographic analysis (ratio of peak areas) of which indicated approximately 71% of a single product, <5% unreacted II, and a number of other components, none of which were present in excess of 5%:[18] ν_{max} (film) 880 cm^{-1}; δ (CCl_4) 4.88 (m).

To a solution of 10 ml of tetrahydrofuran, distilled from lithium aluminum hydride, containing 98 mg of the above-mentioned epoxide mixture at 58 °C, was added dropwise (over a period of 30 min) a solution prepared by vigorously stirring 103 mg of lithium aluminum hydride in 10 ml of dry tetrahydrofuran. Gas chromatographic analysis showed disappearance of starting material only after 16 h, when the reaction mixture was quenched with a solution of sodium potassium tartrate, then extracted with ether. Drying and concentration with a rotary evaporator gave 107 mg of crude product, gas chromatographic analysis of which indicated three major products in the ratio 15:23:62, in the order of increasing retention time. The second most abundant constituent showed the same retention time as intermedeol (IV) by gas chromatography. The analytical sample of intermedeol was only obtained after repeated chromatography on neutral alumina (activity I) followed by preparative gas chromatography (Carbowax 20M column). The intermedeol thus obtained was identical with the natural product by ir and NMR spectral comparisons, and in gas chromatographic retention time alone and on admixture.[5]

The most abundant product, VIII, was eluted from the alumina column after intermedeol in benzene/hexane (1:1): δ (CCl_4) 0.83 (3 H, s), 0.95 (3 H, d, J = 6 Hz), 1.68 (3 H, s), 3.68 (1 H, m), 4.83 (2 H, m). Oxidation of VIII with Jones reagent gave ketone VII, mp 43–45 °C (lit.[3] mp 49.5–50 °C), identical by ir and NMR spectra with the spectra of an authentic sample prepared by reduction of VI with lithium in liquid ammonia as previously described.[14]

Attempted Conversion of VI into Intermedeol. Preparation of Ketol X. Ketone VI[14] (5.45 g, 0.025 mol) and 1.85 g (0.025 mol) of *tert*-butyl alcohol were dissolved in 50 ml of anhydrous ether. This solution was added dropwise, over a period of 1 h, to a solution of 250 ml of liquid ammonia to which 0.38 g (0.55 g-atom) of lithium had been added. After stirring for an additional 1 h, the ammonia was allowed to evaporate under anhydrous conditions and when evaporation seemed to cease, 25 ml of anhydrous ether was added to the residue and this solution was allowed to evaporate in a hood. This procedure was repeated in order to remove the last traces of ammonia and finally the residue was taken up in 50 ml of anhydrous ether and this ethereal solution, after vigorous stirring, was slowly dropped (30 min) into 25.5 g (0.25 mol) of freshly distilled acetic anhydride at room temperature under a nitrogen atmosphere. After stirring for an additional 30 min, this solution was rapidly added to a two-phase system of 150 ml of pentane and 150 ml of a saturated sodium bicarbonate solution at 0–5 °C. Solid sodium bicarbonate was added, over a period of 2–3 h, while the temperature was maintained below 5 °C until neutralization was complete. The layers were separated, the aqueous layer was filtered and then extracted with pentane, and the combined

pentane layers were washed sequentially with sodium bicarbonate solution, then saturated brine solution, and finally dried and evaporated to give a crude residue of 6.36 g. Gas chromatography (Carbowax 20 M column) showed in order of increasing retention time 9% of an unidentified substance, 16% VII, 4% unidentified substance, 65% IX, and 6% VI (ratio of peak areas). Chromatography on Merck acid-washed alumina (activity II) gave enol acetate IX in the petroleum ether eluent, ketone VII in the petroleum ether–benzene (9:1) eluent, and the α,β-unsaturated ketone VI in the petroleum ether–benzene (1:1) to benzene eluents. Hot box distillation gave the analytical sample of IX: bp 100–110 °C (bath) (0.1 mm); ν_{max} (neat) 1750, 1685, 1640, 1220, 892 cm^{-1}; δ (CCl_4) 0.92 (3 H, s), 1.43 (3 H, m), 1.72 (3 H, m), 2.03 (3 H, s), 4.85 (2 H, b); positive plain ORD curve.

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found C, 77.55; H, 9.90.

To 3.02 g of crude enol acetate in 150 ml of dry chilled ether, 2.37 g of *m*-chloroperbenzoic acid (83.8%) in 40 ml of dry ether was added. After 14 h at 5 °C, gas chromatography showed that little enol acetate had been consumed and the solution was therefore left at 25 °C in the dark for 25 h. Ether was removed with the rotary evaporator and addition of 50 ml of petroleum ether resulted in precipitation of *m*-chlorobenzoic acid, which was removed by filtration. Evaporation of the petroleum ether gave a quantitative yield of crude product: δ (CCl_4) 1.32, 1.73, 2.02, 2.06, 4.85. Gas chromatography suggested decomposition on the column and the crude epoxide was used without further purification. To a solution containing the above crude epoxide in 100 ml of ethanol was added a solution prepared by dissolving 5 g of potassium hydroxide in 25 ml of ethanol and 3 ml of water. The entire solution was stirred at 60 °C for 2 h, then most of the alcohol was removed at reduced pressure and 100 ml of water was added to the residue, which was then extracted with ether. Washing with brine, drying over magnesium sulfate, and evaporation of the ether gave crude product in 95% yield. Gas chromatographic analysis of the crude product indicated the presence of seven products with the hydroxy ketone composing only about 20% of the mixture (based on peak areas). Chromatography on Merck acid-washed alumina (activity II) gave the hydroxy ketone in the benzene eluent as a viscous gum: bp 110–115 °C (0.1 mm) (bath); ν_{max} (neat) 3477, 1714, 1661, 1637, 1069, 1052, and 895 cm^{-1}; δ (CCl_4) 1.16 (3 H, s), 1.18 (3 H, s), 1.73 (3 H, m), 4.86 (2 H, b).

Attempted preparation of the thioketol of X appeared, by NMR analysis, to result in at least partial migration of the isopropenyl double bond, and reduction of the crude product with Raney nickel gave no product corresponding to intermedeol by gas chromatographic analysis. Reduction of X with lithium aluminum hydride in ether resulted in disappearance of the carbonyl group, as detected by ir, but the product could not be converted into the desired secondary tosylate, the characteristic isopropenyl double bond peak at 890 cm^{-1} in the ir having disappeared. Regardless, lithium aluminum hydride reduction of this crude product likewise gave no material with the retention time of intermedeol by gas chromatography.

Conversion of Intermedeol (IV) into 5β*H*,10α-Eudesmol (XI). Intermedeol (0.134 g) was dissolved in 65 ml of *tert*-butyl alcohol and a solution of 1.02 g of sodium periodate, 0.252 g of potassium carbonate, and 0.03 g of potassium permanganate in 70 ml of water was added with stirring at room temperature. After stirring for 17 h, 120 ml of water was added to the solution which was then extracted with benzene. The combined organic layers were washed with water, then dried over magnesium sulfate. Evaporation of the solvent gave 0.105 g of a yellow oil, which was distilled to give ~80% (peak area, gas chromatography) of ketol XII: bp 115 °C (0.3 mm) (bath); ν_{max} (neat) 3440, 1705, 1455, 1380, 1285, and 910 cm^{-1}; δ ($CDCl_3$) 0.92 (3 H, s), 1.10 (3 H, s), 2.18 (3 H, s).

The ketol was dehydrated as follows. To ketol (0.120 g) dissolved in 4 ml of dry pyridine was added 0.3 ml of phosphorus oxychloride. After mixing, the homogeneous solution was allowed to stand at room temperature for 20 h, then poured over 40 g of ice and the resulting mixture extracted with ether. The ether extracts were washed with water, 2% hydrochloric acid, and again with water until neutral and finally dried over magnesium sulfate, then filtered and evaporated to give 0.111 g of the enone: ν_{max} (neat) 1710, 1450, 1378, 1284, and 887 cm^{-1}; δ ($CDCl_3$) 0.73 (3 H, s), 2.13 (3 H, s), 4.42 and 4.73 (2 H, m).

5β*H*,10α-Eudesmol (XI) was prepared from the above enone as follows. To 0.275 g of magnesium turnings in 2 ml of dry ether was added 0.1 ml of methyl iodide to initiate the reaction, after which 1.60 g of methyl iodide in 5 ml of dry ether was added drop by drop. Another 2 ml of dry ether was added and after an additional 15 min of stirring, 0.11 g of the above-mentioned enone dissolved in 5 ml of ether was added and the entire solution refluxed for 6 h. The reaction was quenched with a saturated ammonium chloride solution and the mixture was thoroughly extracted with ether. After washing with water and drying, evaporation of the ether extract gave 0.089 g of crude XI (~85% purity by peak areas in gas chromatography).

Chromatography on silica gel gave XI in the hexane–ether (98:2) eluent and distillation, bp 105–110 °C (0.2 mm) (bath), gave a colorless liquid which crystallized on standing, mp 45–50 °C. Further chromatography on alumina (activity II) gave material of mp 62–66 °C in the benzene–ether (1:1) eluent. This alcohol (XI) was shown to be homogeneous by thin layer chromatography (silica gel, 95:5 chloroform–ether) and by gas chromatography on a 3% QF-1 column and not to be identical with an authentic sample of β-eudesmol (XIII): $[\alpha]^{25}D$ −17.5° (*c* 5.00, $CHCl_3$); ν_{max} (neat) 3420, 1640, 1450, 1380, and 890 cm^{-1}; ν_{max} (CCl_4) 3610, 1640, 1455, 1380, and 888 cm^{-1}; δ ($CDCl_3$) 0.76 (3 H, s), 1.26 (6 H, s), 4.51 and 4.76 (2 H, m); mass spectrum 204.1880 (calcd for $M^+ - H_2O$, 204.1878).[26]

Anal. Calcd for $C_{15}H_{26}O$: C, 81.08; H, 11.71. Found: C, 81.18; H, 11.83.

Dehydration of Neointermedeol. A. Reaction with Boron Trifluoride Etherate. Neointermedeol[29] (118 mg) was dissolved in 2.5 ml of dry benzene and to this solution was added 0.25 ml of freshly distilled boron triifluoride etherate. After stirring at room temperature for 3 min, 5 ml of water was added, the layers separated, the aqueous layer further extracted with ether, and the combined organic layers washed with water, dried, and concentrated on the rotary evaporator to give 108 mg of crude product, gas chromatograph and NMR of which indicated the presence of approximately 90% δ-selinene. Distillation gave pure δ-selinene (bp 130 °C, 0.06 mm) which was identified by its uv and ir spectra[37] and NMR spectrum: δ ($CDCl_3$) 0.98 (3 H, s), 1.10 (6 H, d, J = 6.5 Hz), 6.2 (1 H, s).

B. Reaction with Thionyl Chloride. Neointermedeol[29] (250 mg) was dissolved in 5 ml of dry benzene to which was added 100 mg of pyridine. After cooling to 5 °C 1.35 g of thionyl chloride was added. After maintaining the solution at 10–20 °C for 90 min, it was poured into an aqueous bicarbonate solution which was extracted with ether. The usual workup gave 0.25 g of crude product, gas chromatography of which showed the absence of starting material but the appearance of one major and two minor peaks of lower retention time. Chromatography on a silver nitrate–silica column gave selina-4,11-diene: δ ($CDCl_3$) 1.05 (3 H, s), 1.62 (3 H, s), 1.75 (3 H, s), 4.75 (2 H, m); ν_{max} (neat) 1640, 887 cm^{-1}.[30] Further elution yielded fractions containing predominantly selina-4,11-diene as determined by gas chromatography and NMR but the NMR spectra showed the presence of high-field doublets at ~δ 0.9 and a broad signal at ~δ 5.3.[31,32]

Registry No.—I, 28290-20-2; II, 60132-29-8; IV, 60064-79-1; V, 60132-30-1; VI, 2303-31-3; VIII, 60132-31-2; IX, 60064-80-4; X, 60064-81-5; XI, 60132-32-3; XII, 60132-33-4; XII enone analogue, 60064-82-6; XV, 5945-72-2.

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Synthesis of a Tetracyclic Ajmalicine Analogue

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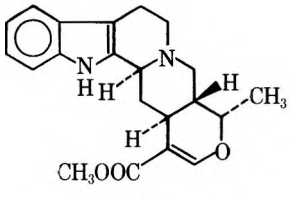
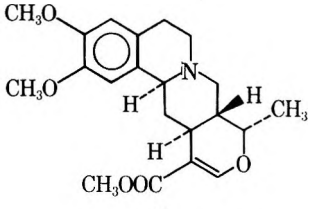
The synthesis of a tetracyclic analogue (**2**) of the heteroyohimbine alkaloid ajmalicine (**1**) is described. The synthesis makes use of a novel alternative to the Korte reaction for the preparation of the dihydropyran ester portion (**11**) of the molecule.

A number of syntheses of indole alkaloid analogues lacking the pyrrole ring of the natural products has been reported.[1] These syntheses were undertaken either with the aim of obtaining medicinally useful substances or as model studies for the synthesis of the natural alkaloids. With the former goal in mind it appeared worthwhile to prepare such a tetracyclic version of the heteroyohimbine alkaloid ajmalicine (**1**)[2] as a potential hypotensive agent.

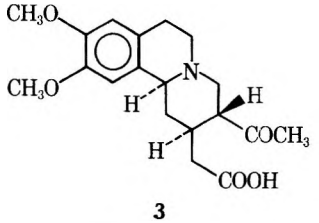


1



2

We selected **2** as our target, reasoning that it could be prepared from the intermediate **3**, used in van Tamelen's emetine synthesis,[3] by applying the methods developed for the synthesis of ajmalicine from the corresponding indole-containing intermediate **4**, described in the same paper.[3]



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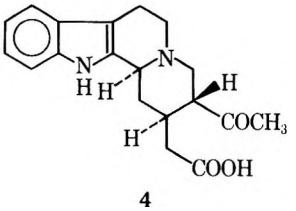
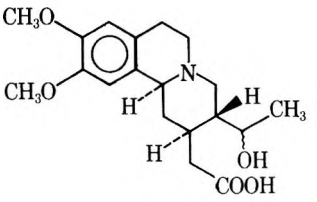


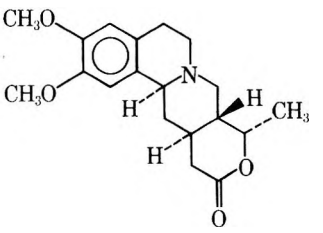
4

Reduction of **3** with sodium borohydride in aqueous potassium hydroxide gave the hydroxy acid **5**. The NMR spectrum of this substance showed that it was a 50:50 mixture of the two epimeric alcohols [a methyl doublet at δ 1.26 (J = 6.75 Hz) collaped on irradiation at δ 4.71, while a doublet at δ 1.30 (J = 6.20 Hz) collapsed on irradiation at δ 4.29].

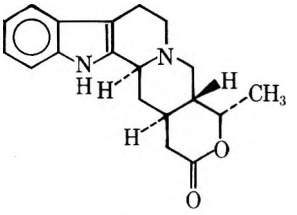
The lactone **6** was prepared from **5** either with 1-cyclohexyl-3-(2-morpholinylethyl)carbodiimide metho-*p*-toluenesulfonate in pyridine or with ethanolic hydrogen chloride. One recrystallization of the crude lactone gave material which was a single isomer (NMR), presumably having the configuration indicated by analogy with van Tamelen's pentacyclic lactone **7** which was converted to ajmalicine.[3] Surprisingly, although a variety of conditions was tried, treatment of **6** with triphenylmethylsodium in dioxane followed by addition of methyl formate did not lead to the formation of the α-hydroxymethylene lactone. van Tamelen found that the lactone **7** underwent condensation under these conditions.[3] Conceivably, in the case of **7**, proton abstraction α to the carbonyl group was facilitated by an intramolecular process involving initial deprotonation of the indole N–H.



5



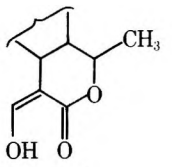
6



7

We had intended to complete the synthesis of **2** by making use of the Korte reaction,[4] which involves treatment of a hydroxymethylene lactone **8** with methanolic HCl at room

temperature to give an α-formyl-δ-hydroxy ester **9**. This then cyclizes to the acetal **10**. Elimination of methanol with polyphosphoric acid[4] or with methanolic HCl[3] at the reflux gives the dihydropyran ester **11**.



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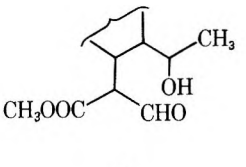
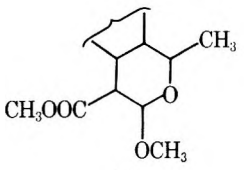
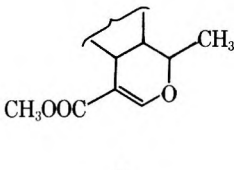


9

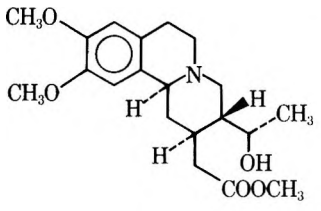


10

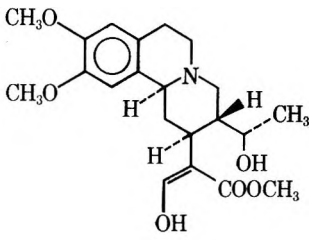


11

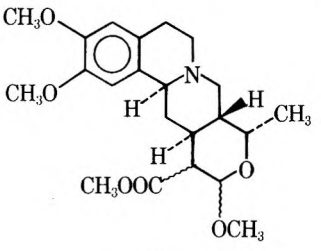
An alternative to this procedure was obviously required. We realized that the ring-opened intermediate **9** is merely the hydroxymethylene derivative of the hydroxy ester corresponding to the original lactone, and we therefore decided to attempt to complete the synthesis of **2** via the hydroxy ester **12**. This substance was obtained by treatment of **5** with diazomethane. Again, as in the case of the lactone, one recrystallization gave material which was a single isomer (NMR). Condensation of **12** with methyl formate was readily achieved, and gave the hydroxymethylene derivative **13**, which was not purified. Cyclization to the acetal **14** was effected with



12



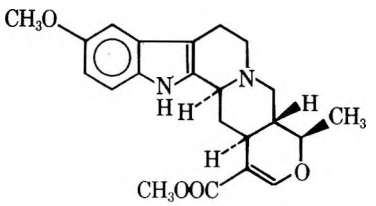
13



14

methanolic hydrogen chloride. Cyclization was accompanied by some elimination of methanol (to give **2**) but elimination was not increased by prolonging the reaction time. More complete elimination leading to isolation of **2** was achieved by refluxing a solution of **14** and *p*-toluenesulfonic acid in chloroform using a sulfuric acid trap to absorb the methanol produced in the reaction. The product was converted to the hydrochloride; one recrystallization gave analytically pure material.

The NMR spectrum of the purified product indicated that the substance was stereochemically homogeneous; in particular the methyl doublet at δ 1.16 (J = 6.5 Hz) was very similar to that reported by Shamma and Richey[5] for ajmalicine (δ 1.16, J = 6.7 Hz), whereas in raumitorine (**15**), an alkaloid stereochemically identical with ajmalicine except for the orientation of the methyl group, the doublet appears at δ 1.29.[6] In synthetic 19-epiajmalicine[7] the doublet is at δ 1.33 (J = 6.5



15

Hz). The configuration of the remaining three asymmetric centers of **2** must be as shown, as the substance was prepared from **3** which in turn was converted to emetine by van Tamelen.[3] The presence of complex bands in the ir between 2700 and 2900 cm^{-1} confirmed the trans nature of the quinolizidine system in **2**.[8] The mass spectrum of **2** was analogous to that of ajmalicine.[9] The only important difference (apart from the obvious shift in molecular weight of the fragment ions) was the low intensity of the m/e 177 peak of **2** relative to the corresponding peak (m/e 156) of ajmalicine. These peaks presumably arise from reverse Diels–Alder fragmentation of the tetrahydropyridine rings of **2** and ajmalicine. Such a process would appear to be more favorable in the case where the indole double bond was involved.

The ajmalicine analogue **2** demonstrated significant hypotensive activity in the anesthetized cat and dog when administered intraduodenally at 30 mg/kg; however, the hypotension was accompanied by an unacceptable level of CNS stimulation.

Experimental Section

Ir spectra were recorded on a Perkin-Elmer 137 spectrophotometer and NMR spectra on a Varian A-60D spectrometer in Me_2SO-d_6 solution.

2-Carboxymethyl-3-(1-hydroxyethyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine Hydrochloride (5 HCl). A solution of **3** (30 g) and sodium borohydride (11.7 g) in water (550 ml), adjusted to pH 11 with KOH, was refluxed for 25 h. After cooling, the solution was made acidic (pH 2) with concentrated HCl and the solvent removed on the rotary evaporator. The residue was extracted with boiling ethanol to give 29.2 g of **5** hydrochloride, mp 250–262 °C. The melting point was unchanged after recrystallization from water.

Anal. Calcd for $C_{19}H_{28}ClNO_5$: C, 59.14; H, 7.31; N, 3.64; Cl, 9.19. Found: C, 59.05; H, 7.13; N, 3.56; Cl, 9.06.

2,3-Dimethoxy-9-methyl-5,8,8a,11,12,12a,13,13a-octahydro-6*H*,9*H*-benzo[*a*]pyrano[3,4-*g*]quinolizin-11-one (6). Method A. A solution of 5 HCl (2.8 g) and 1-cyclohexyl-3-(2-morpholinylethyl)carbodiimide metho-*p*-toluenesulfonate (3.6 g) in pyridine (400 ml, freshly distilled from KOH) was maintained at 100 °C for 4.5 h under a nitrogen atmosphere. The reaction mixture was evaporated under reduced pressure and the resulting oil dried for 17 h at 20 °C (0.05 mm). The residue was dissolved in $CHCl_3$ (150 ml) and extracted with 5% H_2SO_4 (3 × 50 ml). The combined acid extracts were washed with $CHCl_3$ (2 × 10 ml), then neutralized with solid $NaHCO_3$ and extracted with $CHCl_3$ (3 × 75 ml). The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated to give the lactone as an oil (1.5 g) which crystallized on treatment with ethyl acetate. This material was apparently a mixture of **6** and the epimer with the methyl group in the β configuration, with **6** predominating: NMR δ 1.36 (d, J = 6.6 Hz) more intense than δ 1.42 (d, J = 6.6 Hz). Recrystallization from ethanol gave **6** (0.7 g): mp 211–214 °C; NMR δ 1.36 (d, J = 6.6 Hz).

Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.66; H, 7.89; N, 4.43.

Method B. A solution of **5** HCl (2.0 g) in 5% ethanolic HCl was refluxed for 2.5 h. The reaction mixture was evaporated to dryness, dissolved in water (200 ml), made basic by the addition of solid K_2CO_3, and extracted with $CHCl_3$ (2 × 150 ml). The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated to give the lactone as a colorless oil (0.7 g) which crystallized on treatment with ethyl acetate. Recrystallization from ethanol gave **6** (0.6 g), mp 211–214 °C, identical with the material obtained using method A.

2-Carbomethoxymethyl-3-(1-hydroxyethyl)-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine (12). A solution of diazomethane in ether[10] (100 ml), prepared from *N*-nitrosomethylurea (10.3 g), was added to a solution of **5** HCl (6.4 g) in

methanol (75 ml) at 0–5 °C. After 18 h at room temperature, the solution was heated on the steam bath until ether boiled mildly and then the solvent was removed on the rotary evaporator. The residue (6.8 g) was dissolved in ether/$CHCl_3$ (1:1, 300 ml) and extracted with 2% K_2CO_3 (300 ml). The organic layer was dried over anhydrous K_2CO_3 and evaporated to give 4.2 g of **12**. This material was dissolved in methanol (10 ml) and excess methanolic HCl added. Evaporation and recrystallization of the residue from methanol/benzene gave **12** HCl as the hydrate: 2.0 g; mp 142–144 °C; NMR δ 1.14 (d, 3, J = 6.6 Hz), 3.66 (s, 3), 3.78 (s, 6), 6.8 (s, 2).

Anal. Calcd for $C_{20}H_{32}ClNO_6$: C, 57.44; H, 7.72; N, 3.35; Cl, 8.48; H_2O, 4.34. Found: C, 57.05, H, 7.82; N, 3.31; Cl, 8.26; H_2O, 4.56.

12-Carbomethoxy-2,3,11-trimethoxy-9-methyl-5,8,8a,11,-12,12a,13,13a-octahydro-6*H*,9*H*-benzo[*a*]pyrano[3,4-*g*]quinolizine (14). A solution of triphenylmethylsodium in ether[11] was prepared from triphenylmethyl chloride (42 g) in anhydrous ether (1000 ml). This was added under nitrogen pressure to a solution of **12** (6.1 g) in dry dioxane[12] (150 ml) at 15 °C until the deep red color of triphenylmethylsodium persisted. Methyl formate (4.8 g) was added and the solution stirred for 16 h while the ice water cooling bath warmed to room temperature. The entire mixture was poured into 2.4 M HCl (320 ml). The aqueous layer was extracted with ether (2 × 300 ml) and evaporated to dryness under reduced pressure and the resulting solid azeotroped twice with methanol. The residue (11.1 g) containing crude product and inorganic material was dissolved in 3.4% methanolic HCl (38 g) and refluxed for 3.5 h. The reaction mixture was evaporated to dryness and the residue distributed between ether (200 ml) and 5% K_2CO_3 (100 ml). The aqueous layer was separated and extracted with ether (2 × 100 ml). The combined ether solutions were dried over anhydrous K_2CO_3 and evaporated to give 3.9 g of **14**.

12-Carbomethoxy-2,3-dimethoxy-9-methyl-5,8,8a,12a,13,-13a-hexahydro-6*H*,9*H*-benzo[*a*]pyrano[3,4-*g*]quinolizine Hydrochloride (2 HCl). A solution of **14** (3.9 g) and *p*-toluenesulfonic acid (2.3 g) in $CHCl_3$ (350 ml) was azeotroped for 120 h using a Dean-Stark apparatus containing concentrated H_2SO_4 (20 ml) in the trap. The reaction mixture was poured into 5% K_2CO_3 (100 ml). The $CHCl_3$ layer was separated and the aqueous layer extracted with $CHCl_3$ (2 × 100 ml). The combined $CHCl_3$ solutions were dried over anhydrous K_2CO_3 and the solvent removed on the rotary evaporator. The crude oil was triturated with benzene to give four crops of crystalline material. Infrared spectroscopy indicated that three crops (1.8 g) consisted essentially of the desired compound. Intense bands at 1680 and 1600 cm^{-1} indicated the carbonyl and the conjugated double bond, respectively, of the desired compound; a small band at 1725 cm^{-1} indicated the presence of an impurity. The remaining crop of material (164 mg) showed strong absorption at 1725 cm^{-1} and was not combined with the above material for purification as the hydrochloride. The 1.8-g sample described above and 4.2 g of material obtained from 16 g of **14** in five separate reactions were combined and dissolved in ether (900 ml). The solution was dried (Na_2SO_4) and the hydrochloride salt was precipitated with anhydrous hydrogen chloride. The entire mixture was evaporated under reduced pressure and the remaining semisolid recrystallized from methanol/ether to give 3.7 g of **2** HCl as the two-thirds hydrate, mp 181–186 °C.

Anal. Calcd for $C_{21}H_{28}ClNO_5 \cdot \frac{2}{3}H_2O$: C, 59.81; H, 7.07; N, 3.31; Cl, 8.31; H_2O, 2.82. Found: C, 60.10; H, 7.06; N, 3.41; Cl, 8.47; H_2O, 2.55.

Acknowledgments. We thank Dr. V. Boekelheide for valuable discussions, the Analytical Research Department for analyses and spectral data, and the Pharmacology Department for biological data.

Registry No.—**2**, 60184-19-2; **2** HCl, 60209-13-4; **3**, 60209-14-5; **5** HCl epimer A, 60184-20-5; **5** HCl epimer B, 60209-15-6; **6**, 60184-21-6; **6** β-methyl epimer, 60209-16-7; **12**, 60184-22-7; **12** HCl, 60209-17-8; **14**, 60184-23-8.

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Stereospecific Synthesis of the Four 20,22-Epoxycholesterols and of (*Z*)-20(22)-Dehydrocholesterol[1]

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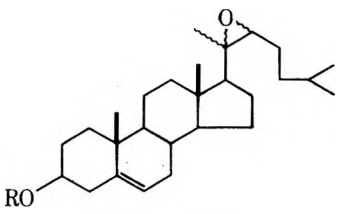
Received May 21, 1976

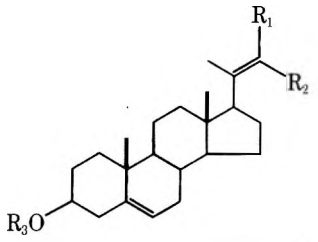
(20*R*,22*S*)-, (20*R*,22*R*)-, and (20*S*,22*R*)-epoxycholesterol have been synthesized stereospecifically from (20*R*,22*R*)-, (20*R*,22*S*)-, and (20*S*,22*S*)-3β,20,22-trihydroxycholest-5-ene 3β-acetate (**4a, 5a,** and **21**), respectively, via their 22-mesylates. (*Z*)-20(22)-Dehydrocholesterol has been prepared by pyrolysis of the 1,3-dioxolane derivative of (20*R*,22*S*)-3β,20,22-trihydroxycholest-5-ene 3β-acetate (**5a**). The stereoselective oxidations of (*E*)-3β-acetoxy-5,20(22)-cholestadiene with *m*-chloroperbenzoic acid gave (20*S*,22*S*)-20,22-epoxycholesterol (after hydrogenolysis of the 3β-acetate) and with osmium tetroxide yielded **21**. A total stereoselectivity has been obtained in the synthesis of the glycol (20*R*,22*R*)-3β,20,22-trihydroxycholest-5-ene 3β-acetate (**4a**) from the aldehyde (20*R*)-3β-acetoxy-20-tetrahydropyranyloxypregn-5-ene-20-carbaldehyde (**10b**) by an isoamylmagnesium bromide Grignard reaction.

In continuation of our work[3–5] on the mechanism of the biochemical conversion of cholesterol to pregnenolone and in view of suggestions[6–8] that 20,22-epoxycholesterol (**1a–d**)[9] and 20(22)-dehydrocholesterol (**2a,b**)[9] are obligatory intermediates in the biochemical transformation of cholesterol to pregnenolone, mediated by mitochondrial preparations of the rat adrenal cortex, it appeared important to prepare such sterols by stereospecific syntheses. There is no mention of the configuration of either the 20,22 double bond or of the 20,22-epoxide by these authors.[6–8] However, since

(20*R*,22*R*)-20,22-dihydroxycholesterol (**4b**) is a proven intermediate[3,4] immediately before the appearance of pregnenolone, it is tempting to speculate that if (a) 20(22)-dehydrocholesterol and 20,22-epoxycholesterol are "essential intermediates", as claimed by Kraaipoel et al.,[6-8] and if (b) these biochemical reactions proceed similarly to the chemical interconversions we present, then this would suggest the sequence (*Z*)-20,22-dehydrocholesterol → (20*R*,22*S*)-20,22-epoxycholesterol → (20*R*,22*R*)-20,22-dihydroxycholesterol. We have tested these two putative intermediates, the *E* olefin **2b**, and the three other 20,22-epoxides **1b**, **1c**, and **1d** and



1a, 20*R*, 22*S*; R = H
b, 20*R*, 22*R*; R = H
c, 20*S*, 22*S*; R = H
d, 20*S*, 20*R*; R = H
e, 20*R*, 22*R*; R = Ac
f, 20*S*, 22*S*; R = Ac



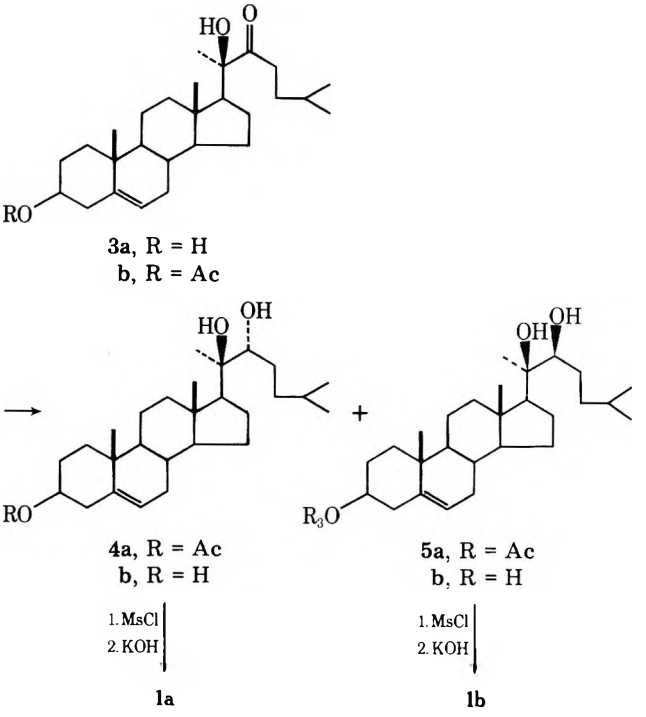
2a, R_1 = H; R_2 = C_5H_{11}; R_3 = H
b, R_1 = C_5H_{11}; R_2 = H; R_3 = H
c, R_1 = H; R_2 = C_5H_{11}; R_3 = Ac
d, R_1 = C_5H_{11}; R_2 = H; R_3 = Ac

found them not to be involved as intermediates in the metabolism of cholesterol to pregnenolone. A preliminary report concerning this has already appeared.[10] Since the epoxides and olefins can be synthesized stereoselectively via the corresponding 1,2-glycols,[11,12] we concentrated our efforts on the syntheses of these diols.

On the basis of our previous work,[13] we devised a synthetic route for **4a** and **5a** as shown in Scheme I.

Reduction of the acetate **3b**[13] with sodium borohydride gave the isomeric alcohols **4a** and **5a** in a ratio of 1:6 (85% yield), which could readily be separated by HPLC. Lithium aluminum hydride reduction of **4a** and of **5a** gave the known triols[13] **4b** and **5b**. Since this scheme was not suited for the preparation of large amounts of the more desirable 22*R* isomer **4b**, an alternate method, which had already been applied to the synthesis of crustecdysone,[14] was applied to the synthesis of **4b**. As outlined in Scheme II, treatment of pregnenolone acetate (**6**), first with acetone cyanohydrin and then with dihydropyran, gave a crude product which was separated[15] by fractional crystallization into the pure 20*R* isomer **7b**[13] and the 20*S* isomer **8b**. The isomer **7b** underwent a normal Grignard reaction to give **3a**. In the case of the isomer **8b**, however, the Grignard reaction led exclusively to a reductive cleavage of the C-20 hydroxy function to give (20*R*)-3β-acetoxycholest-5-en-22-one (**11b**). The cyanohydrin **7b** was reduced with diisobutylaluminum hydride to yield the imine which was then hydrolyzed to the aldehyde **10a**. Acetylation of **10a** with pyridine–acetic anhydride gave the acetate **10b** in 45% overall yield. The product showed ir absorption at 2680 and 1695 (–CHO), 1720 and 1245 (–$COOCH_3$), 1025 and 960

Scheme I



3a, R = H
b, R = Ac

4a, R = Ac
b, R = H

5a, R = Ac
b, R = H

1. MsCl
2. KOH

1a **1b**

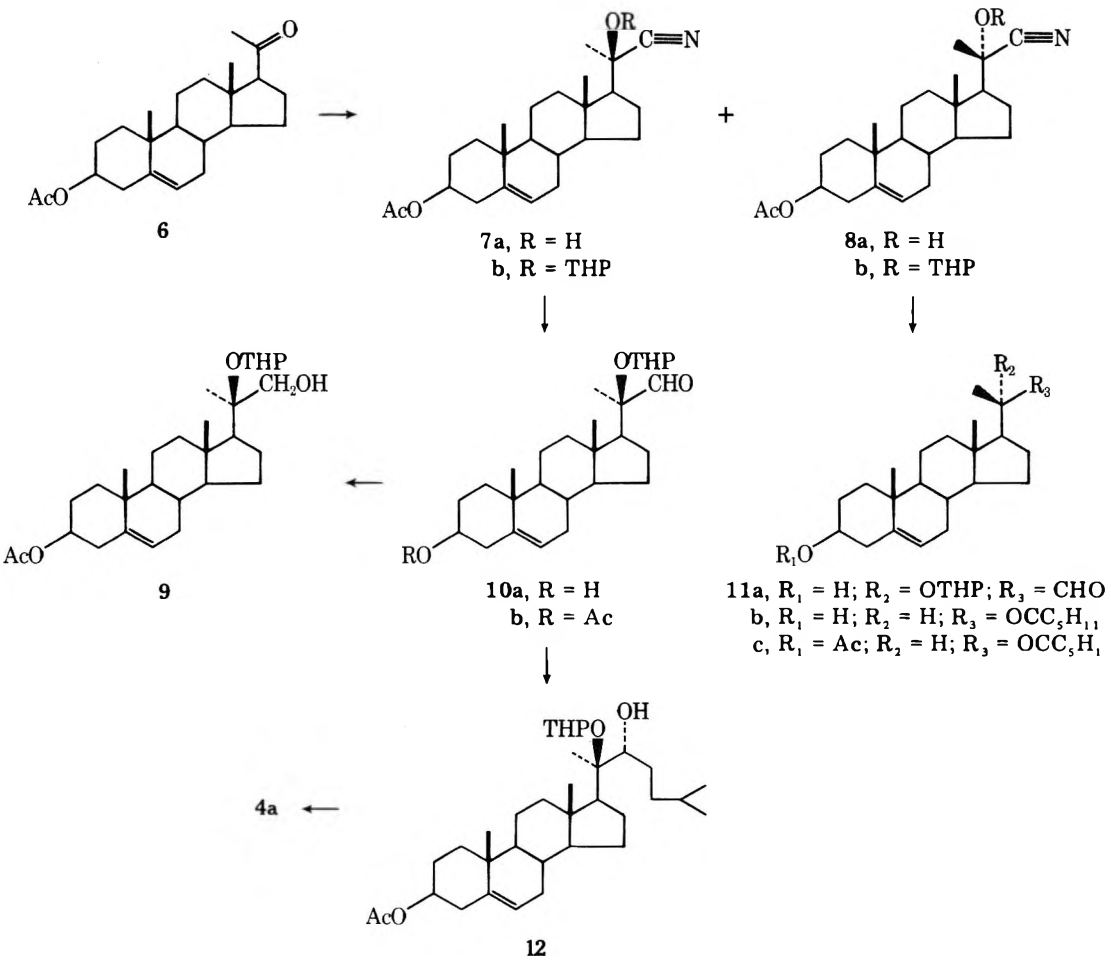
cm^{-1} (THP ether). The NMR spectrum gave signals at 9.75 (s, 1 H, –CHO), 4.67 (m, 1 H, –OCHO–), 1.02 (C-19 methyl), 0.78 ppm (C-18 methyl). Treatment of the aldehyde **10b** with isoamylmagnesium bromide at −70 °C gave three products (see Experimental Section) from which the desired product **12** could be isolated. The ir spectrum of **12** showed absorption at 3350 (–OH), 1720 and 1245 (–$COOCH_3$), 1025 and 960 cm^{-1} (THP ether) and the NMR spectrum (100 MHz) revealed the completed side chain 0.85 and 0.91 (26/27-CH_3), 2.02 (–$OCOCH_3$), and 4.75 ppm (–OCHO–). The mass spectrum showed peaks at *m/e* 444 ($M^+ - 102$), 429 ($M^+ - 117$), 426 ($M^+ - 120$), 384 ($M^+ - 162$), 85 (base peak). Removal of the tetrahydropyranyl protective group of **12** with dilute hydrochloric acid gave the acetate glycol **4a**. For routine syntheses crude **12** was converted, without purification of intermediates, to **4a**, which was readily obtained pure by preparative TLC. However, the reaction of the 20*S* aldehyde with isoamylmagnesium bromide, under the same conditions as used for **12**, yielded a galaxy of unidentified products which were not further investigated.

The epoxides **1a** and **1b** were synthesized by conventional procedures. Treatment of (20*R*,22*R*)-20,22-dihydroxycholesterol 3β-acetate (**4a**) and (20*R*,22*S*)-20,22-dihydroxycholesterol 3β-acetate (**5a**) with freshly distilled methanesulfonyl chloride in pyridine gave the 22-mesylates which were directly converted by aqueous potassium hydroxide treatment to the corresponding epoxides **1a** and **1b**, in yields of 66 and 80%, respectively. The mass spectra of these epoxides showed major peaks at *m/e* 400 (M^+, base peak), 385 ($M^+ - 15$), 382 ($M^+ - 18$). The products had a strong ir absorption at 3350 cm^{-1} (–OH) and the NMR spectra gave a characteristic signal for **1a** at 2.7 (22-H) and at 2.65 ppm (22-H) for **1b**.

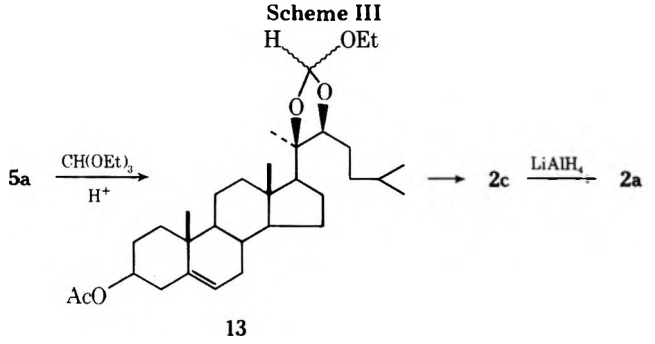
In addition to the already known (*E*)-20(22)-dehydrocholesterol[16-18] we sought the corresponding *Z* isomer **2a**. This was prepared according to Scheme III.

Following the procedure of Eastwood et al.,[19,20] the glycol **5a** was reacted with triethyl orthoformate to give the 1,3-dioxolane **13**, which, without further purification, was pyrolyzed at reduced pressure under acidic conditions. The resulting acetate **2c** was hydrogenolyzed with lithium aluminum hydride to give **2a** in an overall yield of 45%. Table I shows the

Scheme II



Scheme III



striking differences in melting point and the proton resonances of the NMR spectra of **2c** and of **2d**, a difference also borne out by their ^{13}C NMR spectra.[21] In addition an alternate synthesis (Scheme IV) was carried out in order to provide labeled substrates for biological experiments.[10]

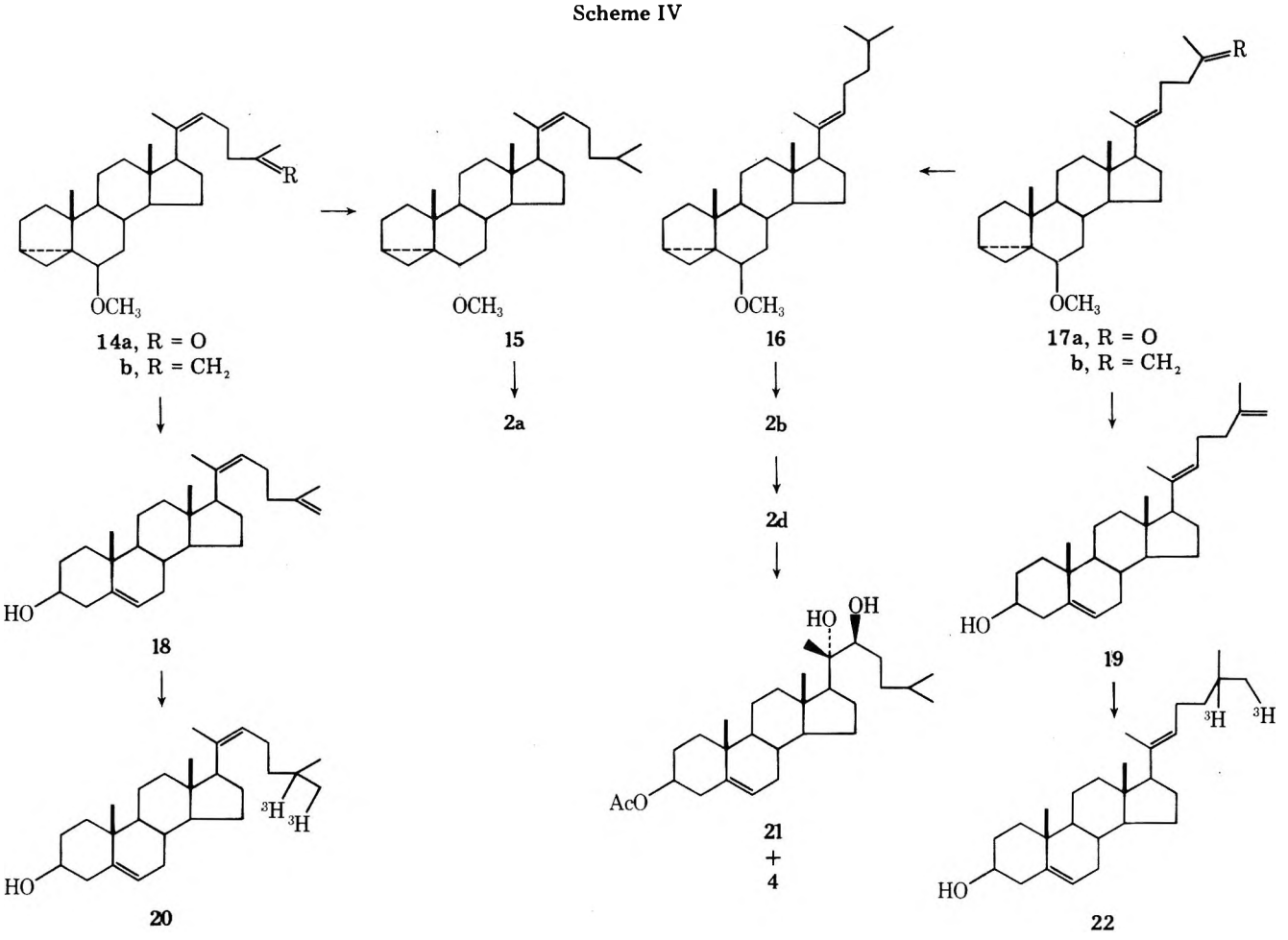
The known (*Z*)- and (*E*)-20(22)-dehydro ketones[22] **14a** and **17a** were treated with methylenetriphenylphosphorane to give their respective 20(22),25-dienes, **14b** and **17b**. Selective hydrogenation of the terminal double bond over tris(triphenylphosphine)rhodium chloride gave the desired *E* isomer **16** and the *Z* isomer **15**, which were hydrolyzed to **2b** and **2a** under the condition of McKennis.[23] This reduction was also carried out with tritium (experimental details will be given in a subsequent communication) to give the 25,26-tritiated products **20** and **22**, respectively.

Olefins **2a** and **2b** were each selectively oxidized with *m*-chloroperbenzoic acid. The oxidation of the *E* olefin gave two epoxides **1b** and **1c** in the ratio of 2:3. Only after acetylation could the mixture be separated on preparative TLC. Their respective configurations were established by comparison with the epoxide **1b** of known configuration, since it was derived from the known glycol **5a**.[24] The NMR spectra of these two epoxides (from **2b**) show different signals for the 18-CH_3 and for the 22-H (see Table I). As opposed to the epoxidation of the *E* isomer **2b**, the *Z* isomer **2a** gave only one epoxide upon treatment with *m*-chloroperbenzoic acid. This product had the 20*R*,22*S* configuration and was identical in all respects with an authentic sample of **1a**, obtained from **4a** (Scheme I). The stereospecific attack of the 20(22) double bond of this reaction can readily be explained by steric hindrance.[11,25] Selective oxidation of **2d** with osmium tetroxide followed by hydrolysis of the formed osmates with aqueous sodium bisulfite in pyridine gave (20*R*,22*R*)- and (20*S*,22*S*)-3β,20,22-trihydroxycholest-5-ene 3β-acetate (**4a** and **21**) (76% yield) in a ratio of 1:13. Their configurations were established by comparison with an authentic sample of **4a** in Scheme I and the proton chemical shifts of 21-CH_3 define the C-20 configuration.[26] These two glycols were separated by HPLC and the

Table I

	δ, ppm			
	18-Me	21-Me	22-H	Mp, °C
1b	0.80		2.65	135–137
1c	0.68		2.82	123–125
2c	0.69	1.72	5.29	82–83
2d	0.54	1.61	5.15	123–125

Scheme IV



20*S*,22*S* glycol **21** was converted, as indicated in Scheme I, to the epoxide **Id.**

Experimental Section

General. Low-resolution mass spectra were measured with either a LKB 9000 mass spectrometer or Finnigan 1015 mass spectrometer. NMR spectra, reported in parts per million, were obtained in $CDCl_3$ solution using tetramethylsilane as internal reference. The 60-MHz NMR spectra were taken on a Varian Associates DA-60 spectrometer, and the 100-MHz NMR spectra were run on a Varian Associates HA-100 spectrometer. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y., and Instranal Laboratory, Inc., Rensselaer, N.Y. All melting points reported are uncorrected.

All preparative thin layer chromatography (TLC) plates were 20 × 20 cm, and 1000-mm thick silica gel.

Anhydrous tetrahydrofuran was prepared by distillation from lithium aluminum hydride. Anhydrous dimethyl sulfoxide was obtained by vacuum distillation from calcium hydride into 4A molecular sieves. Anhydrous methylene chloride was provided by washing with concentrated sulfuric acid, then with aqueous potassium carbonate and water, followed by drying over calcium chloride, and distillation from P_2O_5.

$NaBH_4$ Reduction of Acetate Ketol 3b to Alcohols 4a and 5a. To the stirred solution of 1.6 g of **3b**[13] in 35 ml of tetrahydrofuran and 20 ml of methanol in an ice bath, 314 mg of sodium borohydride was added slowly. The mixture was then stirred for 30 min in the ice bath and at 25 °C for 2 h. After dilute hydrochloric acid solution had been added to consume the excess hydride, the reaction mixture was poured into ice water. The resulting precipitate was filtered, washed with water, and dried to give 1.55 g of a mixture of alcohols, which were separated by HPLC. This separation was carried out in methylene chloride–methanol (1:4) on 2 × 8 ft Bondapak C18/Porasil B column. The 22*R* and 22*S* isomers, **4a** and **5a**, were completely resolved in two recycles in a ratio of 1:6. The former had the longer retention time, and the smaller R_f.

4a had mp 192–194 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 4.60 (m, 1 H, C-3 proton), 3.40 (m, 1 H, C-22 proton), 2.03 (s, 3 H, CH_3COO–), 1.23 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.92 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.88 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.48; H, 10.47.

5a had mp 182–184 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 4.60 (m, 1 H, C-3 proton), 3.23 (m, 1 H, C-22 proton), 2.03 (s, 3 H, CH_3COO–), 1.27 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.92 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.88 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.41; H, 10.23.

(20*R*)-3β-Acetoxy-20-(2′-tetrahydropyranyloxy)pregn-5-ene-20-carbonitrile (7b) and (20*S*)-3β-Acetoxy-20-(2′-tetrahydropyranyloxy)pregn-5-ene-20-carbonitrile (8b). A mixture of **6** (50 g), potassium cyanide (5 g), and 230 ml of acetone cyanohydrin was stirred for 3 h at room temperature and poured into 750 ml of water. The resulting precipitate was filtered and washed with water–acetic acid (49:1), ethanol, and ether–hexane (1:5), and dried in a vacuum desiccator overnight to give 40 g of mixture of **7a** and **8a.**

To a cooled solution of crude cyanohydrin mixture (40 g) and *p*-toluenesulfonic acid (800 mg) in 450 ml of anhydrous tetrahydrofuran was added 50 ml of dihydropyran. The mixture was allowed to stand overnight, poured into cold saturated sodium bicarbonate solution, and extracted thoroughly with methylene chloride. The combined extracts were dried (Na_2SO_4) and evaporated in vacuo to give 50 g of nitriles **7b** and **8b** in ca. 1:1 ratio, as well as a small amount of unchanged cyanohydrin which could be removed by recrystallizations from methanol. The combined crystals were then recrystallized from cyclohexane to enrich the 20*R* isomer **7b** in the crystal portion and the 20*S* isomer in the filtrate. Pure **7b** could be obtained by five to eight recrystallizations from cyclohexane. The 20*S* isomer enriched mixture was recrystallized from methanol (four to six times) to give pure **8b. 8b** had a greater R_f than **7b** (2% ethyl acetate in benzene as eluent).

7b had mp 219–222 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 5.08 (m, 1 H, –OCHO–), 4.60 (m, 1 H, C-3 proton), 2.03 (s, 3 H, CH_3COO–), 1.60 (s, 3 H, C-21 methyl), 1.03 ppm (s, 6 H, C-18 and C-19 methyls).

8b had mp 179–180 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 5.13 (m, 1 H, –OCHO–), 4.60 (m, 1 H, C-3 proton), 2.03 (s, 3 H, CH_3COO–), 1.63 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.97 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{43}NO_4$: C, 74.16; H, 9.23; N, 2.98. Found: C, 73.94; H, 9.16; N, 3.21.

(20*R*)-3β-Acetoxy-20-(2′-tetrahydropyranyloxy)pregn-5-ene-20-carbaldehyde (10b). To a solution of 2 g of **7b** in 150 ml of anhydrous ether and 60 ml of anhydrous benzene at −70 °C, 20 ml of a 20% solution of diisobutylaluminum hydride in hexane was slowly added with a syringe and under a nitrogen atmosphere. The resulting solution was stirred for 15 h at room temperature. The aluminum complex was decomposed by cautious addition of a cold 2 N sodium hydroxide solution in the ice bath and the mixture was stirred for an additional 30 min at room temperature. The ether layer was separated from the aqueous layer which was extracted with ether. The ethereal extract was filtered with the aid of Celite, dried (Na_2SO_4), and evaporated in vacuo. To the resulting residue in 10 ml of ethanol, 2 ml of acetic acid and 3.5 ml of water were added while stirring for 30 min at room temperature. Then the mixture was diluted with water and the resulting precipitate filtered and washed thoroughly with water. After drying 1.24 g of hydroxy aldehyde **10a** was obtained which was sufficiently homogeneous on TLC to be converted to **10b:** NMR δ (60 MHz) 9.75 (s, 1 H, –CHO), 5.37 (m, 1 H, C-6 proton), 4.67 (m, 1 H, –OCHO–), 1.34 (s, 3 H, C-21 methyl), 1.02 (s, 3 H, C-19 methyl), 0.78 ppm (s, 3 H, C-18 methyl).

The acetate aldehyde **10b** was prepared by dissolving **10a** in 10 ml of pyridine and 1 ml of acetic anhydride. The solution was allowed to stand overnight at room temperature, after which time it was dumped into ice. By recrystallization from methanol 0.9 g was obtained: 151–153 °C; NMR δ (60 MHz) 9.72 (s, 1 H, –CHO), 5.37 (m, 1 H, C-6 proton), 4.67 (m, 1 H, –OCHO–) 4.58 (m, 1 H, C-3 proton), 2.03 (s, 3 H, CH_3COO–), 1.34 (s, 3 H, C-21 methyl), 1.02 (s, 3 H, C-19 methyl), 0.78 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{44}C_5$: C, 73.69; H, 9.38. Found: C, 73.69; H, 9.50.

(20*S*)-3β-Hydroxy-20-(2′-tetrahydropyranyloxy)pregn-5-ene-20-carbaldehyde (11a). The solution of 2 g of **8b** in 150 ml of anhydrous ether was converted to 1.1 g of **11a** in the same manner as described for **10b:** mp 113–116 °C; ir (KBr pellet) 3540 (OH), 1710 and 2680 (C=O), 1025 and 960 cm^{-1} (THP ether); NMR δ (60 MHz) 9.73 (s, 1 H, –CHO), 5.37 (m, 1 H, C-6 proton), 4.67 (m, 1 H, –OCHO–), 1.42 (s, 3 H, C-21 methyl), 1.00 (s, 3 H, C-19 methyl), 0.78 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.29; H, 9.69.

(20*R*,22*R*)-3β,20,22-Trihydroxycholest-5-ene 3β-Acetate (4a) from 10b. To a stirred solution of **10b** (300 mg) in 30 ml of anhydrous methylene chloride, cooled to −70 °C under a nitrogen atmosphere, was added dropwise over a period of 5 min 30 ml of a solution of isoamylmagnesium bromide, which was prepared from 500 mg of magnesium, 3.5 ml of isoamyl bromide, and 15 ml of anhydrous ether, and in the end the ether was replaced by dry methylene chloride (40 ml). Then the dry ice bath was removed and immediately 15 ml of saturated sodium sulfate solution was added dropwise. After stirring at room temperature for 30 min, the mixture was dried (Na_2SO_4) and filtered through a Celite plug, and the solvent evaporated in vacuo to give 360 mg of crude oily alcohol **12.** An aliquot of the crude product was purified on a preparative TLC (15% acetone in hexane as eluent), revealing three compounds in a ratio of 1:12:2 (in order of increased polarity). The least polar fraction was identical with starting material **10b** in all aspects. The middle fraction **12** had NMR δ (100 MHz) 5.37 (m, 1 H, C-6 proton), 4.75 (m, 1 H, –OCHO–), 2.02 (s, 3 H, CH_3COO–), 1.28 (s, 3 H, C-21 methyl), 1.01 (s, 3 H, C-19 methyl), 0.88 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.80 ppm (s, 3 H, C-18 methyl); mass spectrum (70 eV) *m/e* 459 ($M^+ - 85$), 442 ($M^+ - 102$), 427 ($M^+ - 117$), 424 ($M^+ - 120$), 382 ($M^+ - 162$), 85 (base peak).

Anal. Calcd for $C_{34}H_{56}O_5$: C, 74.95; H, 10.36. Found: C, 74.89; H, 10.93.

The most polar fraction 9 had NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 4.73 (m, 1 H, –OCHO–), 3.72 and 3.23 (2 d, 2 H, J = 12 Hz, $-CH_2OH$), 2.03 (s, 3 H, CH_3COO–), 1.37 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.80 ppm (s, 3 H, C-18 methyl).

To the solution of crude **12** in 4 ml of THF–H_2O (9:1) 0.05 N hydrochloric acid solution was added until it became turbid. The mixture was stirred for 20 h and poured into cold saturated sodium bicarbonate solution. The mixture was extracted with methylene chloride and back-washed with saturated sodium chloride solution and water. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The crude product was cleaned on preparative TLC (20% acetone in hexane as eluent) to give 70 mg of **4a** which was identical with the authentic sample (Scheme I) in all aspects.

Grignard Reaction of 8b with Isoamylmagnesium Bromide (11c). Following the method of Chaudhuri et al.,[24] 2 g of **8b** was reacted with isoamylmagnesium bromide and the resulting imine was hydrolyzed in acetic acid and benzene. The crude product **11b,** without further purification, was acetylated in the usual manner. Recrystallization from methanol gave 650 mg of **11c**[27] with mp 139–140 °C, and identical ir and NMR spectra with a sample of authentic material.

(20*R*,22*S*)-20,22-Epoxycholesterol (1a) and (20*R*,22*R*)-20,22-Epoxycholesterol (1b). To the ice-cold solution of 200 mg of acetate glycol **4a** in 1.5 ml of pyridine was added 0.14 ml of methanesulfonyl chloride (freshly distilled at atmospheric pressure). The solution was kept in the ice bath for 10 min and at room temperature for 20 min. Then the solution of 380 mg of potassium hydroxide in 3 ml of water was added and, after heating under reflux for 30 min, the solution was cooled to room temperature and slowly diluted with water. The precipitate was filtered, washed thoroughly with water, and dried to give 194 mg of crude epoxide. Purification by preparative TLC (15% acetone in hexane at eluent), followed by recrystallization from methanol, gave 115 mg of **1a:** mp 113–114 °C; NMR δ (100 MHz) 5.37 (m, 1 H, C-6 proton), 3.50 (m, 1 H, C-3 proton), 2.68 (m, 1 H, C-22 proton), 1.28 (s, 3 H, C-21 methyl), 1.01 (s, 3 H, C-19 methyl), 0.89 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.79 ppm (s, 3 H, C-18 methyl); mass spectrum (22.5 eV) M^+ *m/e* 400 (base peak).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.68; H, 10.86.

Conversion of 5a to 1b. When 200 mg of **5a** was treated in the same manner as described above, 140 mg of epoxide **1b** was obtained: mp 135–137 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 3.50 (m, 1 H, C-3 proton), 2.65 (m, 1 H, C-22 proton), 1.33 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.92 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.80 ppm (s, 3 H, C-18 methyl); mass spectrum (22.5 eV) M^+ *m/e* 400 (base peak).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.94; H, 10.81.

(*Z*)-3β-Hydroxycholesta-5,20(22)-diene (2a). A solution of acetate glycol **5a** (500 mg), ethyl orthoformate (4 ml), and benzoic acid (10 mg) was stirred at 110 °C for 3 h. To the crude 1,3-dioxolane **13,** after evaporation of the solvent in vacuo, 100 mg of benzoic acid was added. The mixture was heated at 170–175 °C for 15 min at 5 Torr. After cooling, the oily product was dissolved in ether and the solution was washed with saturated sodium bicarbonate solution, dried (Na_2SO_4), and evaporated in vacuo. The crude product was purified by column chromatography over alumina. Elution with hexane gave 220 mg of olefin **2c.** An analytical sample was prepared by recrystallization from methanol: mp 82–83 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 5.29 (m, 1 H, C-22 proton), 4.60 (m, 1 H, C-3 proton), 2.03 (s, 3 H, CH_3COO–) 1.72 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.88 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.69 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.76; H, 10.71.

2a was prepared by the addition of 200 mg of **2c** in 10 ml of anhydrous ether to 25 mg of $LiAlH_4$ in 15 ml of anhydrous ether and stirring at reflux for 30 min under anhydrous conditions. The excess hydride was decomposed by cautious addition of 2 N sodium hydroxide solution. Finally the precipitate was filtered with the aid of Celite and washed with methylene chloride. Evaporation of the solvent gave 172 mg of syrup which failed to crystallize: NMR δ (100 MHz) 5.37 (m, 1 h, C-6 proton), 5.29 (m, 1 H, C-22 proton), 3.50 (m, 1 H, C-3 proton), 1.72 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.88 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.69 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.38; H, 11.53.

(*Z*)-6β-Methoxy-3α,5-cyclo-5α-cholesta-20(22),25-diene (14b) and (*E*)-6β-Methoxy-3α,5-cyclo-5α-cholesta-20(22),25-diene (17b). A mixture of 78 mg of 54.3% sodium hydride mineral oil dispersion in 1.4 ml of anhydrous dimethyl sulfoxide was stirred at 70 °C under a nitrogen atmosphere until no hydrogen evolution could be detected. The mixture was cooled to room temperature and a solution of 0.63 g of methyltriphenylphosphonium bromide in 5 ml of anhydrous dimethyl sulfoxide was added, immediately producing a yellowish solution. Then a solution of 350 mg of **14a**[22] in 2 ml of anhydrous tetrahydrofuran was added and the resulting mixture was stirred at 60 °C for 3 h. The reaction mixture was then cooled and poured into ice water. The mixture was extracted thoroughly with

hexane and the combined extracts were washed with water and saturated sodium chloride solution, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over alumina. Elution with hexane gave 240 mg of oily diene **14b**: NMR δ (60 MHz) 5.30 (m, 1 H, C-22 proton), 4.70 (s, 2 H, >C=CH_2), 3.35 (s, 3 H, -OCH_3), 2.78 (m, 1 H, >CHOMe), 1.73 (s, 6 H, C-21 and C-26 methyls), 1.03 (s, 3 H, C-19 methyl), 0.72 (s, 3 H, C-18 methyl), 0.30–0.67 ppm (m, 3 H, cyclopropyl); mass spectrum (22.5 eV) *m/e* 396 (M^+), 381 ($M^+ - 15$), 364 ($M^+ - 32$), 349 ($M^+ - 47$), 285 ($M^+ - 111$), 253 (base peak, $M^+ - 143$).

Anal. Calcd for $C_{28}H_{44}O$: C, 84.78; H, 11.18. Found: C, 84.67; H, 11.11.

Conversion of 17a to 17b. When 350 mg of **17a** was treated in the same manner as described above, 200 mg of **17b** was obtained as oil: NMR δ (60 MHz) 5.18 (m, 1 H, C-22 proton), 4.70 (s, 2 H, >C=CH_2), 3.32 (s, 3 H, -OCH_3), 2.78 (m, 1 H, >C**H**OCH_3), 1.73 (s, 3 H, C-27 methyl), 1.65 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.58 (s, 3 H, C-18 methyl), 0.30–0.67 ppm (m, 3 H, cyclopropyl); mass spectrum (22.5 eV) *m/e* 396 (M^+), 381 ($M^+ - 15$), 364 ($M^+ - 32$), 349 ($M^+ - 47$), 285 ($M^+ - 111$), 253 (base peak, $M^+ - 143$).

Anal. Calcd for $C_{28}H_{44}O$: C, 84.78; H, 11.18. Found: C, 84.99; H, 11.26.

(*Z*)-6β-Methoxy-3α,5-cyclo-5α-cholest-20(22)-ene (15) and (*E*)-6β-Methoxy-3α,5-cyclo-5α-cholest-20(22)-ene (16). To a solution of 160 mg of diene **14b** in 2.5 ml of benzene, 25 mg of tris(triphenylphosphine)rhodium chloride was added and the homogeneous solution was stirred under an atmosphere of hydrogen and stopped when the theoretical amount of hydrogen had been absorbed (ca. 6 h). The solution was filtered through a dry column of 15 g of alumina. The column was washed with hexane and the combined solvent fractions were evaporated in vacuo to give 90 mg of **15**: NMR δ (100 MHz) 5.30 (m, 1 H, C-22 proton), 3.33 (s, 3 H, -OCH_3), 2.78 (m, 1 H, >C**H**OMe), 1.70 (s, 3 H, C-21 methyl), 1.02 (s, 3 H, C-19 methyl), 0.87 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.70 (s, 3 H, C-18 methyl), 0.30–0.67 ppm (m, 3 H, cyclopropyl).

Anal. Calcd for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.58; H, 11.64.

E olefin **16** was prepared from **17b** in the manner described above for the *Z* isomer (60% yield): NMR δ (60 MHz) 5.20 (m, 1 H, C-22 proton), 3.35 (s, 3 H, -OCH_3), 2.78 (m, 1 H, >C**H**OMe). 1.30 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.92 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.58 (s, 3 H, C-18 methyl), 0.30–0.67 ppm (m, 3 H, cyclopropyl).

Anal. Calcd for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.24; H, 11.57.

(*Z*)-3β-Hydroxycholesta-5,20(22)-diene (2a) and (*E*)-3β-Hydroxycholesta-5,20(22)-diene (2b). To 2 ml of dioxane containing 1.5 ml of water at room temperature under a nitrogen atmosphere, 100 mg of **15** in 1.1 ml of dioxane was added and the mixture heated to 80–85 °C until it became homogeneous. Then 5.5 mg of *p*-toluenesulfonic acid was added and heating was continued at 80 °C for 6 h. The reaction mixture was cooled, poured into saturated sodium bicarbonate solution, and extracted with ether. The ethereal extract was washed with water, and dried (Na_2SO_4). The residue, after removal of the solvent in vacuo, was purified by preparative TLC (10% ethyl acetate in benzene as eluent) to give 87 mg of oily diene **2a** which was identical in all respects with the material from Scheme III.

The *E* diene **2b**[16-18] was prepared in the same manner as described above to give the known product in 89% yield.

Selective Oxidation of 2b with *m*-Chloroperbenzoic Acid, 1b and 1c. To a cold solution of 450 mg of diene **2d** in 9 ml of methylene chloride, 200 mg of *m*-chloroperbenzoic acid in 9 ml of methylene chloride was added. The mixture was allowed to stand for 20 h at 0–2 °C and then was transferred to a separatory funnel with the aid of more methylene chloride. The organic layer was washed with 2 N sodium hydroxide solution, water, and brine, and dried (Na_2SO_4). The residue, after removal of solvent in vacuo, was purified by preparative TLC (5% acetone in hexane) to give 147 mg of **1e** and 219 mg of **1f**. The former had the greater R_f. An analytical sample was prepared by recrystallization from methanol.

1e had mp 103–104 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 4.60 (m, 1 H, C-3 proton), 2.63 (m, 1 h, C-22 proton), 2.03 (s, 3 H, CH_3COO–), 1.32 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.90 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.80 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.91; H, 10.49.

1f had mp 91–93 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 4.60 (m, 1 H, C-3 proton), 2.82 (m, 1 H, C-22 proton), 2.03 (s, 3 H, CH_3COO–), 1.30 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.90 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.68 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.79; H, 10.39.

1c was prepared by treating **1f** with lithium aluminum hydride in the same manner as described for **2a** (92% yield). An analytical sample was prepared by recrystallization from methanol: mp 123–125 °C; NMR δ (60 MHz) 5.73 (m, 1 H, C-6 proton), 3.50 (m, 1 H, C-3 proton), 2.82 (m, 1 H, C-22 proton), 1.30 (s, 3 H, C-21 methyl), 1.02 (s, 1 H, C-19 methyl), 0.92 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.68 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.92; H, 11.13.

Oxidation of 2a to 1a with *m*-Chloroperbenzoic Acid. 2a (150 mg) was oxidized with *m*-chloroperbenzoic acid in the same manner as described above. The crude product was purified by preparative TLC to give 102 mg of **1a** which was identical with the authentic sample in all aspects.

(20*S*,22*S*)-20,22-Dihydroxycholesterol 3β-Acetate (21). A mixture of 1.7 g of **2d** and 1 g of OsO_4 in 70 ml of anhydrous ether was allowed to stand at room temperature for 19 h. Then the solvent was evaporated in vacuo. To this mixture was added 100 ml of pyridine and 3.5 g of sodium bisulfite in 80 ml of water, and stirred at room temperature for 18 h. This mixture was poured into water and extracted with ether. The ethereal extract was washed with 2 N hydrochloric acid solution, saturated sodium bicarbonate solution, and water, and dried (Na_2SO_4). Purification on preparative TLC (20% acetone in hexane as eluent) gave 1.4 g of glycol mixture **21** and **4a** which were separated by HPLC in a ratio of 13:1 in the same system as described for **4a** and **5a**. The former had the shorter retention time. An analytical sample was prepared by recrystallization from methanol: mp 175–178 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 4.60 (m, 1 H, C-3 proton), 3.72 (m, 1 H, C-22 proton), 2.03 (s, 3 H, CH_3COO–), 1.07 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.90 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.88 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.81; H, 10.30.

Epoxide **1d** was prepared from **21** (300 mg) in the same manner as described in Scheme I. Purification by preparative TLC (15% acetone in hexane as eluent) gave 185 mg of epoxide **1d**. An analytical sample was prepared by recrystallization from methanol: mp 133–135 °C; NMR δ (100 MHz) 5.37 (m, 1 H, C-6 proton), 3.50 (m, 1 H, C-3 proton), 2.45 (m, 1 H, C-22 proton), 1.30 (s, 3 H, C-21 methyl), 1.01 (s, 3 H, C-19 methyl), 0.90 (s, 3 H, C-18 methyl), 0.89 ppm (d, 6 H, J = 6 Hz, C-26 and C-27 methyls).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.90; H, 10.91.

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Registry No.—**1a**, 60132-86-7; **1b**, 60084-21-1; **1c**, 60132-87-8; **1d**, 60182-58-3; **1e**, 60084-22-2; **1f**, 60132-88-9; **2a**, 60132-89-0; **2b**, 59905-87-2; **2c**, 60132-90-3; **2d**, 54548-85-5; **3b**, 60084-23-3; **4a**, 60084-24-4; **5a**, 60183-23-5; **6**, 1778-02-5; **7a**, 60182-59-4; **7b**, 60084-25-5; **8a**, 60132-91-4; **8b**, 60084-26-6; **9**, 60084-27-7; **10a**, 60084-28-8; **10b**, 60134-79-4; **11a**, 60084-29-9; **12**, 60084-30-2; **13**, 60084-31-3; **14a**, 53139-52-9; **14b**, 60084-32-4; **15**, 60084-33-5; **16**, 60084-34-6; **17a**, 53139-53-0; **17b**, 60084-35-7; **21**, 60132-92-5; isoamyl bromide, 107-82-4.

References and Notes

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Stereochemistry of 1,3-Cyclohexadienes. Conformational Preferences in 9-Substituted 9,10-Dihydrophenanthrenes

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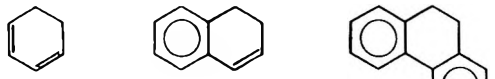
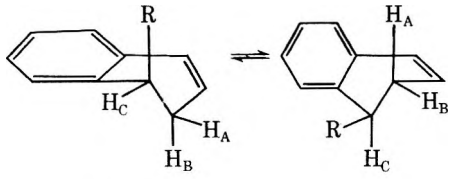
A series of 9-R-9,10-dihydrophenanthrenes [R = CH_3, CN, $C(CH_3)_3$, $COCH_3$, CO_2CH_3, $CO_2CH_2CH_3$, OH, $Si(CH_3)_3$] as well as two related 5,6-dihydrochrysenes, are studied by NMR analysis of the three spin H_9, H_{10}, $H_{10'}$ system. The coupling constants thus obtained are then used to determine the conformational preferences of these mobile ring systems with regard to the location of substituents in pseudoaxial or pseudoequatorial positions. All substitutes except cyano were found to preferentially adopt the pseudoaxial conformation.

The majority of studies concerned with the stereochemistry of 1,3-cyclohexadiene ring systems (**1**–**3**) have dealt with



1 **2** **3**

derivatives of 1,2-dihydronaphthalene (**2**).[1-5] In the case of 1-substituted 1,2-dihydronaphthalenes, NMR investigations into the equilibrium between **4a′** and **4e′** were carried out by computer analysis of the ABC spectra resulting from the benzylic and allylic protons.[2-4] In both **4a′** and **4e′** the protons



4a′ **4e′**

H_B and H_C interact in a pseudoaxial/pseudoequatorial relationship and the spin interactions are equivalent, leading to a J_{ae} coupling constant which is independent of the position of equilibrium, and values of 6.8 Hz have been determined.[2] On the other hand, protons H_A and H_C interact as pseudoequatorial/pseudoequatorial in **4a′** and pseudoaxial/pseudoaxial in **4e′**, and the time average value of this coupling constant is directly related to the conformational populations. Thus, using values of $J_{aa} = 16$ and $J_{ee} = 2$ Hz, and the relationship

$$J_{AC} = xJ_{ee} + (1 - x)J_{aa} \quad (1)$$

the fraction (x) of the conformations with the group in the pseudoaxial position was calculated for a number of R groups.[4]

Although the 9,10-dihydrophenanthrene system (**3**) would appear to be closely related, discrepancies have been noted in comparing coupling constant data with the dihydronaphthalenes. Thus, one report[1] based on ^{13}C satellite resonances provides values of 8.3 and 5.8 Hz for **3**, presumably corresponding to the average $\frac{1}{2}(J_{aa} + J_{ee})$ value (9.4 in **2**) and to J_{ae} (7.0 in **2**), respectively. Furthermore, 9,10-dihydro-4,5-dimethylphenanthrene shows $\frac{1}{2}(J_{aa} + J_{ee}) = 10.59$ and $J_{ae} = 3.97$ Hz,[6] whereas the values for 9-dimethylamino-9,10-dihydro-4,5-dimethylphenanthrene are $\frac{1}{2}(J_{aa} + J_{ee}) = 7.92$ and $J_{ae} = 3.5$ Hz.[7] Katritzky et al.[2] have suggested that the contrast between 1,2-dihydronaphthalene and 9,10-dihydrophenanthrene may be due to differences in dihedral angles, although de la Mare et al.[5] have presumed approximately equal dihedral angles for both systems in a more recent NMR study. Furthermore, these latter workers have suggested that their coupling constant data for *cis*- and *trans*-9-acetoxy-10-chloro-9,10-dihydrophenanthrene compare favorably with the corresponding values for 9-dimethylamino-9,10-dihydro-4,5-dimethylphenanthrene when electronegativities are taken into account. However, a recent NMR investigation[6] on 9,10-dihydro-4,5-dimethylphenanthrene itself has suggested a much larger dihedral angle between the benzene rings in this system as a result of 4- and 5-methyl steric interaction.

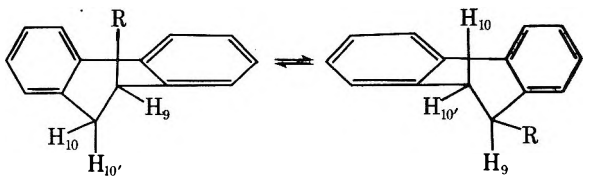
We now report NMR special analysis of a series of 9-substituted 9,10-dihydrophenanthrenes (**5a′** ⇌ **5e′**). These studies were conducted in order to obtain accurate coupling constant data for comparison with the 1,2-dihydronaphthalene ring system and to determine the conformational preferences of the 9 substituents.

Since H_9 and H_{10} are dipseudoequatorial in **5a′** and dipseudoaxial in **5e′**, $J_{9,10}$ is expected to reflect the relative contributions from each conformation. On the other hand, H_9

Table I. NMR Data for 9-R-9,10-Dihydrophenanthrenes [a]

Registry no.	R (solvent) [b]	$J_{9,10}$	$J_{9,10'}$	$J_{10,10'}$	δ_9	δ_{10}	$\delta_{10'}$	Rms error	δ_{arom}, ppm	% pseudo-axial [c]
56666-55-8	CN (CCl_4)	9.89	6.37	−14.57	223.66	175.25	178.90	0.026	7.3, 7.8	44
52978-94-6	CH_3 (CS_2)	5.24	6.70	−14.73	213.71	213.01	247.47		7.1, 7.6	77
60084-36-8	$C(CH_3)_3$ (CD_3CN)	1.50	7.11	−16.57	160.93	190.93	182.10	0.100	7.2	100
60084-37-9	$COCH_3$ (CCl_4)	3.81	6.02	−15.38	223.63	199.19	188.06	0.095	7.25, 7.7	86
32892-19-6	CO_2CH_3 (CCl_4)	5.76	6.64	−15.40	223.00	177.95	192.28	0.023	7.05, 7.5	73
60084-38-0	$CO_2CH_2CH_3$ (CCl_4)	5.38	6.86	−14.57	216.25	174.64	186.08	0.022	7.05, 7.5	75
60084-39-1	OH [e] ($CDCl_3$)	2.9	5.9	−15.2	287.0	183.0	183.0		7.3, 7.8	94
56465-93-1	$Si(CH_3)_3$ ($CDCl_3$)	1.95	6.79	−15.5	144.0	172.3	196.8		7.3, 7.8	100

[a] 60 MHz unless otherwise indicated. [b] In many cases, δ_{10} and $\delta_{10'}$ were nearly identical, and several solvents were tried to maximize the difference. [c] See ref 4b. [d] 100 MHz, methyl decoupled (this analysis was performed by Professor J. B. Stothers). [e] Chemical shift data provided for $CDCl_3$ solution, J values determined after addition of $Eu(fod)_3$.



5a′ **5e′**

R = CH_3, CN, $C(CH_3)_3$, $COCH_3$, CO_2CH_3, $CO_2CH_2CH_3$, OH, $Si(CH_3)_3$

and $H_{10'}$ are related as pseudoequatorial/pseudoaxial in both **5a′** and **5e′**, so that $J_{9,10'}$ should be constant and independent of the position of the equilibrium. The values of $J_{9,10}$ and $J_{9,10'}$ were determined by computer analysis[8] of the three spin (ABC or ABX) system, and in each case the value closest to 6.8 Hz ($J_{pa,pe}$ in 1,2-dihydronaphthalene) was assigned as $J_{9,10'}$. As an example, this region of the NMR spectrum for 9-*tert*-butyl is shown in Figure 1. It is interesting to note the rather striking difference in complexity when CD_3CN was used as solvent (trace b), and this is due (primarily) to an upfield shift of $H_{10'}$ relative to CCl_4 as solvent (trace a). Fortunately, in all cases one of the J values was within 0.9 Hz of 6.8 (and usually closer), and the other value ranged from 1.50 for *tert*-butyl to 9.89 Hz for cyano. The data are summarized in Table I, and it should be noted that in contrast to the cyclohexane ring system, the axial and equatorial protons cannot be distinguished on the basis of chemical shift alone, since there is considerable variation in whether H_{10} or $H_{10'}$ appears at higher field.

In calculating the percent of the conformations with the group pseudoaxial using eq 1, we employed the values of $J_{pa,pa}$ = 16 and $J_{pe,pe}$ = 2 Hz used for the 1,2-dihydronaphthalenes.[2-4] This seemed valid, since the values for $J_{pa,pe}$ correspond so closely between the two systems, and **5** with R = $Si(CH_3)_3$ shows $J_{pe,pe}$ = 1.95. Although we classify both the trimethylsilyl and *tert*-butyl derivatives as 100% axial, we prefer to use the trimethylsilyl $J_{pe,pe}$ value since the *tert*-butyl group may be causing some distortion (e.g., the larger $J_{10,10'}$ value). It is interesting to note that the value of 73% pseudoaxial for R = CO_2CH_3 compares very favorably with a value of 74% determined previously for 1,4-dicarbomethoxy-1,4-dihydronaphthalene.[4]

The observed pseudoaxial preference of benzylic substituents in **5** can be attributed to destabilization of the pseudoequatorial position by the adjacent aryl proton (i.e., peri interaction) and the absence of additional steric effects (cf. 1,3 interactions in cyclohexanes). Similar factors appear to govern the conformational properties of the related 1,2- and 1,4-dihydronaphthalene and the 9,10-dihydroanthracene[9,10] ring systems. As compared to the other substituents, the cyano group (**5**, R = CN) provides significantly different results, and seems to show a slight pseudoequatorial preference. However, when one takes into account the very small conformational

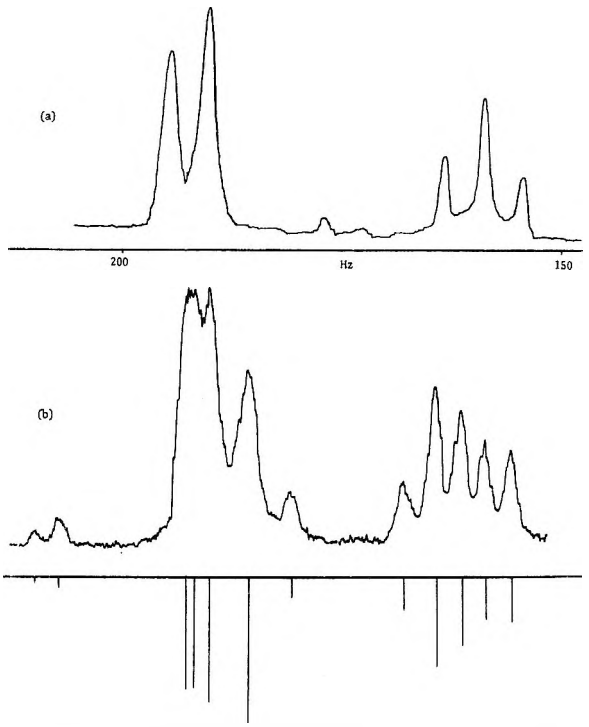


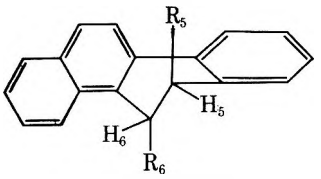
Figure 1. Partial NMR spectrum (benzylic protons; H_9, H_{10}, $H_{10'}$) of 9-*tert*-butyl-9,10-dihydrophenanthrene: (a) in CCl_4; (b) in CD_3CN (lower trace is theoretical).

free-energy difference (A value = 0.2)[11] for cyano, it is apparent that the aforementioned peri interaction will be greatly reduced. In fact, 2-substituted 1,2-dihydronaphthalenes, in which peri interactions are absent, show pseudoequatorial group preference,[4] and it may be inferred that this will be the general conformational preference in the absence of additional, important steric effects. In this regard, it should be noted that vicinal coupling constants are dependent on group electronegativities as well as bond angle.[12,13] On the other hand, such corrections are not expected to cause significant changes in these results, because the effects of electronegativities on values of $J_{pa,pa}$ and $J_{pe,pe}$ used in the calculation must be small since the variation in $J_{pa,pe}$ is less than 1.0 Hz.[4b]

The 9-hydroxyl compound (**5**, R = OH) exhibits a pseudoaxial preference (94%) unexpectedly high in comparison to the conformational free-energy differences usually found for hydroxy,[11] and also the $J_{9,10'}$ value of 5.9 Hz represents the largest deviation from the 6.8 Hz value of the compounds studied. It should be noted, however, that the NMR spectrum of this compound showed simply a doublet and triplet for the

benzylic protons (under a variety of solvent conditions) and $Eu(fcd)_3$ was added until an ABX pattern resulted; although shift reagents did not affect coupling constants or conformations in 1,4-cyclohexadienes[14] (as determined by certain measurements before and after addition), it cannot be certain in this case whether such effects are taking place.

We also examined the NMR spectra of the related compounds of 6-methyl- and *trans*-5,6-dimethyl-5,6-dihydrochrysene (**6** and **7**). Since the values for $J_{5,6}$ were small in both



6, $R_5 = H$; $R_6 = CH_3$
7, $R_5 = R_6 = CH_3$

cases [**6**, $J_{5,6}$ = 1.91 ($J_{H',6}$ = 6.0); **7**, $J_{5,6}$ = 1.6 Hz] it would appear that the pseudoaxial for **6** and dipseudoaxial for **7** are the exclusive conformations of these systems. This is not surprising, of course, in view of the added steric interaction with the additional benzene ring as compared to 9-methyl-**5**, which itself indicates 77%, pseudoaxial preference.

Since we have been observing time-averaged spectra resulting from a rapid ring inversion process, these spectra may be expected to be temperature dependent. In fact, we have observed a number of these compounds at lowered temperature (CS_2), and there is no significant change until crystallization takes place (e.g., R = OH, −25 °C; R = $CO_2CH_2CH_3$, −50 °C; R = CN, −75°C). However, in view of the fact that the barrier to ring inversion in *cis*-9,10-dialkyl-9,10-dihydrophenanthrenes is not large,[15] it was not unexpected that this process cannot be "frozen out" in temperature ranges which maintain solubility.

Synthesis of the majority of the dihydrophenanthrenes for this study was accomplished through metal–ammonia reduction of the corresponding phenanthrenes. Although the cyano, acetyl, and carboxylate groups are known to be susceptible to reduction by alkali metals in liquid ammonia, competitive reduction was not a serious problem under the conditions employed. The method appears to be quite general, and several 9-R-9,10-dihydrophenanthrenes (R = phenyl, carboxyl, benzyl) not included in Table I (owing to problems in interpretation of the NMR spectra) were also synthesized by this method.

Experimental Section

Material and Methods. 9-Methyl-9,10-dihydrophenanthrene was synthesized through reduction of 9-methylphenanthrene with lithium in ammonia in the presence of colloidal iron.[16] 9,10-Dihydrophenanthrene-9-carboxylic acid was prepared by reduction of phenanthrene-9-carboxylic acid with sodium in ammonia.[17] 9-Acetyl-, 9-cyano-, and 9-bromophenanthrene were purchased from the Aldrich Chemical Co. 9-Phenylphenanthrene was synthesized through photocyclization of triphenylethylene.[18] Microanalyses for C, H, and N where appropriate for all new compounds were obtained and were correct in ±0.3%.

NMR spectra were recorded at 60 MHz on a JEOL C6OHL, and at 270 MHz on a Bruker Hx-270. The 270-MHz spectra were used in certain cases to estimate coupling constants, and the NMR data provided in Table I are from 60-MHz spectra usually coupled with computer simulation. The LAOCN 3 program (QCPE, Indiana University) was used on either a CD6600 or IBM 360 computer. Line positions were determined using a Hewlett-Packard 5301A frequency counter.

Reactions in Liquid Ammonia. The general procedures developed in prior studies[19] for the controlled reduction of polycyclic aromatic compounds were employed. The recommended precautions for the exclusion of moisture, air, peroxides in ethereal solvents, and ferrous metal salts in ammonia were scrupulously observed, and products were isolated rapidly by partition between ether and water.

2-Cyano-9,10-dihydrophenanthrene. A solution of 9-cyanophenanthrene (2.03 g, 10 mmol) in tetrahydrofuran (100 ml) followed by lithium wire (174 mg, 22 mmol) were added to 200 ml of refluxing ammonia, affording a red-purple solution. After 30 min, reaction was quenched with solid NH_4Cl (20 g) and worked up conventionally to yield 9-cyano-9,10-dihydrophenanthrene (1.85 g, 90%) as a yellow oil which crystallized from CCl_4 as a colorless solid, mp 83–84 °C.

9-Acetyl-9,10-dihydrophenanthrene. Reduction of 9-acetylphenanthrene (1.10 g, 5 mmol) with lithium (76 mg, 11 mmol) in ether (100 ml) and ammonia (150 ml) at −33 °C afforded a dark green solution. Reaction was quenched after 4 min by addition of NH_4Cl (20 g) and worked up in the usual manner to yield 1.13 g of a colorless solid. Chromatography on silica gel and elution with benzene–hexane (1:2) gave pure 9-acetyl-9,10-dihydrophenanthrene (578 mg, 52%) as a pale yellow oil, ir (CCl_4) 1705 cm^{-1} (CO). Several minor products also obtained were not identified.

Treatment of the ketone (371 mg) with *p*-toluenesulfonic acid (30 mg) and ethylene glycol (10 ml) in dry benzene (30 ml) at reflux for 6 h furnished after workup the corresponding ketal (436 mg, 97%). Crystallization from methanol afforded pure 9-(1-ethylenedioxyethyl)-9,10-dihydrophenanthrene as white needles (401 mg, 90%), mp 83.5–85 °C. The latter (273 mg) was reconverted quantitatively to 9-acetyl-9,10-dihydrophenanthrene on heating in aqueous acetone (5%) in the presence of *p*-toluensulfonic acid (20 mg) at reflux temperature for 1 h.

Methyl 9,10-Dihydrophenanthrene-9-carboxylate. Methyl phenanthrene-9-carboxylate was synthesized from the parent acid by reaction with thionyl chloride following a conventional procedure. Recrystallization of the crude ester from methanol afforded the pure methyl ester (76%) as white needles: mp 118–119 °C (lit.[20] 118–119 °C); NMR (CCl_4) δ 3.97 (s, 3, CH_3), 7.42–8.0 (m, 6, $H_{1,2,3,6,7,8}$), 8.37 (s, 1, H_{10}), and 8.50–9.2 ppm (m, 2, $H_{4,5}$); GLC on a 5 ft × 0.125 in. column of 1.5% OV 101 at 195 °C gave a single sharp peak.

Reduction of the methyl ester (313 mg, 133 mmol) with lithium (20 mg, 2.9 mmol) in ether (30 ml) and ammonia (80 ml) at −40 °C gave a dark green solution. Reaction was quenched after 15 min by solid NH_4Cl (20 g) and worked up in the usual manner. Chromatography of the solid product (311 mg) on silica gel and elution with benzene–chloroform (1:3) gave pure methyl 9,10-dihydrophenanthrene-9-carboxylate (179 mg, 52−) as a pale yellow oil. The NMR spectrum matched that reported;[21] GLC on 1.5% OV 101 gave a single sharp peak.

Ethyl 9,10-Dihydrophenanthrene-9-carboxylate. Ethyl phenanthrene-9-carboxylate was synthesized by the same method as the methyl ester. Purification was effected by chromatography on silica gel eluted with acetone. The pure ethyl ester (98%) was obtained as an oil: NMR (CCl_4) δ 1.43 (t, 3, J = 7.0 Hz, CH_3), 4.40 (q, 2, J = 7.0 Hz, CH_2), 7.35–7.90 (m, 6, $H_{1,2,3,6,7,8}$), 8.26 (s, 1, H_{10}), and 8.34–8.94 ppm (m, 2, $H_{4,5}$); GLC on 1.5% OV 101 gave a single sharp peak.

Reduction of the ethyl ester (555 mg) by the method employed for the methyl ester gave pure ethyl 9,10-dihydrophenanthrene-9-carboxylate as a colorless oil (188 mg, 34%); GLC analysis showed a single sharp peak.

9-Trimethylsilyl-9,10-dihydrophenanthrene. 9-Trimethylsilylphenanthrene was synthesized from 9-bromophenanthrene (2.57 g, 10 mmol) via reaction with *n*-butyllithium and chlorotrimethylsilane. The method of Eaborn[22] was employed except that reaction with the lithium reagent was conducted at room temperature, rather than reflux, and a larger excess of the silane was employed. The crude product was chromatographed on silica gel eluted with hexane to furnish pure 9-trimethylsilylphenanthrene (82%) as an oil which crystallized on standing: NMR (CCl_4) δ 0.50 (s, 9, CH_3), 7.37–8.20 (m, 6, $H_{1,2,3,6,7,8}$), 7.87 (s, 1, H_{10}), and 8.30–8.67 (m, 2, $H_{4,5}$).

A solution of 9-trimethylsilylphenanthrene (1.33 g, 5.3 mmol) in ether (80 ml) was added to 150 ml of refluxing ammonia, followed by lithium wire (84 mg, 12 mmol). Reaction was quenched after 10 min by addition of NH_4Cl (20 g) to the dark green solution. Chromatography of the product on Florisil furnished pure 9-trimethylsilyl-9,10-dihydrophenanthrene as a colorless oil, mass spectrum (70 eV) *m/e* 252.

9-Hydroxy-9,10-dihydrophenanthrene. Phenanthrene 9,10-oxide[23] (400 mg, 2 mmol) was treated with $LiAlH_4$ (160 mg, 4 mmol) in refluxing ether (30 ml) for 40 min, then 100 ml of water and 1 ml of acetic were added. Conventional workup gave 9-hydroxy-9,10-dihydrophenanthrene (397 mg, 98%) essentially pure by NMR. Recrystallization from benzene–hexane gave the analytical sample as white needles, mp 105–106 °C.

9-Phenyl-9,10-dihydrophenanthrene. Reduction of 9-phenylphenanthrene (200 mg, 0.8 mmol) with lithium in ether and ammonia

at −78 °C by the standard method[19] gave 9-phenyl-9,10-dihydrophenanthrene (200 mg, 99%) as a colorless oil which solidified on standing, mp 80–82 °C. Chromatography on Florisil gave the analytical sample, mp 82–83 °C.

9-Benzyl-9,10-dihydrophenanthrene. 9-Benzylphenanthrene was prepared from 9-bromophenanthrene through reaction of the Grignard derivative with benzyl chloride.[24] Reduction of 9-benzylphenanthrene with lithium in ammonia in the presence of colloidal iron under conditions similar to those employed with the 9-methyl analogue[16] gave 9-benzyl-9,10-dihydrophenanthrene (94%) as oil. Chromatography on silica gel effected removal of residual starting material and furnished the pure title compound.

9-*tert*-Butyl-9,10-dihydrophenanthrene. 9-*tert*-Butylphenanthrene was synthesized through reaction of phenanthrene 9,10-oxide[23] with *tert*-butyllithium followed by acid-catalyzed dehydration. Complete purification required several chromatographies on silica gel impregnated with trinitrofluorenone.[25] The pure 9-*tert*-butylphenanthrene had mp 64–65 °C (lit.[26] 64–65 °C).

Reduction of 9-*tert*-butylphenanthrene (234 mg, 1 mmol) with lithium in ether and ammonia by the standard method have an oil containing 9-*tert*-butyl-9,10-dihydrophenanthrene and recovered starting material (7:3). Chromatography twice on neutral alumina and elution with hexane gave pure 9-*tert*-butyl-9,10-dihydrophenanthrene (86 mg, 35%) free of the parent aromatic hydrocarbon.

5-Methyl- and 5,6-Dimethyl-5,6-dihydrochrysene. The method for the reductive methylation of chrysene previously reported[27] was modified to improve the yield. A solution of chrysene (2.74 g, 12 mmol) in THF (200 ml) was added to 100 ml of refluxing ammonia. Sodium metal (220 mg, 14 mmol) was added, and the resulting deep blue solution was stirred for 4 min, then methyl bromide was bubbled into the solution for 2 min, followed by NH_4Cl (20 g). Conventional workup afforded 2.31 g of a solid. Chromatography on neutral alumina eluted with hexane gave initially 5,6-dimethyl-5,6-dihydrochrysene as a minor product. Recrystallization from chloroform–hexane gave the pure dimethyl compound as a white solid, mp 104–106 °C. Further elution with hexane furnished pure 5-methyl-5,6-dihydrochrysene (1.57 g, 93%) as a colorless solid, mp 132–133 °C.

Acknowledgment. Support of this research by grants from the U.S. Public Health Service CA-11968 (R.G.H.) and the Indiana University Office of Research and Advanced Studies (P.W.R.) is gratefully acknowledged. The Hx-270 Bruker superconducting NMR spectrometer was provided through the University of Chicago Cancer Research Center Grant CA-14599. We also wish to thank Dr. Frederick Beland for synthesis of the sample of pure 9-*tert*-butylphenanthrene, Mr. Walter Flack for modification of the LAOCN 3 program to run on the IBM 360, and Mrs. Sarah Land for testing the program.

Registry No.—9-Cyanophenanthrene, 2510-55-6; 9-acetylphenanthrene, 2039-77-2; 9-(ethylenedioxyethyl)-9,10-dihydrophenanthrene, 60084-40-4; methyl phenanthrene-9-carboxylate, 1217-49-8; phenanthrene-9-carboxylic acid, 837-45-6; ethyl phenanthrene-9-carboxylate, 4895-92-5; 9-trimethylsilylphenanthrene, 18209-95-5; 9-bromophenanthrene, 573-17-1; phenanthrene 9,10-oxide, 585-08-0; 9-*tert*-butylphenanthrene, 17024-05-4; chrysene, 218-01-9; 5,6-dimethyl-5,6-dihydrochrysene, 60084-41-5; 5-methyl-5,6-dihydrochrysene, 34908-52-6; 9-phenyl-9,10-dihydrophenanthrene, 5235-80-3; 9-phenylphenanthrene, 844-20-2; 9-benzyl-9,10-dihydrophenanthrene, 60084-42-6; 9-benzylphenanthrene, 605-05-0.

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Syntheses and Absolute Configurations of Tricyclo[4.3.0.0^{3,7}]nonane ("Brexane"), 3-Oxatricyclo[4.3.0.0^{4,9}]nonane ("3-Oxabrexane"), and Tricyclo[4.2.0.0^{3,7}]octan-2-one ("Norbrexan-2-one")[1]

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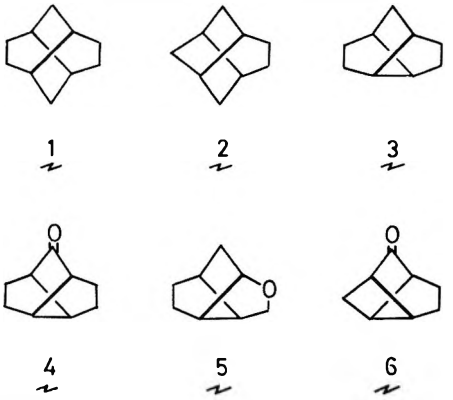
(−)-(1*S*,3*S*,6*R*,7*R*)-Brexane (tricyclo[4.3.0.0^{3,7}]nonane) (**3**) was prepared from (+)-(1*R*,4*R*,7*S*)-7-*syn*-methoxycarbonylbicyclo[2.2.1]heptan-2-one (**12**). Examination of the circular dichroism curve of the intermediate, (−)-brexan-2-one (tricyclo[4.3.0.0^{3,7}]nonan-2-one) (**4**), which exhibited a (−) Cotton effect, confirmed the absolute configuration. Starting from (−)-(1*S*,4*S*,7*R*)-7-*syn*-methoxycarbonylbicyclo[2.2.1]heptan-2-one (**16**), 3-oxabrexane (3-oxatricyclo[4.3.0.0^{4,9}]nonane) (**5**), and norbrexan-2-one (tricyclo[4.2.0.0^{3,7}]octan-2-one) (**6**) were synthesized in optically active forms.

A feature common to tricyclo[4.4.0.0^{3,8}]decane ("twistane")[2] (**1**) and tricyclo[4.3.0.0^{3,8}]nonane ("twist-brendane")[3] (**2**), whose preparations in optically active forms have been recently reported from our laboratory, is the "twist carbon frame" inherent to their gyrochiral[4] cage-shaped molecules (D_2 and C_2 symmetry, respectively). These twisted carbon

skeletons are undoubtedly responsible for their rather large optical rotations for hydrocarbon,[5] and we have been successful at correlating their signs of rotation to the senses of twist in their carbon frameworks.[6] In highly symmetrical twistane (1), we find five "frozen" twist-boat six-membered rings with identical direction of twist and two types of methylene group. Removal of one of these methylene groups gives



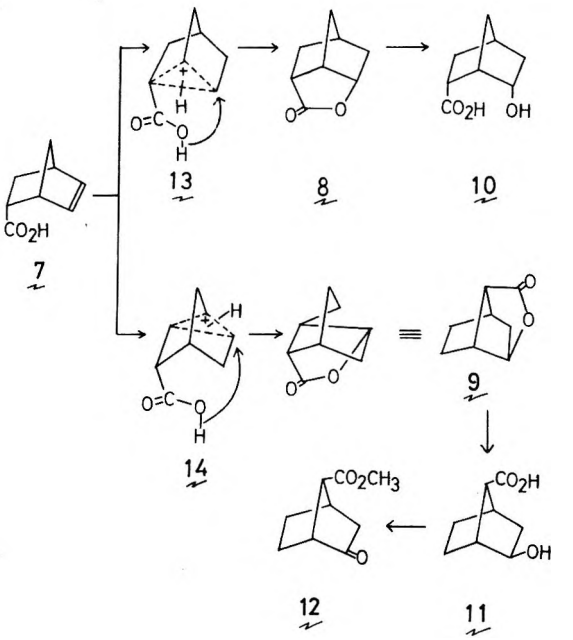
rise to two lower homologues: twist-brendane (2) and tricyclo[4.3.0.0^{3,7}]nonane ("brexane")[7] (3), respectively. Although these cage-shaped tricyclic compounds (2 and 3) share a similar geometrical feature, both belonging to C_2 point group, twist-brendane (2) has a twisted seven-membered ring along C_2 axis interlocked with an oppositely twisted six-membered ring along the axis perpendicular to the C_2 axis, whereas brexane (3) has a five-membered ring twisted along the C_2 axis with an eight-membered ring of the opposite sense of twist. As a part of our continuing effort toward syntheses of high symmetry chiral cage-shaped molecules[8] in optically active forms as well as determination of their absolute configurations, we are interested in comparison of the chiroptical properties between these two types of cage-shaped compounds. Moreover, these stereochemical interests, information on the absolute configuration of (−)-brexan-2-one (4), which is one of the precursor of our synthesis of (−)-brexane (3), is indispensable for our recent investigation on the phytochemical conversion of cage-shaped compounds.[9] In this paper we describe the syntheses and absolute configuration determinations of optically active (−)-brexane (3) and (−)-brexan-2-one (4) together with the preparation of 3-oxatricyclo[4.3.0.0^{4,9}]nonane ("3-oxabrexane")[10] (5) and tricyclo[4.2.0.0^{3,7}]octan-2-one ("norbrexan-2-one")[11] (6) in optically active forms.

Results and Discussion

Synthesis of (−)-Brexane (3). Isomerization with 75% sulfuric acid[12] converted (+)-(1*R*,2*R*,4*R*)-*endo*-2-carboxybicyclo[2.2.1]hept-5-ene (7)[13] into a mixture of the endo and exo lactone (8 and 9) which was then hydrolyzed with 2 N sodium hydroxide to yield a mixture of sodium salts of the corresponding hydroxy acids (10 and 11).

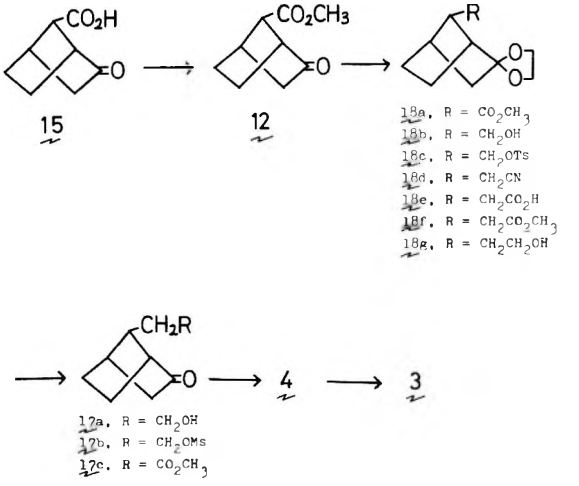
Marked difference observed in their lactonization rates furnished a means to their separation: adjustment of the pH of the hydrolysate to 5 made the endo acid (10) readily lactonize to give 8, $[\alpha]^{14}D$ +2.2°, whereas the exo acid (11) remained intact. Permanganate oxidation followed by esterification with diazomethane converted the exo acid (11) into the keto ester (12), $[\alpha]^{13}D$ +2.6°. Stereochemical correlations between the starting material (7) and the lactones (8 and 9) could be deduced by postulating (1) participation of the nonclassical ions (13 and 14)[14] and (2) their conversions into lactones (8 and 9), respectively, on intramolecular nucleophilic attack by carboxyl group via stereochemically most favored paths. This correlation indicated the (1*R*,4*R*,7*S*)-configuration for (+)-7-*syn*-methoxycarbonylbicyclo[2.2.1]heptan-2-one (12), and this assignment of configuration was supported by the circular dichroism curves of (−)-brexan-2-one (4) prepared from (+) keto ester 12 (vide infra).

Scheme I



Since carrying out the synthesis of optically active brexane required the optically active keto ester 12 in substantial quantity, we divert attention from the above approach to the second one in which optical resolution was performed on the racemic 7-*syn*-carboxybicyclo[2.2.1]heptan-2-one (15). The acid (15) was prepared from a mixture of racemic endo and exo isomers of 2-carboxybicyclo[2.2.1]hept-5-ene (7) by the same procedure described above. Optical resolution of the bicyclic carboxylic acid (15) was accomplished via cinchonidine salts, and the separated enantiomeric acids were esterified with diazomethane to afford (−) methyl ester (16), $[\alpha]^{17}D$ −11.6°, and (+) methyl ester (12), $[\alpha]^{13}D$ +3.47°. Since our plan to build the tricyclic framework was the intramolecular alkylation of the bicyclic keto mesylate (17b), modification of the carboxylate group was our next step, which was straightforwardly carried out as depicted in Scheme II.[15]

Scheme II

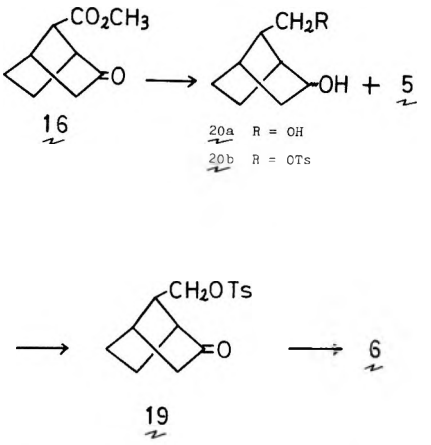


After protection of the keto group of the (+) methyl ester (12) by ketalization with ethylene glycol, the resultant ketal ester (18a) was reduced with lithium aluminum hydride to afford the alcohol (18b) which was further converted into the

nitrile (**18d**) via the tosylate (**18c**). Heating of the nitrile (**18d**) with potassium hydroxide in ethylene glycol led to the formation of the carboxylic acid (**18e**) which was not isolated but was converted into the methyl ester (**18f**) with diazomethane. Hydride reduction of **18f** and removal of the protecting group with 5% sulfuric acid furnished the keto alcohol (**17a**). After the keto mesylate (**17b**) derived from **17a** was heated with sodium hydride in dimethylformamide for 17 h, the ring closure product was purified by chromatography to give (−)-tricyclo[4.3.0.0^{3,7}]nonan-2-one ("brexan-2-one") (**4**), bp 116 °C (20 mm), $[\alpha]^{14}D$ −201°. Wolff–Kishner reduction of (−)-brexan-2-one (**4**) completed the synthesis of (−)-brexane (**3**), $[\alpha]^{15}D$ −94.3°.

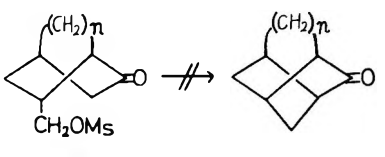
Syntheses of 3-Oxabrexane (5) and Norbrexan-2-one (6). We now divert our attention from the tricyclo[4.3.0.0^{3,7}]-nonane series of compounds to preparation of optically active norbrexan-2-one (**6**), a lower homologue of brexan-2-one (**4**). This time again, our choice among synthetic approachs was intramolecular alkylation of the bicyclic keto tosylate (**19**).

Scheme III

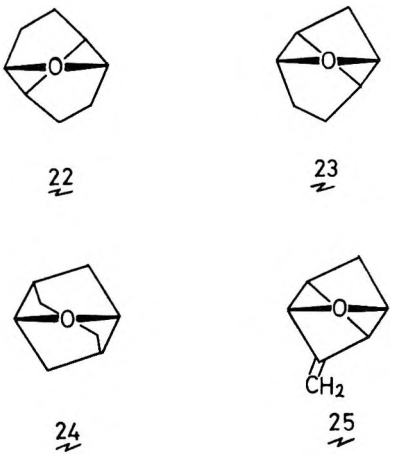


After lithium aluminum hydride reduction of (−)-(1*S*,4*S*,7*R*) keto ester (**16**) (the enantiomer of **12**), the resulting diol (**20a**) was treated with 1 equiv of tosyl chloride in cold pyridine to secure the monotosylate (**20b**). Silica gel chromatography of the reaction mixture revealed, besides the expected monotosylate (**20b**), the formation of a compound $C_8H_{12}O$, mp 63–64 °C, $[\alpha]^{20}D$ −168°. The ir, NMR, and mass spectral evidences all indicate that this compound is (−)-3-oxabrexane (**5**) whose racemate[10] was reported to melt at 64–65°C. Oxidation of the monotosylate (**20b**) with Jones reagent to the keto tosylate (**19**) and treatment of the latter with sodium hydride in dimethylformamide gave an oil, bp 60 °C (20 mm), whose parent peak in the mass spectrum was 122. The CD spectrum (to be discussed later) and the ir spectrum, which lacked olefinic peaks and showed a carbonyl peak at 1754 cm^{-1}, indicated the tricyclic structure **6** for this product. Although the yield of this cyclization was found to be rather low (yield 3.5%), it is relevant to note here that similar attempted intramolecular alkylations have failed in the compounds **21** (n = 1 and 2).

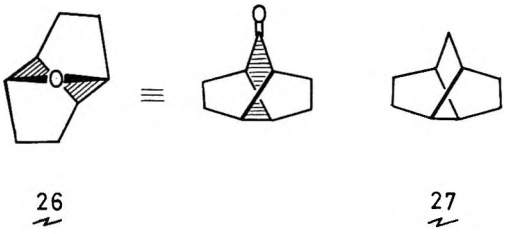
Scheme IV



Chiroptical Properties and Absolute Configurations. CD spectral analyses of the various tricyclic ketones (**22**,[2] **23**,[3a] **24**,[3b] and **25**[16]), prepared in our laboratory from the intermediates with known absolute configurations, indicated that

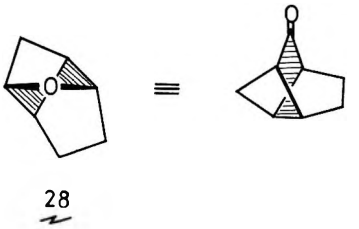


the sign of the CD curve due to n–π^* transition around 300 nm can be predicted by applying the octant rule to the "outer ring"[17] in the projection formula which holds the carbonyl group at the "point of twist".[18] Applying this generalization to (−)-brexan-2-one (**4**) with CD absorptions at 294 ($[\theta]$ −7.24 × 10^3) and 300 nm ($[\theta]$ −7.36 × 10^3), we had the absolute configuration **26** for this tricyclic ketone, which was found

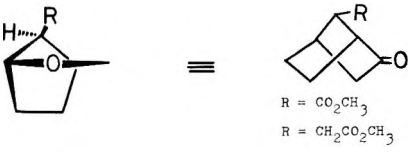


compatible with our assignment of (1*R*,4*R*,7*S*) configuration to the (+) bicyclic keto ester (**12**) by chemical correlation. These facts eventually lead to the absolute configuration **27**, (−)-(1*S*,3*S*,6*R*,7*R*)-tricyclo[4.3.0.0^{3,7}]nonane, for (−)-brexane (**3**), and the absolute configurations **5** and **6**, respectively, to (−)-3-oxabrexane and norbrexan-2-one both prepared from (−)-(1*S*,4*S*,7*R*) bicyclic keto ester (**16**) as shown in Scheme III.

The conclusion was further supported by the (+) sign observed in the CD curve of norbrexan-2-one (**6**), which is compatible with the prediction derived from application of the octant rule to its projection formula **28.**



Finally, attention is called to the Cotton effects of the intermediate bicyclic keto carboxylates (**12** and **17c**). Application of the octant rule to the projection formula **29**, with a



plausible assumption that the substitution at C_7 should make a predominant contribution, suggests that these bicyclic ke-

tones would give positive Cotton effects, which was found in agreement with our observations.

Experimental Section

Infrared spectral data were obtained from a Hitachi EPI-S2 spectrophotometer. Nuclear magnetic resonance spectra were obtained from a JNM-MH-100 spectrometer. Ultraviolet spectra were recorded on a Beckman DB spectrometer. Optical rotations were measured with a JASCO-DIP-SL automatic polarimeter. Circular dichroism data were measured on a JASCO J-20 spectropolarimeter with a CD attachment. Elemental analyses were determined on a Yanagimoto CHN-Corder type II. All melting points and boiling points are uncorrected.

Hydration of (+)-*endo*-2-Carboxybicyclo[2.2.1]hept-5-ene (7). (+)-*endo*-2-Carboxybicyclo[2.2.1]hept-5-ene (**7**), $[\alpha]^{15}D$ +72.1° (10.0 g, 0.0724 mol), was mixed with 75% sulfuric acid and the mixture was agitated for 4 h at room temperature. After pouring onto 1 kg of ice, it was extracted continuously for 3 days with ether and the extract was washed with saturated sodium bicarbonate solution. This alkaline solution was extracted continuously for 2 days with ether. Both ethereal extracts were combined, washed with water, and dried over magnesium sulfate. Removal of the solvent gave a mixture of lactones (**8** and **9**) (3.46 g, yield 34%). This mixture (2.52 g, 0.0182 mol) was mixed with 13 ml of 2 N sodium hydroxide solution and it was agitated for 1 h at room temperature. The pH of the clear solution was adjusted to 5 with concentrated sulfuric acid. After the solution had stood for 10 min at room temperature, the pH of the solution was then adjusted to 8 with solid sodium bicarbonate. The slightly alkaline solution was extracted continuously for 3 days with ether. The extract was dried over magnesium sulfate and removal of the solvent gave endo lactone (**8**) which was purified by sublimation to yield 1.65 g of **8**, mp 148–151 °C (racemate[12] mp 157–158 °C), $[\alpha]^{14}D$ +2.2° (c 1.58, ethanol).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.35; H, 7.32.

The alkaline solution was acidified with concentrated hydrochloric acid and extracted with ether. The extract was washed with water and dried over magnesium sulfate. Removal of the solvent gave hydroxy acid **11** (0.77 g). This was used for the succeeding reaction without further purification.

(+)-7-*syn*-Methoxycarbonylbicyclo[2.2.1]heptan-2-one (12). Hydroxy acid **11** (0.77 g, 4.93 mmol) was dissolved in water (8 ml) with potassium hydroxide (0.40 g). A solution of potassium permanganate (1.10 g, 7.00 mmol) in water (13 ml) was added to the solution and then it was stirred for 3 h at room temperature. A few milliliters of ethanol were then added to the mixture to decompose excess of potassium permanganate and manganese dioxide was filtered off. The filtrate was acidified with sulfuric acid and extracted with ether. The extract was washed with water and dried over magnesium sulfate. After filtration of magnesium sulfate, the ethereal solution was treated with excess of diazomethane in ether. After working up as usual, the solvent was evaporated and the residue was distilled to give keto ester **12** (0.36 g, yield 43%): bp 98 °C (5 mm); $[\alpha]^{13}D$ +2.6° (c 1.17, ethanol); CD (c 1.01×10^{-2}, isooctane) $[\theta]$ (nm) 0 (265), $+3.10 \times 10^2$ sh (293), $+4.71 \times 10^2$ (302), $+3.62 \times 10^2$ (313), 0 (330).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.37; H, 7.19. Found: C, 64.05; H, 7.27.

Optical Resolution of 7-*syn*-Carboxybicyclo[2.2.1]heptan-2-one (15). Racemic 7-*syn*-carboxybicyclo[2.2.1]heptan-2-one (**15**) was prepared by the procedure reported previously.[12] A salt from the carboxylic acid (62.5 g, 0.405 mol) with cinchonidine (119 g, 0.405 mol) was systematically recrystallized from acetone. The levorotatory salt (50.2 g, yield 28%), mp 155–157° dec, $[\alpha]^{15}D$ −72.5° (c 0.614, ethanol), was obtained as a sparingly soluble crystal, which was treated with 5% sodium hydroxide solution at room temperature. After filtration of cinchonidine, the filtrate was acidified with hydrochloric acid and extracted with ether. The extract was washed with water and dried over magnesium sulfate. Removal of the solvent gave a solid which was esterified with diazomethane in ether by the usual manner. The methyl ester was distilled to yield (+) methyl ester **12** (16.8 g): bp 138–141 °C (13 mm); $[\alpha]^{13}D$ +3.47° (c 1.60, ethanol); ir (neat film) 1750, 1725, 1440, 1298, 1200, and 1145 cm^{-1}; NMR (CCl_4) δ 1.4–2.0 (m, 5 H), 2.1–2.4 (m, 1 H), 2.62–2.72 (m, 2 H), 2.75–2.88 (m, 1 H), and 3.64 (s, 3 H); CD (c 8.23×10^{-3}, isooctane) $[\theta]$ (nm) 0 (264), $+4.01 \times 10^2$ sh (292.5), $+5.89 \times 10^2$ (302), $+4.62 \times 10^2$ (313), 0 (332); uv max (isooctane) 284 nm (ϵ 17.0), 290 (17.5), 300 sh (16.0).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.09; H, 7.26.

Condensation of the mother liquor of the cinchonidine salt gave the levorotatory salt (21.1 g, yield 12%), mp 193–195 °C dec, $[\alpha]^{18}D$ −89.7° (c 0.836, ethanol). This was treated by the same manner described above to yield (−) methyl ester **16** (6.05 g), bp 109–111 °C (5 mm), $[\alpha]^{17}D$ −11.6° (c 1.08, ethanol).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 63.91; H, 7.29.

(+)-2-Ethylenedioxy-7-*syn*-methoxycarbonylbicyclo[2.2.1]-heptane (18a). To a boiling solution of (+) methyl ester **12** (16.4 g, 0.0976 mol) and *p*-toluenesulfonic acid (100 mg) in benzene (500 ml) was added dropwise ethylene glycol (13 ml) during 2 h, and the mixture was refluxed for an additional 7 h. After cooling to room temperature, the reaction mixture was washed with saturated sodium bicarbonate solution and water and dried over magnesium sulfate. After evaporation of the solvent, the residue was distilled to yield **18a** (18.6 g, yield 90%): bp 124–128 °C (5 mm); $[\alpha]^{14}D$ +27.2° (c 1.10, ethanol); ir (neat film) 1730, 1335, 1218, 1190, and 958 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.50; H, 7.64.

(+)-2-Ethylenedioxy-7-*syn*-hydroxymethylbicyclo[2.2.1]-heptane (18b). A solution of (+) ketal ester **18a** (18.6 g, 0.0877 mol) in dry ether (350 ml) was added dropwise to a suspension of lithium aluminum hydride (3.40 g, 0.0894 mol) in dry ether (200 ml). After refluxing for 5 h, the reaction complex was decomposed with saturated ammonium chloride solution with ice cooling. Inorganic solids were filtered off, and the filtrate was dried over magnesium sulfate. After removal of the solvent, the residue was distilled to yield **18b** (15.7 g, yield 97%): bp 136–138 °C (5 mm); $[\alpha]^{16}D$ +0.26° (*c* 3.08, ethanol); ir (neat film) 3350, 1330, 1118, 1080, 1020, and 950 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.93; H, 8.86.

(−)-2-Ethylenedioxy-7-*syn*-cyanomethylbicyclo[2.2.1]heptane (18d). To a stirred solution of (+)-**18b** (15.7 g, 0.0853 mol) in dry pyridine (50 ml) was added *p*-toluenesulfonyl chloride (21.1 g, 0.110 mol) with ice cooling, and stirring was continued for 6 h at this temperature. The mixture was poured onto ice and acidified with hydrochloric acid, followed by extraction with ether. The extract was washed with dilute hydrochloric acid, saturated sodium bicarbonate solution and water and dried over magnesium sulfate. Removal of the solvent gave an oily tosylate (**18c**) which was dissolved in dry dimethyl sulfoxide (85 ml). After addition of sodium cyanide (8.00 g, 0.163 mol), the reaction mixture was stirred for 18 h at 90 °C. A solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was poured onto ice and extracted with ether. The extract was washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water and dried over magnesium sulfate. After evaporation of the solvent, the residue was distilled to yield **18d** (12.4 g, yield 75%): bp 135–138 °C (5 mm); $[\alpha]^{16}D$ −8.19° (c 0.830, ethanol); ir (neat film) 2250, 1335, 1118, 1082, 1015, and 950 cm^{-1}; NMR (CCl_4) δ 1.3–1.9 (m, 6 H), 1.95–2.22 (m, 3 H), 2.45 (s, 1 H), 2.58–2.60 (d, 1 H), and 3.73–3.88 (m, 4 H).

Anal. Calcd for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.07; H, 7.75; N, 7.31.

(+)-2-Ethylenedioxy-7-*syn*-methoxycarbonylmethylbicyclo[2.2.1]heptane (18f). A mixture of (−)-nitrile **18d** (12.4 g, 0.0604 mol) and potassium hydroxide (10.8 g, 0.193 mol) in ethylene glycol (80 ml) was heated for 6 h at 155 °C. After cooling to room temperature, it was diluted with water and washed with either to remove unsaponified materials. The water layer was acidified with hydrochloric acid and extracted with ether. The extract was washed with water and dried over magnesium sulfate. Removal of the solvent gave an oily product (12.8 g) which, without further purification, was dissolved in dry ether (300 ml). To this solution was added dropwise an excess of a solution of diazomethane in ether with ice cooling. After an usual working up, the product was distilled to yield **18f** (13.2 g, yield 91%): bp 135–139 °C (5 mm); $[\alpha]^{14}D$ + 0.77° (*c* 2.05, ethanol); ir (neat film) 1735, 1435, 1330, 1210, 1170, 1080, 1020, and 950 cm^{-1}.

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.44; H, 8.02.

(−)-7-*syn*-Methoxycarbonylmethylbicyclo[2.2.1]heptan-2-one (17c). A mixture of (+) ketal ester **18f** (1.53 g, 6.77 mmol) and 5% aqueous sulfuric acid (10 ml) was stirred for 15 h at room temperature and then extracted with ether. The extract was washed with saturated sodium bicarbonate solution and water, and dried over sodium sulfate. After evaporation of the solvent, the residue was distilled to give **17c** (789 mg, yield 64%): bp 125–127 °C (5 mm); $[\alpha]^{15}D$ −1.04° (*c* 1.92, ethanol); ir (neat film) 1735, 1438, 1290, 1255, and 1175 cm^{-1}; CD (*c* 3.60×10^{-2}, isooctane) $[\theta]$ (nm) -6.66×10 (274), 0 (283), $+4.05 \times 10^2$ sh (298), $+6.77 \times 10^2$ (308), $+6.00 \times 10^2$ (318.5), 0 (340); uv max (isooctane) 275 nm sh (ϵ 18.0), 283 (21.4), 296 (22.2), 305 nm (20.3).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.10; H, 7.72.

(−)-2-Ethylenedioxy-7-*syn*-(2-hydroxyethyl)bicyclo[2.2.1]-heptane (18g). A solution of (+) methyl ester **18f** (11.4 g, 0.0504 mol) in dry ether (200 ml) was added to a suspension of lithium aluminum hydride (1.90 g, 0.0500 mol) in dry ether (100 ml) over 90 min, and the mixture was refluxed for an additional 5.5 h. After saturated ammonium chloride solution was added to the chilled mixture, inorganic solid was filtered off and the filtrate was dried over magnesium sulfate. After evaporation of the solvent, the residue was distilled to yield **18g** (9.71 g, yield 97%): bp 143–146 °C (5 mm); $[\alpha]^{15}D$ −6.51° (*c* 1.92, ethanol); ir (neat film) 3400, 1330, 1118, 1080, 1050, and 1020 cm^{-1}.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.74; H, 9.29.

(+)-7-*syn*-(2-Hydroxyethyl)bicyclo[2.2.1]heptan-2-one (17a). A mixture of (−) ketal alcohol **18g** (4.56 g, 0.0231 mol) and 5% sulfuric acid (30 ml) was agitated for 15 h at room temperature and then extracted with ether. The extract was washed with saturated sodium bicarbonate solution and water and dried over sodium sulfate. After evaporation of the solvent, the residue was distilled to give 17a (2.49 g, yield 70%): bp 146–150 °C (5 mm); $[\alpha]^{15}D$ +1.84° (*c* 1.23, ethanol); ir (neat film) 3400, 1735, and 1050 cm^{-1}.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.98; H, 9.31.

(−)-Brexan-2-one (4). To a solution of (+) keto alcohol **17a** (2.28 g, 0.0148 mol) in dry pyridine (8 ml) was added methanesulfonyl chloride (3.38 g, 0.0295 mol) at 0–5 °C and then the mixture was stirred for 6 h at this temperature. After being kept overnight at room temperature, the mixture was poured onto ice. It was acidified with hydrochloric acid and extracted with chloroform. The extract was washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water and dried over sodium sulfate. Removal of the solvent gave mesylate **17b** (2.63 g), which was, without further purification, dissolved in dimethylformamide (30 ml). This solution was added dropwise to a suspension of sodium hydride (1.00 g, 0.415 mol) in dimethylformamide (20 ml) and the mixture was stirred for 17 h at 60 °C under a nitrogen atmosphere. After cooling with ice, the reaction mixture was poured onto ice and extracted with ether. The extract was washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water and dried over magnesium sulfate. After evaporation of the solvent, the residue was chromatographed on neutral alumina (Woelm, activity III). Fractions eluted with pentane–ether (9:1 volume) were distilled to yield (−)-brexan-2-one (**4**) (966 mg, yield 48% based on **17a**): bp 116 °C (20 mm); $[\alpha]^{14}D$ −201° (c 0.677, ethanol); ir (neat film) 1838, 1742, 1070, and 770 cm^{-1}; NMR (CCl_4) δ 1.56 (s, 1 H), 1.65–1.75 (m, 3 H), 1.75–1.85 (m, 1 H), and 2.24–2.35 (m, 4 H); CD (*c* 3.29 × 10^{-3}, isooctane) [θ] (nm) 0 (241), −7.24 × 10^3 (294), −7.36 × 10^3 (300), −4.56 × 10^3 sh (311.5), 0 (332); uv max (isooctane) 281 nm sh (ϵ 17.9), 290 (21.3), 300 (19.8).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.06; H, 8.85.

(−)-Brexane (3). A mixture of (−)-brexan-2-one (**4**, 480 mg, 3.53 mmol), potassium hydroxide (0.26 g), 80% hydrazine hydrate (0.4 ml), and triethylene glycol (4 ml) was heated for 1.5 h at 160 °C and then for an additional 3 h at 200–210 °C. After cooling to room temperature, the reaction mixture was poured onto ice and extracted with pentane. The extract was washed with water and dried over magnesium sulfate. After careful evaporation of the solvent, the residue was chromatographed on neutral alumina (Woelm, activity III). The first fraction eluted with pentane was concentrated to give (−)-brexane (**3**, 90 mg, yield 21%): $[\alpha]^{15}D$ −94.3° (*c* 0.214, ethanol); ir (neat film) 2950, 2880, 1462, and 1308 cm^{-1}; mass spectrum *m/e* 122 (M^+).

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.34; H, 11.56.

(−)-7-*syn*-Hydroxymethylbicyclo[2.2.1]heptan-2-ol (20a). A solution of (−) methyl ester **16** (2.55 g, 0.0152 mol) in dry ether (60 ml) was added dropwise to a suspension of lithium aluminum hydride (1.00 g, 0.0263 mol) in dry ether (30 ml), and the mixture was refluxed for 5 h. After cooling with ice, saturated ammonium chloride solution was added to the chilled reaction mixture and inorganic solids were filtered off. The filtrate was dried over sodium sulfate and the solvent was evaporated. The residue was distilled to give (−) diol **20a** (1.25 g, yield 58%), bp 138–140 °C (5 mm), $[\alpha]^{18}D$ −4.90° (*c* 1.62, ethanol).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.25; H, 9.94.

(−)-3-Oxabrexane (5) and (+) Tosylate (19). To a solution of (−) diol **20a** (2.69 g, 0.0189 mol) in dry pyridine (10 ml) was added *p*-toluenesulfonyl chloride (3.60 g, 0.0189 mol) at 0–5 °C, and the mixture was agitated for 3 h at this temperature. After being kept overnight at room temperature, the mixture was poured onto ice. It was acidified with hydrochloric acid and extracted with ether. The extract was washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water and dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel. The fractions eluted with pentane–ether (4:1 volume) gave a wax, which was sublimed at 38–45 °C (20 mm) to yield (−)-3-oxabrexane (**5**, 43 mg, yield 1.7%): mp 63–64 °C (in a sealed tube); $[\alpha]^{20}D$ −168° (*c* 1.10, ethanol); ir (KBr) 1305, 1100, 1028, 970, 932, 880, and 845 cm^{-1}; NMR ($CDCl_3$) δ 1.08–1.78 (m, 6 H), 2.10–2.35 (m, 3 H), 3.64–3.95 (m, 2 H), and 4.03–4.15 (m, 1 H); mass spectrum *m/e* 124 (M^+).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.13; H, 9.61.

From the fractions which came out with ether, an oily tosylate (**20b**, 3.33 g) was obtained. This was dissolved in acetone (45 ml) and 8 N Jones reagent was added dropwise to the solution at 0–5 °C until red-brown color persisted. After stirring for 1.5 h at this temperature, the mixture was diluted with water (50 ml) and extracted with ether. The extract was washed with saturated sodium bicarbonate solution and water and dried over sodium sulfate. Evaporation of the solvent yielded (+) keto tosylate **19** (3.07 g, yield 55%): $[\alpha]^{21}D$ +8.7° (*c* 0.757, ethanol); ir (neat film) 1728, 1354, 1174, and 961 cm^{-1}.

This tosylate (**19**) was, without further purification, used for the cyclization reaction to norbrexan-2-one (**6**).

Norbrexan-2-one (6). A solution of (+) tosylate **19** (3.07 g, 0.0104 mol) in dimethylformamide (30 ml) was added under a nitrogen atmosphere dropwise to a suspension of sodium hydride (2.00 g, 0.0833 mol) in dimethylformamide (20 ml), and the mixture was stirred for 63.5 h at 60 °C and for an additional 13 h at 80 °C. After addition of methanol (7 ml) with ice cooling, the reaction mixture was poured onto ice and extracted with ether. The extract was washed with 5% hydrochloric acid, saturated sodium bicarbonate solution, and water and dried over sodium sulfate. After evaporation of the solvent, the residue was chromatographed on neutral alumina (Woelm, activity III). The fractions eluted with pentane gave an oily product, which was distilled to give norbrexan-2-one (**6**, 44 mg, yield 3.5%): bp 60 °C (bath temperature) (20 mm); ir (neat film) 1754, 1100, 1030, 975, and 880 cm^{-1}; mass spectrum *m/e* 122 (M^+); CD (*c* 7.05 × 10^{-3}, isooctane) [θ] (nm) 0 (241), +3.73 × 10^3 sh (287), +3.98 × 10^3 (293), +4.00 × 10^3 (296), +2.46 × 10^3 sh (306), 0 (325).

Registry No.—**3**, 60133-47-3; **4**, 60133-48-4; **5**, 60133-49-5; **6**, 60133-50-8; **7**, 58001-99-3; **8**, 60133-51-9; **9**, 60133-52-0; **11**, 60104-05-4; **12**, 60133-53-1; (±)-**15**, 60104-06-5; (−)-**15** salt, 60133-55-3; **16**, 60133-56-4; **17a**, 60104-07-6; **17b**, 60133-57-5; **17c**, 60133-58-6; **18a**, 60104-08-7; **18b**, 60104-09-8; **18c**, 60104-10-1; **18d**, 60104-11-2; **18f**, 60104-12-3; **18g**, 60104-13-4; **19**, 60104-14-5; **20a**, 60104-15-6; **20b**, 60104-16-7.

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The Favorskii Rearrangement of 2-Bromobicyclo[3.2.1]octan-3-one. The Question of Bishomoantiaromaticity

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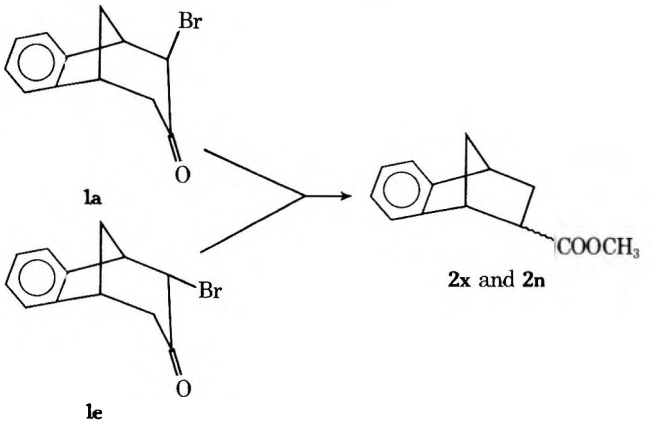
Bicyclo[3.2.1]octan-3-one (**4**) was brominated with *N*-bromosuccinimide (NBS) and benzoyl peroxide in carbon tetrachloride to give axial 2-bromobicyclo[3.2.1]octan-3-one (**3a**) but no equatorial isomer (**3e**). The Favorskii rearrangement of axial bromo ketone **3a** with sodium methoxide in methanol gives only small amounts of Favorskii ring contraction compared to its benzo analogue 2-bromobenzo[6,7]bicyclo[3.2.1]oct-6-en-3-one (**1a**). The major reaction of bromo ketone **3a** is halide displacement by methoxide ion. The facile rearrangement of **1a** is explained in two ways. Inductive withdrawal of the aromatic ring could stabilize enolate **7** and at the same time retard the solvolytic side reaction by destabilizing ion **15**. Secondly, bishomoantiaromaticity may contribute to the instability of ion **15**. Zwitterion **9** is also bishomoantiaromatic, causing a more rapid and less reversible ring closure to the cyclopropanone.

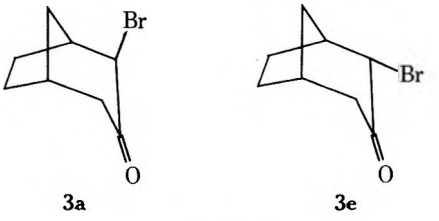
The Favorskii rearrangement has been the subject of intensive research since its discovery in 1894.[1] Monocyclic ring contraction in this base-catalyzed rearrangement of α-halo ketones is well known. However, rearrangement of bicyclic systems has been studied to a lesser extent, with some notable successful rearrangements[2] and other more negative results.[3] Until recently only bridgehead halogenated compounds have been tried. Wilt and Rasmussen[4] were the first to study a substrate having halogen at a position other than a bridgehead. Reaction of axial or equatorial 2-bromobenzo[6,7]bicyclo[3.2.1]oct-6-en-3-one (**1a** and **1e**) with sodium methoxide in either methanol or 1,2-dimethoxyethane (glyme) proceeded smoothly to a mixture of exo and endo epimers of methyl benzonorbornene-2-carboxylate (**2x** and **2n**).



An examination of the literature of this rearrangement in bicyclic rings leaves one confused and unable to predict whether new examples might be synthetically viable. Previous work has not centered on a study of the synthetic usefulness and breadth of this rearrangement. Of the examples cited above, all except one[4] had bridgehead halogens. All of the carbonyl groups except two[2n,4] were located in a one-carbon bridge. Only a few ring sizes have been studied, especially the [3.3.1] and the [2.2.1] skeletons. With the exception of two papers[2o,4] very little mechanistic work has been reported.

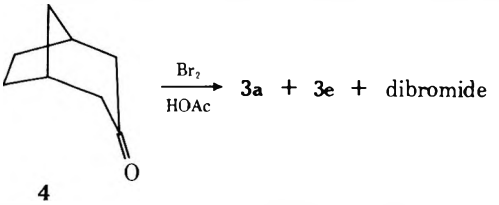
For these reasons we decided to embark on a study of this rearrangement in a number of different bicyclic bromo ketones to determine the effect of ring size, the effect of a bridgehead vs. a nonbridgehead α halogen or α' hydrogen, and the effect of unsaturation on the success of these rearrangements.

Succeeding papers will deal with the first two mentioned effects, but we wish to report an unusual result of unsaturation which appeared when we attempted a Favorskii rearrangement of the aliphatic analogue of bromo ketone **1a**, axial 2-bromobicyclo[3.2.1]octan-3-one (**3a**).



Results

Axial bromo ketone **3a** and its equatorial isomer **3e** have been prepared by Waegell and Jefford, but **3e** was said to be unstable. A mixture of these two isomers along with a dibromide was formed when bicyclo[3.2.1]octan-3-one (**4**) was



treated with bromine in acetic acid.[5] Since the benzo bromo ketone **1** gave essentially the same product composition whether the axial or equatorial isomer was used,[4] it was decided to prepare pure axial bromo ketone **3a** to simplify the study. These bicyclic bromo ketones probably equilibrate rapidly in basic solution, as evidenced by rapid deuteration of the parent ketones bicyclo[3.2.1]octan-3-one (**4**) and benzo[6,7]bicyclo[3.2.1]oct-6-en-3-one with sodium methoxide in methanol-d_4.

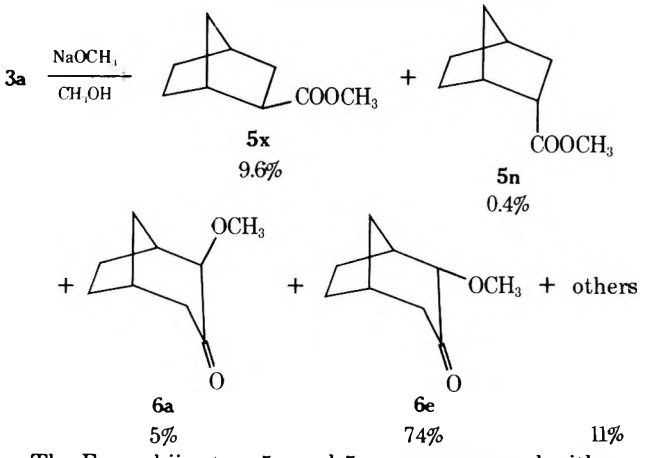
Table I. Products of Bromo Ketones 1a and 3a in $NaOCH_3/CH_3OH$

Bromo ketone	$NaOCH_3$ concn, M	% products[a] Exo ester	Endo ester	Ax CH_3O ketone	Eq CH_3O ketone
1a[b]	2.0	54	14		
3a[c]	2.0	9.6	0.4	5	74
1a[b]	0.1	44	0		
3a[c]	0.1	0	0	100	0

[a] Percentages are based on total area by gas chromatographic analysis. [b] Reference 4. Other products were not identified but included methoxy ketones. [c] This study. At 2 M base, 11% unidentified products were found.

N-Bromosuccinimide (NBS) and benzoyl peroxide in carbon tetrachloride was chosen as the brominating agent since it was found to react in the benzo analogue to form only axial bromo ketone **1a**.[4] Likewise bromination of ketone **4** under these conditions gave axial product **3a**. No evidence of equatorial isomer **3e** was found.

Bromo ketone **3a** was submitted to Favorskii conditions exactly the same as for **1a** (2 M sodium methoxide in methanol, 25 °C, 4 h). Although the benzo analogue **1a** gave a Favorskii yield of 70% (56:14 mixture of exo:endo esters **2x** and **2n**) plus other products including methoxy ketones, the aliphatic bromo ketone **3a** gave only 9.6% methyl norbornane-*exo*-2-carboxylate (the Favorskii product **5x**) and 0.4% endo isomer **5n**, while the major reaction was halide displacement to give 5% axial 2-methoxybicyclo[3.2.1]octan-3-one (**6a**) and 74% equatorial 2-methoxybicyclo[3.2.1]octan-3-one (**6e**).



The Favorskii esters **5x** and **5n** were compared with authentic samples. The two methoxy ketones were assigned configurations on the basis of their NMR spectra which are discussed in the next section.

The reaction of bromo ketone **3a** was also studied in 0.1 M sodium methoxide/methanol. A summary of the products of aromatic bromo ketone **1a** and aliphatic bromo ketone **3a** at both base concentrations is given in Table I.

Note that at each base concentration there is *more* Favorskii rearrangement occurring for aromatic bromo ketone **1a** compared to aliphatic bromo ketone **3a** and that the percentage of Favorskii rearrangement is *increased* with more concentrated base.

Synthetically, a much better Favorskii rearrangement occurs when sodium methoxide in glyme is used. Both bromo ketones give increased amounts of rearrangement with this aprotic solvent. Bromo ketone **3a** gave exo and endo esters **5x** and **5n** *exclusively* in a ratio of 76:24 with glyme.

Discussion

The assignment of axial and equatorial configurations to methoxy ketones **6a** and **6e** was aided by the excellent NMR analysis of a series of substituted cyclohexanones studied by Jefford and Waegell.[5,6] Although it is true that in simple cyclohexane derivatives axial protons often absorb upfield from equatorial protons,[7] cyclohexanones have α axial protons which are downfield compared to α equatorial protons.[8] Jefford and Waegell found that the equatorial bromo ketone **3e** has an α axial proton at δ 4.68 (CCl_4)[6b] and therefore follows this general rule for cyclohexanones, since this is downfield compared to the α equatorial proton of axial bromo ketone **3a** appearing at δ 3.96 (CCl_4).[6b,9] Wilt and Rasmussen found that the benzo bromo ketones **1a** and **1e** follow this generality. The α axial proton of equatorial bromo ketone **1e** appears at δ 4.93 ($CDCl_3$), downfield from the α equatorial proton of axial bromo ketone **1a** located at δ 4.23 ($CDCl_3$).[4] So there is good precedent for assigning α axial and equatorial configurations by chemical shift not only on cyclohexanones but more particularly bicyclo[3.2.1]octan-3-ones.

Table II. Partial NMR Analysis of Methoxy Ketones 6a and 6e in δ (CCl_4)

Methoxy ketone	$CHOCH_3$	OCH_3
6a	3.0–3.2 (eq)	3.21 (ax)
6e	3.4–3.6 (ax)	3.42 (eq)

By this analysis one product was found to be equatorial methoxy ketone **6e**, since its α axial proton is further downfield at δ 3.4–3.6 than the α equatorial proton of axial methoxy ketone **6a**, which appears at δ 3.0–3.2 (see Table II). Examination of the methoxy protons of compounds **6a** and **6e**, however, show that they are outside the dominating magnetic influence of the carbonyl, being farther removed, and the equatorial methoxy protons are farther downfield than the axial methoxy protons (δ 3.42 vs. 3.21).

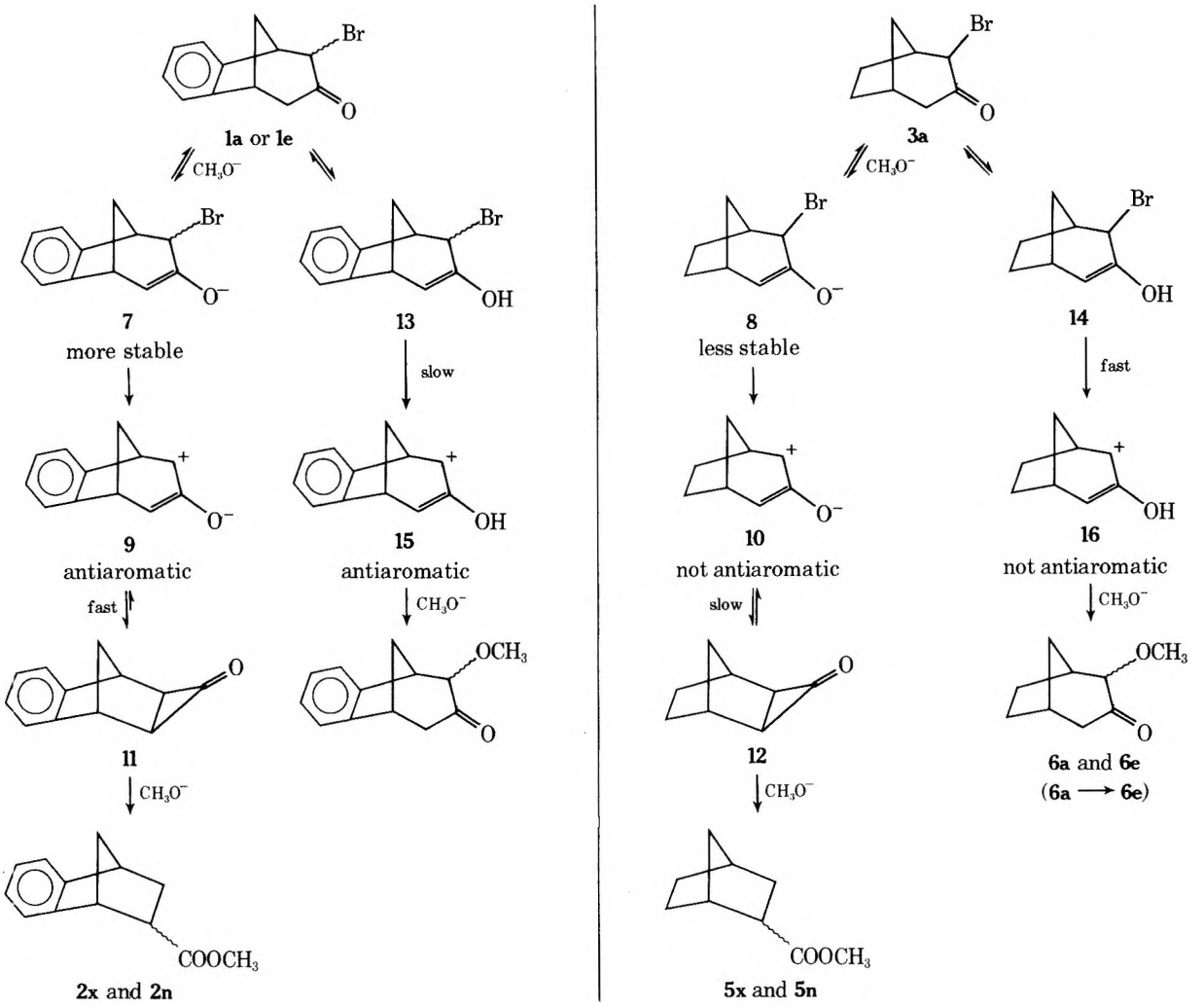
The results of the reaction of bromo ketones **1a** and **3a** are outlined in the most recent mechanism for the Favorskii rearrangement (Chart I). This incorporates current work by Bordwell,[10] House,[11] and Smissman.[12] The important intermediates in the present concept of the Favorskii rearrangement are enolates such as **7** and **8**, zwitterions like **9** and **10**, and cyclopropanones exemplified by **11** and **12**. The competing solvolysis is usually thought of as taking place through enol allylic halides such as **13** and **14** and allylic ions like **15** and **16**. Higher base concentrations or use of unsolvated bases (in glyme) help formation of enolates rather than enol allylic halides. Larger percentages of Favorskii products result. Low base concentrations favor the alternative formation of methoxy ketones at the expense of the rearrangement. Our results substantiate this mechanism.

But if bromo ketones **1a** and **3a** are compared, it is noted that aliphatic bromo ketone **3a** does *not* as readily undergo the Favorskii rearrangement with sodium methoxide/methanol as the aromatic bromo ketone **1a**. This can be explained most logically in one of two ways.

One possibility for the larger percentages of Favorskii product in the benzo analogue is an inductive withdrawal of electron density by the aromatic ring. This may substantially increase the acidity of the α' hydrogen by stabilizing enolate **7** compared to **8**. The inductive withdrawing effect of aromatic rings is well documented for a variety of reaction types and substrates,[13] including benzonorbornenes[14] and benzonorbornadienes.[15] Aromatic electron withdrawal would also retard ionization of the bromide and make ion **15** less stable than **16**. Favorskii product formation would be more favored in the aromatic bromo ketone.

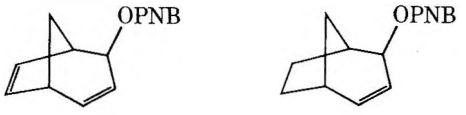
A second explanation differs in degree from the first. Ion **15** is bishomoantiaromatic but **16** is not. This would destabilize **15** dramatically and would favor the Favorskii product. The antiaromatic character of zwitterion **9** also may be a factor

Chart I



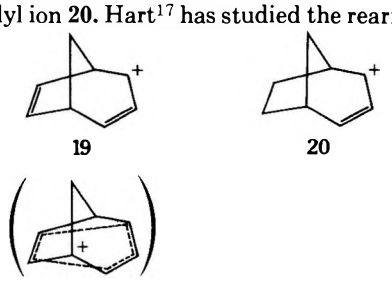
in the product distribution. Although **9** may be more slowly formed relative to **10**, it would have a very short lifetime and would rapidly and less reversibly ring close to cyclopropanone **11**. The ring closure of **10** to **12** would be slower and more reversible. This would explain the greater percentages of Favorskii products in the benzo analogue.

Precedence for bishomoantiaromatic character in this ring system is reported by Winstein,[16] who studied the solvolysis of *p*-nitrobenzoates **17** and **18** in aqueous acetone.



17 **18**

The presence of the additional double bond in **17** is markedly rate retarding, with *exo*-**17** solvolyzing 235 times slower than *exo*-**18**. Winstein suggested that "the rate retardation is probably even larger than can be ascribed to the rate-retarding inductive effect of the second olefinic group." He suggested that **17** solvolyzes very slowly because it forms the unstable ion **19** which is bishomoantiaromatic, whereas **18** yields the allyl ion **20**. Hart[17] has studied the rearrangement



19 **20**

of the nonamethyl derivative of ion **19** by NMR and has drawn attention to "the importance of bishomoantiaromaticity as a factor in these rearrangements." Bishomoantiaromatic ion **19** is analogous to **9** and **15** and ion **20** is similar to **10** and **16**.

Stereochemical results with bromo ketone **3a** are strongly analogous to Winstein's work with *exo*-*p*-nitrobenzoate **18**. In dilute base the axial product is formed preferentially by stepwise loss of the axial bromine, formation of ion **16**, and attack by methoxide on the axial side stereospecifically. Likewise, solvolysis of *p*-nitrobenzoate **18** proceeded stereospecifically and with retention.[16] Only in the more concentrated base does **6e** predominate and this could be formed by epimerization of **6a**. Epimerization studies in 2 M sodium methoxide showed that the axial and equatorial methoxy ketones **6a** and **6e** readily equilibrate.

Experimental Section

Melting and boiling points are uncorrected. The melting points were taken in capillaries in a Thomas-Hoover apparatus. The following instruments were used: Varian T-60 NMR spectrometer, Perkin-Elmer 727 infrared spectrophotometer, and a Varian Aerograph Model 700 Autoprep gas chromatograph. NMR data are given in parts per million (δ) relative to internal Me_4Si, with the usual splitting abbreviations followed by number of protons and interpretation. Only significant ir absorptions are listed in cm^{-1}. Gas chromatography was performed on an SE-30 or QF-1 column with helium carrier gas. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

Bicyclo[3.2.1]octan-3-one (4). This ketone was prepared from norbornene by the method of Jefford et al.[18]

Axial 2-Bromobicyclo[3.2.1]octan-3-one (3a). Ketone **4** (8.68 g, 0.0700 mol), *N*-bromosuccinimide (freshly recrystallized from

water, 12.40 g, 0.0700 mol), benzoyl peroxide (0.96 g), and carbon tetrachloride (60 ml) were refluxed for 22 h. White succinimide began precipitating after 1 h, and a dark mixture was obtained after the full heating period. The mixture was cooled in an ice bath and the succinimide was suction filtered (6.48 g, 0.0654 mol, 94%, mp 123–126 °C, lit.[19] mp 125–126 °C). The precipitate was washed with chilled carbon tetrachloride (2 × 50 ml). The combined filtrate was washed twice with 10% sodium bicarbonate and once with water, dried with magnesium sulfate, and rotary evaporated. Gas chromatographic analysis (SE-30, 192 °C, 56 ml/min) showed unreacted ketone **4** and brominated product in a 31:69 ratio. Addition of more NBS (4.96 g) and further reflux and workup still left some ketone 4 in a 21:79 ratio. Short-path distillation gave a small forerun of 4 which was scraped from the condenser followed by bromo ketone **3a** as a white solid which crystallized in the receiving flask (7.66 g, 0.0378 mol, 54%), bp 80–95 °C (0.25 mm). Further purification gave bp 65–71 °C (0.19–0.25 mm), mp 50–51 °C (lit.[5] mp 49–50 °C). No evidence was obtained for any equatorial isomer **3e** being formed.

Reaction of Bromo Ketone 3a with 2 M Sodium Methoxide in Methanol. A solution of sodium methoxide in methanol (2 M, 150 ml) was stirred with bromo ketone **3a** (1.56 g, 0.00768 mol, 96.3% pure by VPC) at 25 °C for 4 h. A pale yellow color was apparent at the end of this time. The solution was chilled to 0 °C and neutralized with glacial acetic acid. Ether (750 ml) was added and the mixture was cooled in a freezer overnight. The sodium acetate was suction filtered and washed with ether (150 ml). The ether was rotary evaporated. High vacuum caused the residue to solidify because of a small amount of sodium acetate still present. Ether (10 ml) was added and the solid was gravity filtered and washed with ice-cold ether (20 ml). Evaporation of the solvent from the filtrate gave a yellow oil (0.87 g, 0.00565 mol, 74% isolated yield based on $C_9H_{14}O_2$).

Preparative gas chromatography (QF-1, 192 °C, 60 ml/min) was used to separate the products of the reaction. The products and percentages are given in order of increasing retention times: 10% methyl norbornane-2-carboxylate (**5x** and **5n**), 5% axial 2-methoxybicyclo[3.2.1]octan-3-one (**6a**), and 74% equatorial 2-methoxybicyclo[3.2.1]octan-3-one (**6e**). Two other peaks were not identified: 8%, overlapping partially with methoxy ketone **6e**, and 3%, of longer retention time. The same column at 115 °C separated **5x** and **5n** in a 96:4 ratio.

The exo ester **5x** was compared to an authentic sample prepared below and was found to agree in retention time and spectral properties. The peak assigned as the endo ester **5n** had a retention time identical with that of the authentic compound, but spectral properties were not taken owing to the small amount of this product.

The axial methoxy ketone **6a** was a colorless liquid: ir (neat) 3000, 2950, 2900 (C–H), 1715 (C=O), 1450, 1405, 1330, 1170, and 1065 cm^{-1} (C–O); NMR (CCl_4) δ 3.21 (s, 3, CH_3O), 3.0–3.2 (m, 1, $CHOCH_3$), 1.2–2.8 (m, 10).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.53; H, 9.27.

A light orange 2,4-dinitrophenylhydrazone was recrystallized three times from ethanol, mp 189–191 °C.

Anal. Calcd for $C_{15}H_{18}N_4O_5$: N, 16.76. Found: N, 16.69.

The equatorial methoxy ketone **6e** was a colorless liquid: ir (neat) 3050, 2970, 2920 (C–H), 1740 (C=O), 1460, 1200, 1120, 1100 (C–O), 1060, 1020, and 910 cm^{-1}; NMR (CCl_4) δ 3.4–3.6 (m, 1, $CHOCH_3$), 3.42 (s, 3, CH_3O), 2.1–2.6 (m, 4, $CH_2C=O$ and two bridgehead H), 1.4–1.8 (m, 6).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.90; H, 9.22.

A light orange 2,4-dinitrophenylhydrazone was recrystallized from ethanol six times, mp 147–149 °C.

Anal. Calcd for $C_{15}H_{18}N_4O_5$: N, 16.76. Found: N, 17.04.

Reaction of Bromo Ketone 3a with 0.1 M Sodium Methoxide in Methanol. A solution of sodium methoxide in methanol (0.1 M, 20 ml) was stirred with bromo ketone **3a** (0.20 g, 0.00100 mol) at 25 °C for 4 h. The solution was not basic at the end of this time. Acetic acid (3 drops) and ether (80 ml) were added but no precipitate was obtained. The residue was rotary evaporated and analyzed by VPC (QF-1, 191 °C 60 ml/min) and NMR. Only axial methoxy ketone **6a** was present.

Reaction of Bromo Ketone 3a with Sodium Methoxide in Glyme. A suspension of sodium methoxide (0.28 g, 0.00522 mol) and bromo ketone **3a**, (0.20 g, 0.00100 mol) in glyme (8 ml) was stirred magnetically for 1 h at 25 °C. A brown color was formed after 5 min. The mixture was cooled in an ice bath and acetic acid (17 drops) was added to neutralize the base. Addition of ether (80 ml) precipitated the salt, which was suction filtered and washed with ether (50 ml). Rotary evaporation left a residue which was analyzed by VPC (QF-1, 115 °C, 60 ml/min). Only esters **5x** and **5n** were obtained in a ratio of 76:24.

Epimerization of Methoxy Ketones 6a and 6e. A small sample of **6a** was stirred with sodium methoxide in methanol (2 M, 20 ml) and processed as before. VPC analysis (QF-1, 189 °C, 60 ml/min) showed three peaks, identified as **6a** (13%), **63** (82%), and a third compound (5%) having a retention time identical with that of the extra, unidentified peak observed in the Favorskii studies.

Epimerization of equatorial methoxy ketone **6e** was studied in similar fashion to give **6a** (7%), **6e** (86%), and the same unidentified trace product (7%).

Methyl Norbornane-2-carboxylate (5x and 5n). The exo and endo esters **5x** and **5n** were prepared as 69:31 mixture starting with norbornane-2-carbonitrile (Aldrich Chemical Co.) by the normal methods of hydrolysis to the acids[20] and esterification via diazomethane,[21] bp 42–44 °C (0.62–0.71 mm), lit.[22] bp 77 °C (10 mm) for **5x** and 76–77 °C (11 mm) for **5n**. They are easily distinguished by VPC retention times and by the NMR chemical shift of the methyl protons (δ 3.58 for **5x** and δ 3.60 for **5n** in CCl_4).[22]

Deuteration Studies of Bicyclo[3.2.1]octan-3-one (4) and Benzo[6,7]bicyclo[3.2.1]oct-6-en-3-one. The ketone (~0.1 g) was dissolved in CD_3OD (0.5 ml) and 1 drop of 2 M $NaOCH_3$ in CD_3OD was added. Both ketones behaved similarly by exchanging two of the four α hydrogens within the first 2 min, the time required to place the sample in the NMR probe and integrate the spectrum. The other two α protons exchanged gradually over about 6 h.

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Registry No.—**1a**, 54164-79-3; **3a**, 28052-02-0; **4**, 14252-05-2; **5x**, 23057-38-7; **5n**, 16646-41-6; **6a**, 59891-85-9; **6a** 2,4-DNPH, 60031-42-7; **6e**, 59891-86-0; **6e** 2,4-DNPH, 60031-43-8; *N*-bromosuccinimide 128-08-5; sodium methoxide, 124-41-4.

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Sigma Assisted vs. Unassisted Pathways in the Ionization of Tertiary Cyclopropyl Triflates

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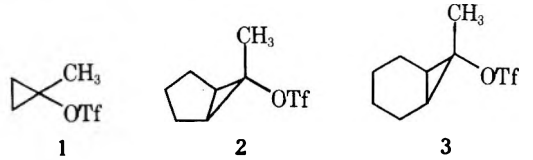
Synthetic schemes have been developed which allow the preparation of *endo*-6-methyl-*exo*-bicyclo[3.1.0]hex-6-yl triflate (**2**) and *endo*-7-methyl-*exo*-bicyclo[4.1.0]hept-7-yl triflate (**3**). Synthesis of the latter involved a copper-catalyzed addition of ethyl diazopropionate to cyclohexene which give principally the *exo*-carboethoxy cyclopropanation product **17**. Similar stereoselectivity was seen in the addition to cyclopentene. Solvolysis rates of 1-methyl cyclopropyl triflate, **1**, **2**, and **3** were rapid in acetic acid at room temperature. Relative rates were 0.95, 1.0, and 8.8, respectively. Solvolysis of **2** was suggested to involve the unopened 6-methylbicyclo[3.1.0]hex-6-yl cation, **25**, which rapidly rearranged to an allylic cation before capture of nucleophile could occur. α-Methyl/hydrogen rate ratios were smaller than expected in view of the stabilization demands of an unopened cyclopropyl cation. In contrast **3** gave unopened products on acetolysis. Product and rate data were interpreted in terms of a slightly opened allylic cation, **31**, with charge residing essentially at the 7 position. Triflate **1** gave only isobutylene on solvolysis in aqueous diglyme containing sodium borohydride.

Cyclopropyl substrates tend to undergo ionization with concerted ring opening to give allylic or partially opened allylic cationic systems.[1] Unopened cyclopropyl cations result only when groups capable of contributing greatly to cationic stability are present.[2] Recently[3] we have shown that concerted opening of cyclopropyl systems can be completely blocked in the ionization step by the incorporation of a bicyclo[2.2.1] system fused to the cyclopropyl system trans to the leaving group. Electrocyclic opening could also be prevented if olefinic or cyclopropyl participating groups were suitably positioned.[3,4] While the substitution products in these systems were completely in accordance with cationic rearrangement processes, the response of ionization rate to solvent ionizing power was quite small. Substrate m values[5] were in the range of the nucleophilic mechanism seen for primary substrates. The suggestion offered was that the low response to solvent ionizing power was in part due to the triflate leaving group and also reflected less than "normal" charge development in the transition state for ionization of cyclopropyl triflates.

In order to further support this suggestion, we sought to use the methyl group as a probe for charge development in developing cyclopropyl cations. We also sought to employ the methyl group as a neighboring group to evaluate its effectiveness in thwarting electrocyclic ring opening during ionization. We report here the results of these studies of α-methyl substitution in a series of cyclopropyl triflates.

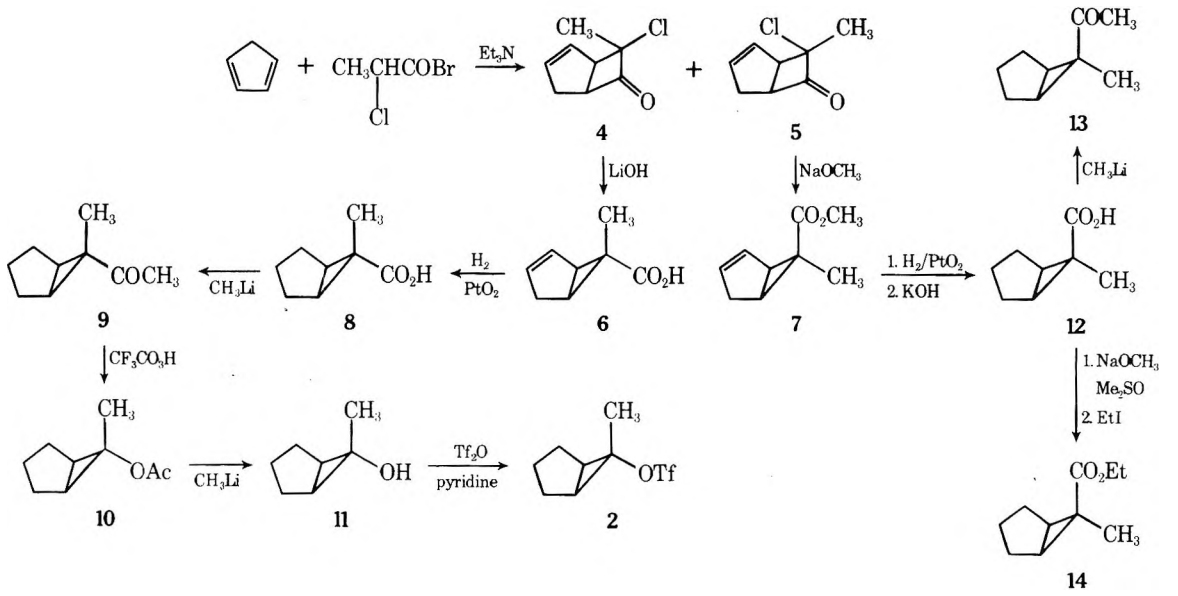
Synthetic Aspects. Of immediate interest was the preparation of triflates **1**, **2**, and **3**. The preparation of **1** has been previously described.[4] Triflate **2** was prepared as shown in Scheme I. The reaction of chloromethylketene, generated from 2-chloropropionyl bromide and triethylamine, and cyclopentadiene led to the known mixture of chloromethylbicyclo[3.2.0]heptenones, **4** and **5**.[6] Chloro ketone **4** was stereospecifically ring contracted with lithium hydroxide to *endo*-6-methyl-*exo*-bicyclo[3.1.0]hex-2-ene-6-carboxylic acid (**6**) using the procedure of Garin and Cammack.[7] Catalytic hydrogenation of the methyl ester of **6** or the unsaturated methyl ketone derived by treatment of **6** with methyllithium gave partial reduction of the cyclopropane ring along with the olefinic linkage. To avoid the cyclopropane bond reduction, it was necessary to carry out the hydrogenation on the free acid using platinum oxide as catalyst. Conversion of the saturated acid **8** to the corresponding methyl ketone **9** was accomplished by treatment with methyllithium. A primary side product of this transformation was the tertiary alcohol derived from addition of methyllithium to **9**. It has been suggested[8] that a major source of tertiary alcohol in the preparation of ketones from acids and organolithium reagents is the addition of unreacted excess organolithium reagent to the ketonic product during the hydrolysis of intermediate, $R_2C(OLi)_2$. In the preparation of **9**, and for many analogous transformations which we have carried out, this problem can be circumvented. Following the suggestion of Jorgenson,[8b] we have destroyed the excess methyllithium by the addition of ethyl acetate to the reaction mixture prior to the addition of water. With this procedure tertiary alcohol formation is negligible.

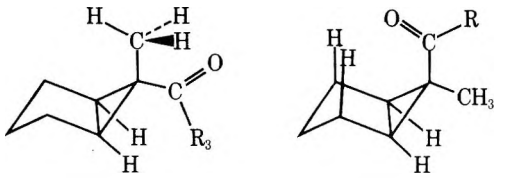
exo-Methyl ketone **9** shows a carbonyl stretching frequency of 1684 cm^{-1}. This compares to a value of 1702 cm^{-1} for the isomeric *endo*-methyl ketone **13**. These significant differences are in line with the decreased conjugation of the carbonyl group with the cyclopropyl system in **13**, and a resultant carbonyl shift to higher energy, as a result of steric factors. Ap-



1 2 3

Scheme I





9, R = CH_3
15, R = OEt

13, R = CH_3
14, R = OEt

parently conjugation in **13** is lessened owing to an unfavorable steric interaction of the *endo*-acetyl group with the fused ring system. Distortion from the preferred conformation necessary for maximal conjugation with the cyclopropyl system, as shown above, results in an increased carbonyl stretching frequency. Similar trends are seen in the ethyl esters **14** and **15** derived from the corresponding acids by alkylation of the carboxylate salts with ethyl iodide in dimethyl sulfoxide. Exo ester **15** has a carbonyl stretching frequency of 1717 cm^{-1} while the value for endo ester **14** is 1727 cm^{-1}.

The remainder of the synthetic sequence shown in Scheme I to triflate **2** was analogous to procedures previously described.

The approach to the synthesis of triflate **3** was undertaken in terms of a carboethoxymethylcarbene addition to cyclohexene. Singlet carboethoxymethylcarbene is expected to yield ethyl acrylate via simple intramolecular hydrogen transfer to the carbenic center. Hence the addition was attempted by way of the triplet state which is known to add to isobutylene to give cyclopropane derivatives.[9] Benzophenone-sensitized photolysis of ethyl diazopropionate in cyclohexene gave small amounts of the desired cyclopropanation product **17**. However, the major product was the radical dimer, **16**. Hydrogen atom abstraction from cyclohexene apparently occurs in preference to addition of triplet carboethoxymethylcarbene to cyclohexene. This approach to synthetically useful amounts of **17** was therefore abandoned.

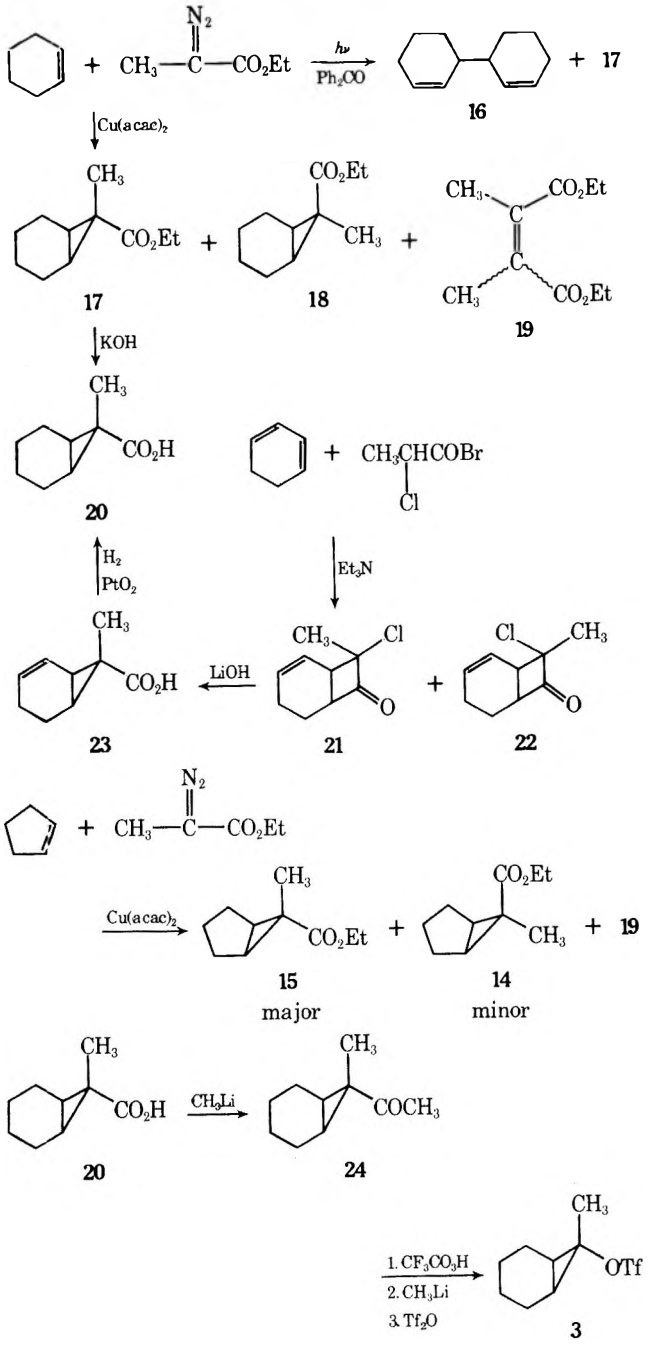
The copper-catalyzed addition of ethyl diazoacetate to cyclohexene has been thoroughly investigated and found to give a predominance of *exo*-7-carboethoxybicyclo[4.1.0]-heptane.[10] We have found that the copper acetylacetonate catalyzed addition of ethyl diazopropionate to cyclohexene gives cyclopropanation products **17** and **18** along with larger amounts of the formal carbene dimers **19**. The *exo*-carboethoxy adduct **17** was the predominant isomer. The stereochemistry of this cyclopropanation product was suggested by the analogous reaction of cyclopentene. The copper acetylacetonate catalyzed reaction of ethyl diazopropionate with cyclopentene gave a 6:1 mixture of *exo*- and *endo*-6-carboethoxy-6-methylbicyclo[3.1.0]hexane (**15** and **14**). Product identification in this case was made by spectral comparison with authentic samples independently prepared as shown in Scheme I. The predominance of the *exo*-carboethoxy isomer **15** in the reaction with cyclopentene suggested a similar stereochemical pathway for cyclohexene.

Proof of the stereochemistry of **17** was accomplished by saponification to give *endo*-7-methyl-*exo*-bicyclo[4.1.0]heptane-7-carboxylic acid (**20**), which could be prepared independently as shown in Scheme II. The known addition of chloromethylketene to 1,3-cyclohexadiene gave a mixture of cycloadducts **21** and **23**.[11] Chloroketene **21** was separated and stereospecifically ring contracted with lithium hydroxide to give the unsaturated acid **23**. This acid could be hydrogenated to give a product identical with that obtained by saponification of **17**.

The stereochemical results of the copper-catalyzed addition of ethyl diazopropionate to cyclopentene and cyclohexene were unexpected in view of the steric requirements of a methyl group vs. the carboethoxy group. Conformational equilibria suggest that a methyl group is sterically more bulky than the carboethoxy group. On this basis, the conclusion must be that some feature other than steric bulk of the two groups controls the stereochemical outcome of the copper complexed carboethoxymethylcarbene addition to cyclopentene and cyclohexene. This stereoselectivity, which is not in accord with steric factors, is not unprecedented. Endo (syn) stereoselectivity is seen in the addition of phenylcarbene,[12] chlorocarbene,[13] and phenylthiocarbene[14] (or carbenoid species), among others, to olefins. Electronic factors in the transition state, which outweigh steric factors, are suggested to account for some cases of syn stereoselectivity.[12] Opposing electronic factors, and not solely steric effects, may control both carboethoxycarbene and carboethoxymethylcarbene (as copper complexes) addition to olefins giving exo (anti) stereoselectivity. The remainder of the synthetic sequence to triflate **3** is shown in Scheme II.

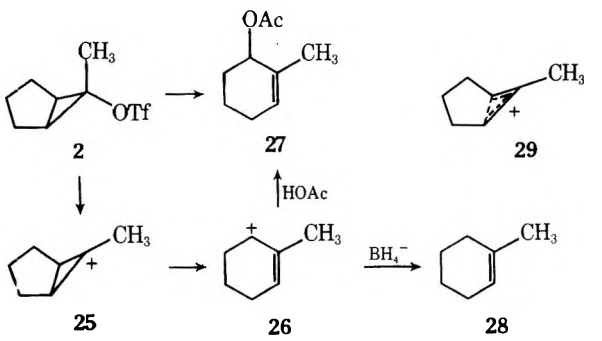
Solvolytic Studies. Triflates **1**, **2**, and **3** proved to be quite reactive. Solvolytic studies were carried out at room temperature in acetic acid. Rate data are given in Table I. In acetic acid, triflate **2** gave 2-methylcyclohex-2-enyl acetate (**27**) as the only product. Even the very nucleophilic borohydride anion cannot intercept structurally unrearranged products. Solvolysis in aqueous diglyme containing sodium borohydride

Scheme II



gave 1-methylcyclohexene (**28**) as the only product. The mechanistic scheme suggested involves formation of the unopened tertiary cyclopropyl cation **25** as the first intermediate. The products suggest that rearrangement of **25** to allylic cation **26** occurs.

A potential intermediate that must be considered is a partially opened allylic cation such as **29**. Schleyer[1] has postulated



that analogous intermediates intervene in the solvolysis of *exo*-bicyclo[3.1.0]hex-6-yl triflate and *exo*-bicyclo[4.1.0]-hept-7-yl tosylate. Rate and product data were completely in line with neither trans allylic cations nor cyclopropyl cation intermediates. To account for rate data and products of retained ring structure and stereochemistry, partially opened allylic cation intermediates were suggested. Theoretical calculations also support the viability of such intermediates.[1c]

None of the retained acetate **10**, which would be expected from a partially opened allylic cation such as **29**, is observed. Apparently opening of **25** by the allowed disrotatory mode to give **26** is the most rapid process even in the presence of borohydride anion.[15] While solvolysis of *exo*-bicyclo[3.1.0]hex-6-yl triflate is suggested to occur via a partially opened allylic cation,[1a] the methyl group appears to be completely effective in blocking the analogous partial opening of triflate **2** during the ionization process.

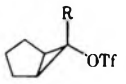
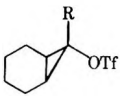
As a sidelight to this investigation, it was found that while borohydride cannot successfully intercept cation **25**, it does succeed in capturing the 1-phenylcyclopropyl cation. Previous studies[20] have shown that solvolysis of 1-phenylcyclopropyl tosylate in acetic acid gave only allylic products. These results can be interpreted in terms of a stepwise process leading to the 2-phenylallyl cation (via the 1-phenylcyclopropyl cation) or possibly a concerted pathway giving the allylic cation directly. We have found that solvolysis of 1-phenylcyclopropyl tosylate in aqueous diglyme containing sodium borohydride gives a hydrocarbon mixture consisting of α-methylstyrene (3.7 parts) and phenylcyclopropane (1 part). These results show that borohydride is nucleophilic enough to intercept some 1-phenylcyclopropyl cations before opening to the allylic cation can occur and provide strong evidence for the discrete intermediacy of the 1-phenylcyclopropyl cation.

Comparison of the rate of solvolysis of *endo*-6-methyl-*exo*-bicyclo[3.1.0]hex-6-yl triflate (**2**) with *exo*-bicyclo[3.1.0]hex-6-yl triflate gives an α-methyl/hydrogen ratio of $10^{7.56}$. This compares to a value of 10^8 suggested by Schleyer[16] as a standard value for secondary substrates. This value is slightly less than the suggested "normal" value. What is the origin of this slight discrepancy? The rationale that immediately comes to mind is the fact that solvolysis of *exo*-bicyclo[3.1.0]hex-6-yl triflate is σ assisted by partial fragmentation of the internal cyclopropane bond, yielding a partially opened allylic cation as the initial intermediate. This fact should result in a less than normal α-methyl/hydrogen rate ratio.

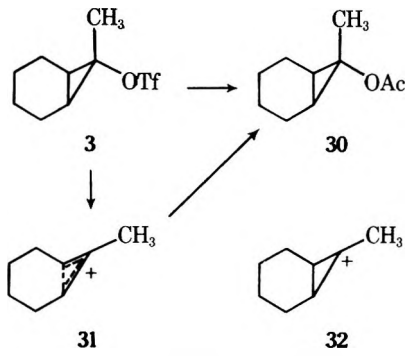
The observed α-methyl/hydrogen ratio of $10^{7.56}$ is also not out of line with the suggestion that transition state charge development in the ionization of cyclopropyl triflates is less than normal.[18] The demand for stabilization on an α-methyl group should be enormous in the extremely unstable cyclopropyl cation. As such, the suggested α-methyl/hydrogen ratio of 10^8 may not reflect the true demand of an unopened cyclopropyl cation. It would not be unreasonable to expect an α-methyl/hydrogen ratio of *greater than* 10^8 owing to this larger than normal demand for stabilization in the unopened cyclopropyl cation. The observed value of $10^{7.56}$ may reflect an early transition state as well as the σ-assisted solvolysis of *exo*-bicyclo[3.1.0]hex-6-yl triflate.

Consider next the acetolysis of *endo*-7-methyl-*exo*-bicyclo[4.1.0]hept-7-yl triflate (**3**). The rate of acetolysis is only slightly faster (8.8 times) than that of **2**. This compares to a rate difference of greater than 5000 for the unmethylated analogues.[4,18] However, a product study shows that only *endo*-7-methyl-*exo*-bicyclo[4.1.0]hept-7-yl acetate (**30**) is produced from **3** in acetic acid. We prefer the mechanistic scheme shown involving partially opened allylic cation **31** as the key intermediate. If tertiary cyclopropyl cation **32** were involved, rapid opening to give an allylic cation, and hence an

Table I. Rates of Solvolysis in Acetic Acid–0.1 M Sodium Acetate

Registry no.	Compd	$k^{25°}$, s^{-1}	k_{rel}	$k_{R=CH_3}/k_{R=H}$
				
60153-71-1	R = CH_3	$(5.82 \pm 0.01) \times 10^{-5}$	1.0	$10^{7.6}$
25327-17-7	R = H	1.61×10^{-12} [a,b]		
				
60153-72-2	R = CH_3	$(5.11 \pm 0.00) \times 10^{-4}$	8.8	$10^{3.9}$
60153-73-3	R = H	6.32×10^{-6} [a,c]		
				
60153-74-4	R = CH_3	$(5.52 \pm 0.04) \times 10^{-5}$	0.95	$10^{3.1}$
25324-42-1	R = H	4.35×10^{-8} [a,b]		($10^{3.0}$)[d]

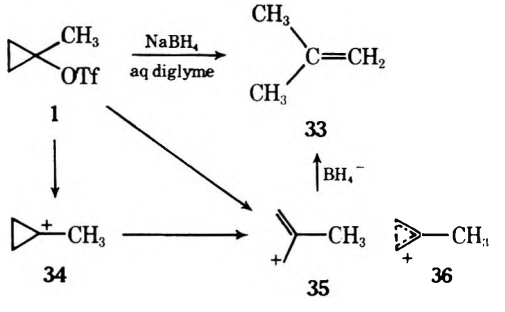
[a] Extrapolated value. [b] Reference 17. [c] Reference 4. [d] For tosylates; ref 1a.



allylic acetate product, would be expected. The opening of **32** might not be as rapid as the comparable opening of **25**, which even the nucleophilic borohydride cannot intercept. However, opening of **32** should be faster than solvent capture by the relatively nonnucleophilic (vs. borohydride) acetic acid solvent.

The small rate enhancement, relative to **2**, seen in the acetolysis of **3** is also consistent with a small amount of σ assistance. In the intermediate partially opened cation **31**, charge should reside essentially at the tertiary center. Internal bond fragmentation should be minimal, but enough to prevent disrotatory opening to give an allylic cation. This is borne out by the formation of only acetate **30** in which configuration is maintained and no diacetate products analogous to those produced in the acetolysis of *exo*-bicyclo[4.1.0]hept-7-yl tosylate. While methyl substitution can completely offset σ participation in the exo-bicyclo[3.1.0]hex-6-yl system, similar substitution is apparently not sufficient to offset the larger amount of σ assistance in bicyclo[4.1.0]hept-7-yl substrates.

Interpretation of rate and product data in the solvolysis of 1-methylcyclopropyl triflate (**1**) is less straightforward. Solvolysis in aqueous diglyme containing sodium borohydride gave isobutylene (**33**) as the sole product. Either a stepwise



formation of allylic cation **35** or a concerted ionization–ring opening is consistent with formation of this product. Borohydride may not be nucleophilic enough to trap unrearranged cation **34** or **34** may be completely bypassed in favor of **35**. As in the case of cyclopropyl tosylate, product analysis does not allow a distinction.

In terms of rate, 1-methylcyclopropyl triflate (**1**) solvolyses at the same rate as *endo*-6-methylbicyclo[3.1.0]hex-6-yl triflate (**2**). Triflate **2** is suggested to give a completely unopened tertiary cyclopropyl cation. A similar postulate that unopened cation **34** is involved in solvolysis of **1** may seem compelling. The α-methyl group can offset all of the σ participation in **2** and most of such participation in **3**. It is not unreasonable to expect that all or most of the σ participation in **1** should also be offset by α-methyl substitution. However, we cannot use solely rate data to implicate **34** and to rule out **35** as being formed directly from **1**. Steric rate acceleration in solvolysis of **2** may be involved along with a σ-assisted solvolysis of **1** (via transition state **36**). The equal solvolysis rates could therefore be fortuitous. The first intermediate in solvolysis of **1** could be allylic cation **35**. In any case, there should be less demand for σ participation in solvolysis of **1** than in unsubstituted cyclopropyl triflate. It would therefore not be unreasonable to expect that the transition state for ionization of **1** should have less cyclopropane bond fragmentation than in solvolysis of unsubstituted cyclopropyl triflate. The negligible rate difference between **1** and **2**, as compared to a 3×10^4 difference between cyclopropyl triflate and bicyclo[3.1.0]hex-6-yl triflate, bears this out.

Experimental Section

NMR spectra were recorded on a Varian A-60A spectrometer. Mass spectra were recorded on an AEI Scientific Apparatus MS 902 spectrometer. Infrared spectra were recorded on a Perkin-Elmer 457 spectrometer or a Perkin-Elmer Infracord spectrometer.

1-Methylcyclopropyl Triflate (1). Triflate **1** was prepared as previously described.[4]

***endo*-6-Methyl-*exo*-bicyclo[3.1.0]hexane-6-carboxylic Acid (8).** Unsaturated acid **6** (3.0 g) was added to a mixture of 100 mg of platinum oxide (previously reduced by shaking with hydrogen at 50 psi) and 25 ml of absolute ether. The mixture was hydrogenated (Parr hydrogenator) at 36 psi for 90 min and filtered through Celite and the solvent was removed by rotary evaporator. The yield of crude acid was 2.95 g (98%): mp 70–75 °C; NMR (CCl_4) δ 2.2–1.4 (8 H, m), 1.14 (3 H, s); mass spectroscopic molecular weight, 140.0841 (calcd for $C_8H_{12}O_2$, 140.0837).

***exo*-6-Acetyl-*endo*-6-methylbicyclo[3.1.0]hexane (9).** Carboxylic acid **8** (2.5 g) was dissolved in 12 ml of ether and the solution was cooled to 0 °C. Methyllithium (17.5 ml of a 2.06 M solution) was diluted with 20 ml of absolute ether and added dropwise over a 15-min

period to the cooled solution. The mixture was then refluxed for 70 min and 2 g of ethyl acetate was carefully added. The mixture was then poured into water and the organic phase separated, washed with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The solvent was removed by distillation through a Vigreux column and the residue was distilled through a short-path condenser to give 2.346 g (95%) of ketone **9**: bp 69–71 °C (2.8 mm); NMR (CCl_4) δ 2.01 (3 H, s), 2.0–1.3 (8 H, m), 1.17 (3 H, s); mass spectroscopic molecular weight, 138.1046 (calcd for $C_9H_{14}O$, 138.1045).

***endo*-6-Methyl-*exo*-bicyclo[3.1.0]hex-6-yl Acetate (10).** Peroxytrifluoroacetic acid, prepared from 0.79 g of 90% hydrogen peroxide and 7.4 g of trifluoroacetic anhydride in 8 ml of methylene chloride, was added dropwise over a 10-min period to a stirred mixture of 1.62 g of ketone **9**, 21 g of dibasic potassium phosphate, and 25 ml of methylene chloride. The mixture was refluxed for 1 h and stirred at room temperature for 3 h. The mixture was then taken up into ether and water. The organic phase was washed with dilute potassium carbonate solution and dried over sodium sulfate. Solvents were removed by distillation through a Vigreux column and the residue was distilled through a short-path condenser to give 1.607 g (89%) of acetate **10**: bp 56–64 °C (3.1 mm); NMR (CCl_4) δ 1.88 (3 H, s), 2.0–1.3 (8 H, m), 1.30 (3 H, s); mass spectroscopic molecular weight, 154.0986 (calcd for $C_9H_{14}O_2$, 154.0994).

***endo*-6-Methyl-*exo*-bicyclo[3.1.0]hex-6-yl Triflate (2).** A mixture of 1.365 g of acetate **10** and 10 ml of ether was cooled to 0 °C as 10 ml of 2.3 M methyllithium was added dropwise. After 15 min, excess ethyl acetate was then added to the mixture. The mixture was then cooled to −78 °C and water was added dropwise. After warming to about 10 °C, the organic phase was separated, washed with saturated sodium chloride solution, and dried over sodium sulfate. Solvents were removed by water aspirator. The crude alcohol **11**, 0.88 g (88%), was used directly in the next step.

A solution of 3.75 g of trifluoromethanesulfonic anhydride in 15 ml of pyridine was cooled to −5 °C and a solution of alcohol **11** (0.88 g) in 5 ml of ether was added dropwise with stirring. After storing at −10 °C for 4.25 h, the mixture was rapidly taken up into cold water and ether. The ether extract was rapidly washed in succession with cold water, cold dilute hydrochloric acid, and cold saturated sodium chloride solution. After drying over anhydrous sodium sulfate, solvents were removed by distillation through a Vigreux column. Care was taken so that the temperature of the solution did not exceed 50 °C. The residue was distilled to give 1.483 g (77% based on crude alcohol **11**) of triflate **2**: bp 41–42 °C (0.35 mm); NMR (CCl_4) δ 2.1–1.6 (8 H, m), 1.63 (3 H, s).

***endo*-6-Carbomethoxy-*exo*-6-methylbicyclo[3.1.0]hex-2-ene (7).** Sodium methoxide was prepared from 5.2 g of sodium and 120 ml of absolute methanol. Chloro ketone **5**[6] (7.11 g), which was separated from the isomeric chloro ketone **4** by fractional distillation, was added to the solution cooled to 0 °C. The mixture was brought to reflux for 2.5 h, cooled, and taken up into ether and water. The organic extract was separated and the aqueous phase was extracted with another portion of ether. The combined ether extracts were washed with water and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Solvents were removed by distillation through a Vigreux column. The residue was distilled to give 6.35 g (92%) of ester **7**, bp 60–62 °C (5 mm) [lit.[19] bp 60–62 °C (2 mm)].

***exo*-6-Methylbicyclo[3.1.0]hexane-*endo*-6-carboxylic Acid (12).** A mixture of 120 mg of platinum oxide, 50 ml of ether, and 6.25 g of unsaturated ester **7** was hydrogenated (Parr hydrogenator) at 40 psi for 2 h. After filtering through Celite, solvents were removed by distillation through a Vigreux column. The residue was distilled to give 6.20 g (99%) of the saturated methyl ester: bp 55–57 °C (3.5 mm); NMR (CCl_4) δ 3.58 (3 H, s), 2.10–1.25 (8 H, m), 1.18 (3 H, s).

A solution of 5.4 g of potassium hydroxide, 30 ml of water, 30 ml of methanol, and 6.1 g of the saturated methyl ester prepared above was refluxed for 6 h. Most of the methanol was removed by distillation. The aqueous solution was extracted with pentane and then added to a solution of 8 ml of concentrated hydrochloric acid in 20 ml of water. The precipitate was collected on a Buchner funnel and dried under vacuum to give 3.86 g (70%) of saturated acid **12**: mp 76–78 °C; NMR (CCl_4) δ 12.33 (1 H, s), 2.2–1.35 (8 H, m), 1.25 (3 H, s); mass spectroscopic molecular weight, 140.0846 (calcd for $C_8H_{12}O_2$, 140.0837).

***endo*-6-Acetyl-*exo*-6-methylbicyclo[3.1.0]hexane (13).** The procedure was analogous to the preparation of the epimeric methyl ketone **9**. The yield of **13** obtained from 1.0 g of **12** and 10 ml of 2.06 M methyllithium was 0.741 g (75%): bp 70–73 °C (8 mm); NMR (CCl_4) δ 2.08 (3 H, s), 2.00–1.20 (8 H, m), 1.13 (3 H, s); mass spectroscopic molecular weight, 138.1046 (calcd for $C_9H_{14}O$, 138.1045).

***endo*-6-Carboethoxy-*exo*-6-methylbicyclo[3.1.0]hexane (14).** A solution of 0.25 g of acid **12** in 3 ml of Me_2SO was treated with 0.15 g of sodium methoxide followed by 0.7 g of ethyl iodide. The mixture was stirred at approximately 35 °C for 3 h. After an aqueous workup, distillation gave 0.277 g (92%) of ethyl ester **14**: bp 51–52 °C (1.1 mm); NMR (CCl_4) δ 4.06 (2 H, q, J = 7 Hz), 2.10–1.00 (14 H, m) with a triplet, J = 7 Hz, at δ 1.24 and a singlet at δ 1.17; mass spectroscopic molecular weight, 168.1154 (calcd for $C_{10}H_{16}O_2$, 168.1150).

***exo*-6-Carboethoxy-*endo*-6-methylbicyclo[3.1.0]hexane (15).** A solution of 0.23 g of acid **8** in 2.8 ml of Me_2SO was treated with 0.15 g of sodium methoxide followed by 0.7 g of ethyl iodide. The mixture was stirred at approximately 35 °C for 3 h. After an aqueous workup, distillation gave 0.239 g (87%) of ethyl ester **15**: bp 65–69 °C (1.1 mm); NMR (CCl_4) δ 3.96 (2 H, q, J = 7 Hz), 2.20–1.50 (8 H, m), 1.18 (3 H, t, J = 7 Hz), 1.08 (3 H, s): mass spectroscopic molecular weight, 168.1154 (calcd for $C_{10}H_{16}O_2$, 168.1150).

Copper Acetonylacetonate Catalyzed Addition of Ethyl Diazopropionate to Cyclohexene. Copper acetylacetonate (40 mg) was dissolved in 21 ml of refluxing cyclohexene. A solution of 2.1 g of ethyl diazopropionate in 10 ml of cyclohexene was added dropwise over a 1-h period. Nitrogen evolution was rapid after the solution color changed from blue to brown. Most of the cyclohexene was removed by distillation and the residue was taken up into ether and washed with dilute hydrochloric acid. After drying over anhydrous sodium sulfate, solvents were removed by distillation. The residue was distilled through a short-path condenser to give 0.97 g, bp 85–105 °C (1.7 mm). Gas chromatographic analysis on a 4-ft 10% SE-54 on Chromosorb P column at 140 °C showed four major products. A 0.83-g portion of the distillate was dissolved in 12 ml of methanol and ozonized exhaustively at −78 °C. A mixture of sodium iodide and sodium thiosulfate in water was then added. After stirring at room temperature for 5 min the mixture was extracted with ether. After drying, solvents were removed by distillation. The residue was distilled at 1.7 mm to give 0.291 g of products. Gas chromatographic analysis showed none of the two products of intermediate retention time. In a separate run, the products of intermediate retention time were isolated by preparative gas chromatography and shown to be ethyl esters of dimethylmaleic and dimethylfumaric acids (**19**). Samples of the two addition products, after ozonolysis, were isolated by preparative gas chromatography. Mass spectral analysis shows m/e 182 for both products. The ratio of **17** to **18** was approximately 7:1. Ester **17** had the following NMR (CCl_4): δ 4.00 (2 H, q, J = 7 Hz), 1.8–1.0 (16 H, m) with a triplet, J = 7 Hz, at δ 1.21 and a singlet at δ 1.17.

Copper Acetylacetonate Catalyzed Addition of Ethyl Diazopropionate to Cyclopentene. A 50-mg portion of copper acetylacetonate was partially dissolved in 21 ml of refluxing cyclopentene and a solution of 2.0 g of ethyl diazopropionate was added dropwise over a 6-h period of the refluxing mixture. After refluxing for 48 h, most of the cyclopentene was removed by distillation. The residue was distilled through a short-path condenser to give 0.85 g of a product mixture, bp 80–97 °C (1.1 mm). Gas chromatographic analysis showed four products. The products of longest retention time were ethyl esters of dimethylmaleic and dimethylfurmaric acids. A 200-mg sample of the product mixture was dissolved in 3.5 ml of methanol and ozonized exhaustively at −78 °C. The workup was the same as previously described. After removal of the solvents by distillation, samples of the two remaining products were isolated by preparative gas chromatography. Infrared spectral comparison showed that the major isomer of longer retention time was identical with ester **15**. The minor isomer of shorter retention time was identical with **14**. The ratio of **15** to **14** was approximately 6:1.

***endo*-7-Methyl-*exo*-bicyclo[4.1.0]hept-2-ene-7-carboxylic Acid (23).** A 118-mg sample of chloro ketone **21**, isolated by preparative gas chromatography, was stirred with 95 mg of lithium hydroxide in 1.3 ml of water. The solution was added to dilute hydrochloric acid and extracted with ether. After drying over sodium sulfate, the solvent was removed by rotary evaporator. The yield of crude acid was 72 mg (68%): mp 82–84 °C; NMR (CCl_4) δ 5.79 (2 H, m), 2.5–1.6 (6 H, m), 1.33 (3 H, s); mass spectroscopic molecular weight, 152.0840 (calcd for $C_9H_{12}O_2$, 152.0837).

***endo*-7-Methyl-*exo*-bicyclo[4.1.0]heptane-7-carboxylic Acid (20).** A 0.291-g sample of the ester mixture obtained by addition of carboethoxymethylcarbene to cyclohexene was heated at reflux for 3 h with 0.2 g of potassium hydroxide in 3 ml of water and 3 ml of methanol. Most of the methanol was removed by distillation and the solution was extracted with a portion of ether. The aqueous phase was added to cold dilute hydrochloric acid and the precipitated acid **20** was collected and air dried. The yield of acid **20** was 0.169 g (69%): mp 89–93 °C; NMR (CCl_4) δ 2.2–1.0 (10 H, m), 1.19 (3 H, s); mass spectroscopic molecular weight, 154.0992 (calcd for $C_9H_{14}O_2$, 154.0994).

A 260-mg sample of unsaturated acid **23** was dissolved in 10 ml of

ether and 20 mg of platinum oxide was added. The mixture was hydrogenated at 36 psi for 1 h and filtered through Celite and the solvent was removed by rotary evaporator. Infrared and NMR spectra of the product were identical with those of the acid obtained by saponification of ester **17**.

***exo*-7-Acetyl-*endo*-7-methylbicyclo[4.1.0]heptane (24).** A 169-mg sample of acid **20** was dissolved in 3 ml of ether and cooled to 0 °C. A 1.5-ml portion of 1.8 M methyllithium, diluted to 4 ml with ether, was added dropwise. The mixture was refluxed for 90 min, then excess ethyl acetate was added. Water was then added, the aqueous phase was separated and dried over anhydrous sodium sulfate, and solvents were removed by distillation. The residue was distilled to give 141 mg (85%) of ketone **24**: bp 75 °C (1.2 mm); NMR (CCl_4) δ 2.03 (3 H, s), 1.75–1.1 (13 H, m) with singlet at δ 1.26.

***endo*-7-Methyl-*exo*-bicyclo[4.1.0]hept-7-yl Acetate (30).** A 203-mg sample of ketone **24** in 2 ml of methylene chloride was refluxed for 1 h with peroxytrifluoroacetic acid prepared from 116 mg of 90% hydrogen peroxide, 993 mg of trifluoroacetic anhydride, and 1 ml of methylene chloride with 2.82 g of dibasic potassium phosphate. An aqueous workup gave, upon distillation, 176 mg (78%) of acetate **30**: bp 60 °C (1 mm); NMR (CCl_4) δ 1.85 (3 H, s), 1.8–0.9 (10 H, m), 1.38 (3 H, s); mass spectroscopic molecular weight, 168.1154 (calcd for $C_{10}H_{16}O_2$, 168.1150).

***endo*-7-Methyl-*exo*-bicyclo[4.1.0]hept-7-yl Triflate (3).** A solution of 200 mg of acetate **30** in 3 ml of ether was cooled to 0 °C and 1.75 ml of 1.8 M methyllithium was added dropwise. The mixture was then cooled to −78 °C and water was added. After warming to about 10 °C, the organic phase was separated, washed with saturated sodium chloride, and dried over anhydrous sodium sulfate. Solvent was removed by rotary evaporator. The residue was dissolved in a small amount of ether and added to a solution of 0.6 g of trifluoromethanesulfonic anhydride in 3 ml of pyridine at −5 °C. After 3 h, the mixture was worked up in the usual manner as rapidly as possible using cold aqueous washes. After the organic extract was dried over anhydrous sodium sulfate, the solvent was removed by distillation through a Vigreux column. The temperature was not allowed to rise above about 40 °C. The residue was distilled to give 0.197 g (64%) of triflate **3**: bp 46–48 °C (0.4 mm); NMR (CCl_4) δ 1.70 (3 H, s), 1.95–1.05 (10 H, m). Triflate **3** was stored at −5 °C and used as soon as possible after preparation.

Solvolysis of *endo*-6-Methyl-*exo*-bicyclo[3.1.0]hex-6-yl Triflate (2) in Acetic Acid. A solution of 0.266 g of triflate **2** in 10 ml of acetic acid containing 0.1 g of acetic anhydride and 0.124 g of sodium acetate was held at room temperature for 9 h and then heated at 50 °C for 2 h. The mixture was then poured into water and extracted with two portions of ether. The combined extracts were washed with water and dilute potassium carbonate and dried over anhydrous sodium sulfate. Solvents were removed by distillation through a Vigreux column and the residue was distilled to give 0.149 g (89%) of acetate **30**: bp 83 °C (15 mm); NMR (CCl_4) δ 5.62 (1 H, m), 5.15 (1 H, m), 1.99 (3 H, s), 2.2–1.5 (9 H, m); mass spectroscopic molecular weight, 154 (calcd for $C_9H_{14}O_2$, 154).

Solvolysis of *endo*-6-Methyl-*exo*-bicyclo[3.1.0]hex-6-yl Triflate (2) in Aqueous Diglyme Containing Sodium Borohydride. A solution was prepared from 8 ml of water, 25 ml of diglyme, 0.4 g of sodium hydroxide, and 2 g of sodium borohydride. Triflate **2** (0.53 g) was added to 16 ml of this mixture and the solution was stirred at 40 °C for 5 h. The mixture was poured into water and extracted with pentane. The organic extract was washed with water and dried over anhydrous sodium sulfate. The pentane was removed by distillation through a Vigreux column. The residue was distilled at atmospheric pressure. The infrared spectrum of the distillate (CCl_4) was identical with that of an authentic sample of 1-methylcyclohexene (Satler spectrum no. 3387). The NMR spectrum showed no trace of 6-methylbicyclo[3.1.0]hexane.

Solvolysis of *endo*-7-Methyl-*exo*-bicyclo[4.1.0]hept-7-yl Triflate (3) in Acetic Acid. A 95-mg sample of triflate **3** was dissolved in 5 ml of acetic acid containing 0.1 M sodium acetate and 1% acetic anhydride. After 25 h, the mixture was poured into water and extracted with ether. Acetic acid was removed by washing with dilute potassium carbonate and the ether was dried over anhydrous sodium sulfate. Solvent was removed by distillation through a Vigreux column. The residue was distilled through a short-path condenser to give 49 mg (80%) of an acetate, homogeneous by gas chromatography, and identical spectrally with acetate **30**, prepared by the Baeyer–Villiger oxidation of ketone **24**.

Solvolysis of 1-Methylcyclopropyl Triflate (1) in Aqueous Diglyme Containing Sodium Borohydride. Triflate **1** (1.0 g) was added to a solution of 2 g of sodium borohydride and 0.3 g of sodium hydroxide in 6 ml of water and 21 ml of diglyme. A distillation head was attached along with a receiver cooled to −78 °C. The solution was heated to approximately 60 °C. A portion of the distillate was transferred to a cooled (−78 °C) NMR tube by allowing the flask containing the crude distillate to warm. The NMR spectrum showed only isobutylene with no trace of 1-methylcyclopropane.

Registry No.—**5**, 13363-88-7; **6**, 29782-06-7; **7**, 36964-16-6; **8**, 54235-92-6; **9**, 60153-75-5; **10**, 60153-76-6; **11**, 60153-77-7; **12**, 54235-93-7; **12** methyl ester, 58808-26-7; **13**, 60153-78-8; **14**, 60153-79-9; **15**, 60153-80-2; **17**, 60153-81-3; **18**, 60153-82-4; **20**, 60153-83-5; **21**, 56084-87-8; **23**, 55999-11-6; **24**, 60153-84-6; **30**, 59514-82-8; peroxytrifluoroacetic acid, 359-48-8; trifluoromethanesulfonic anhydride, 358-23-6; ethyl iodide, 75-03-6; cyclohexene, 110-83-8; ethyl diazopropionate, 6111-99-5; cyclopentene, 142-29-0.

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Secondary Deuterium Isotope Effects in the Solvolysis of Cyclopropyl Triflates

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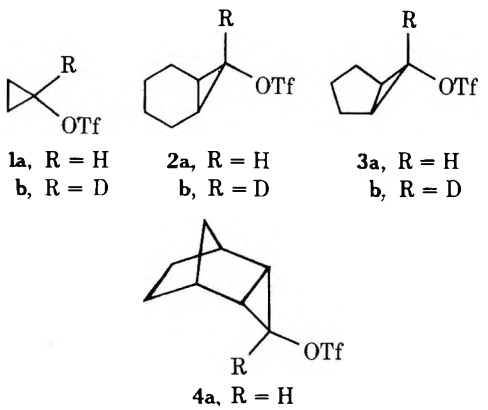
α-Deuterium isotope effects have been measured for solvolysis of cyclopropyl triflate (**1**), *exo*-bicyclo[4.1.0]hept-7-yl triflate (**2**), *exo*-bicyclo[3.1.0]hex-6-yl triflate (**3**), and *endo*-tricyclo[3.2.1.$0^{2,4}$]oct-*exo*-3-yl triflate (**4**) in acetic acid. The respective values are 1.07, 1.08, 1.18, and 1.24. These values are discussed in terms of increasing cyclopropyl cationic character in the cationic intermediates. β-Deuterium isotope effects were determined for 1-methyl cyclopropyl triflate (**8**) and *endo*-6-methyl-*exo*-bicyclo[3.1.0]hex-6-yl triflate (**9**). Values were 1.12 and 1.42, respectively. The former value was considered to implicate a concerted ionization ring opening in **8**. The latter value was consistent with a stepwise ionization, ring opening mechanism for **9**. The β effect of 1.42 was considered small in view of the instability of the cation derived from **9** and rationalized in terms of an early transition state.

Secondary deuterium isotope effects have been used extensively in the study of solvolytic displacement reactions.[1] As tools for mechanistic diagnosis, they have proven to be quite useful. Our interest in cyclopropyl systems[2] has led us to use α and β secondary deuterium isotope effects as probes into mechanisms of solvolysis of cyclopropyl triflates. Previously, in a series of cyclopropyl triflates, rate responses to changing solvent ionizing power were quite small.[2b] In systems where neighboring group participation was possible, rate enhancements were also relatively small.[2] These results suggested an early transition state with little charge development. We have therefore introduced an α deuterium into a series of cyclopropyl triflates to see if such substitution could reveal any information as to the degree of charge development and distribution in the transition state for ionization of these systems. We have also measured the β effects in two tertiary cyclopropyl triflates. The results of these studies and their mechanistic implications are now reported.

α-Deuterium Isotope Effects. The α-deuterium isotope effect has been discussed extensively.[1,3] A value of around unity or slightly inverse is found for substrates solvolyzing by a purely nucleophilic mechanism. In contrast, compounds which solvolyze by "borderline" or limiting mechanisms show progressively increasing α-deuterium isotope effects. A maximum value of about 1.23 has been suggested by Shiner[3a] for the limiting solvolysis of a sulfonate ester. This value is a function of leaving group, being 1.125 for an alkyl bromide.[3a] The phenomenon of neighboring group participation will also result in a lowering of the α effects relative to the maximum value for a limiting solvolysis.[1,4] The α effect gives some measure of the hybridization changes and charge development in the transition state.

Deuterated triflates **1b–4b** were prepared to measure the α effect. The undeuterated triflates **1a–4a** had all been prepared previously.[2,5] The α-deuterated analogues were prepared by base-catalyzed exchange of the methyl ketones as shown in Scheme I. In general, exchange of the cyclopropyl proton was quite slow. These findings were in agreement with the previous observations of slow exchange of "activated" cyclopropyl protons.[6] In fact, the trideuterated ketone **6** could be isolated, uncontaminated with the tetradeuterated ketone, **7**. Additionally, treatment of *exo*-7-carbomethoxybicyclo[4.1.0]heptane with excess lithium diisopropylamide at −78 to 0 °C followed by quenching with deuterium oxide gave no deuterium incorporation in the recovered ester. Although the methyl ketones exchanged more rapidly than the corresponding methyl esters, in general, much more strenuous conditions were required for exchange of the cyclopropyl proton than the methyl protons. Cyclopropyl methyl ketone exchanged the ring proton faster than the corresponding bicyclic ketones. This implies a steric effect in which the fused ring system retards attack of base on the cyclopropyl proton. Conversion of the deuterated ketones to deuterated triflates **1b–4b** was accomplished as outlined in Scheme I.



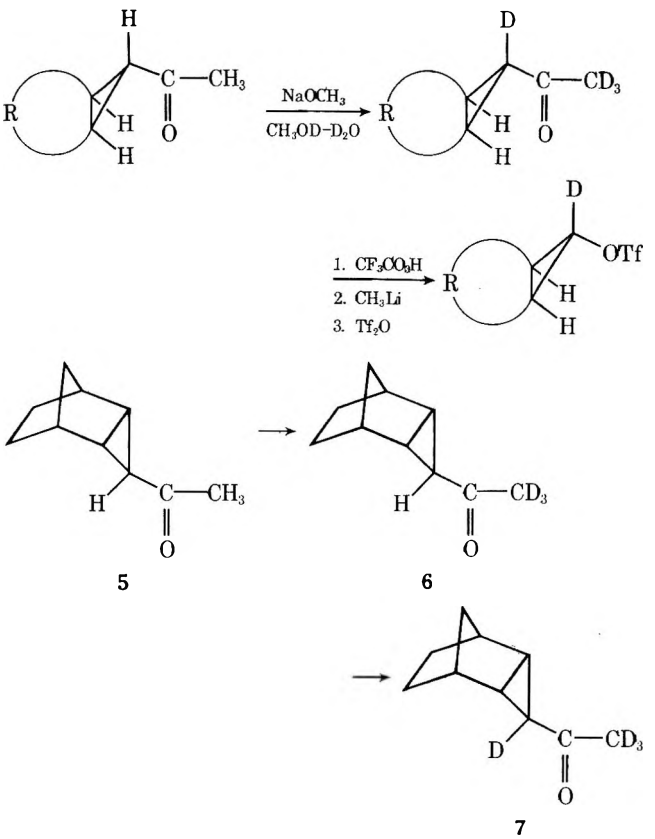
1a, R = H
b, R = D

2a, R = H
b, R = D

3a, R = H
b, R = D

4a, R = H
b, R = D

Scheme I



5 **6** **7**

Table I. Rates of Solvolysis in Acetic Acid–0.1 M Sodium Acetate

Registry no.	Compd	Temp, °C	k, s^{-1}	k_H/k_D
25354-42-1	**1a**	90.0	$(1.24 \pm 0.00) \times 10^{-4}$	1.07 ± 0.01
60153-85-7	**1b**	90.0	$(1.16 \pm 0.01) \times 10^{-4}$	
60153-73-3	**2a**	80.0	$(7.61 \pm 0.05) \times 10^{-5}$	1.08 ± 0.01
60153-86-8	**2b**	80.0	$(7.05 \pm 0.02) \times 10^{-5}$	
25327-17-7	**3a**	150.0	$(2.85 \pm 0.04) \times 10^{-5}$	1.18 ± 0.02
60168-79-8	**3b**	150.0	$(2.41 \pm 0.01) \times 10^{-5}$	
56514-04-6	**4a**	140.0	$(4.30 \pm 0.03) \times 10^{-5}$	1.24 ± 0.01
60184-58-9	**4b**	140.0	$(3.47 \pm 0.01) \times 10^{-5}$	

Table II. Rates of Solvolysis in Acetic Acid–0.1 M Sodium Acetate

Registry no.	Compd	Temp, °C	k, s^{-1}	k_H/k_D
60153-74-4	**8a**	25.0	$(5.52 \pm 0.04) \times 10^{-5}$	1.12 ± 0.01
60153-87-9	**8b**	25.0	$(4.94 \pm 0.03) \times 10^{-5}$	
60153-71-1	**9a**	25.0	$(5.82 \pm 0.01) \times 10^{-5}$	1.42 ± 0.02
60153-88-0	**9b**	25.0	$(4.11 \pm 0.05) \times 10^{-5}$	

Table I gives α-deuterium isotope effects determined in acetic acid. The α effect appears to increase systematically as the degree of allylic cation character in the first cationic intermediate decreases. The relatively small value of the α effect (1.07) seen in cyclopropyl triflate (**1**) is in line with Schleyer's suggestion of an allylic cation as the first intermediate with transition state charge residing at all three positions.[5,7] Significant sigma assistance also accounts for the reduced α-deuterium isotope effect (1.08) seen in *exo*-bicyclo[4.1.0]hept-7-yl triflate (**2**), in which a partially opened allylic cation has been proposed as the first intermediate.[8] The magnitude of the isotope effect implies that substantial charge resides at the allylic positions.

exo-Bicyclo[3.1.0]hex-6-yl triflate (**3**) is also suggested to give a partially opened allylic cation as the first cationic intermediate.[5,8b] However, because of strain in such a cation, internal cyclopropane bond fragmentation is minimal and charge should reside largely at the 6 position. This proposal is borne out by the increased α-deuterium isotope effect (1.18) seen in **3**.

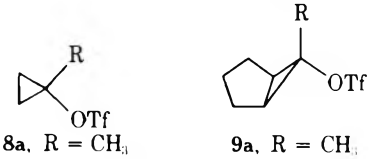
Triflate **4** has been suggested to undergo solvolysis to give a discrete cyclopropyl cationic intermediate with no opening of the internal cyclopropane bond.[2a] The observed α effect is 1.24. This value is in conformity with the value of 1.23 suggested by Shiner[3a] as maximum for a sulfonate ester. However, is this α effect to be expected in a solvolysis which gives a cyclopropyl cationic intermediate? Other evidence may indicate otherwise. Schiavelli[9] has measured the α-deuterium isotope effect for solvolysis of a bromoallene in which the hybridization change is $sp^2 \rightarrow sp$. The value of the α effect was 1.22, a value *larger than* the proposed maximum value of 1.125 for an $sp^3 \rightarrow sp^2$ hybridization change in the limiting solvolysis of alkyl bromides. This increased isotope effect was rationalized in terms of exchange equilibrium constants which predict a larger α effect for an $sp^2 \rightarrow sp$ hybridization change.

The bonding in cyclopropane has been discussed in terms of carbon $sp^{2.5}$ hybridization of the C–H bonds.[10] This accounts for, among other things, the increased acidity of cyclopropanes relative to less strained analogues. The overall hybridization change in ionization of triflate **4** should therefore be from $sp^{2.5} \rightarrow sp^{1.5}$. Although pertinent exchange equilibrium constants are not available, it would not be unreasonable to expect that the maximum α effect for this process should be between the maximum effect suggested by Shiner (1.23) and the maximum effect for an $sp^2 \rightarrow sp$ change (1.17×1.23).

As such the value of 1.24 observed for triflate **4** may be smaller than "normal" considering the hybridization changes involved. This could reflect the early transition state proposed for cyclopropyl triflates suggested on the basis of low response to solvent ionizing power.

β-Deuterium Isotope Effects. The β-deuterium isotope effect is thought to arise from a decreased C–D hyperconjugative interaction relative to C–H hyperconjugation.[3a] Attempts have been made to attribute this effect, as well as the α effect, to solely steric factors.[11] Shiner has pointed out the shortcomings of these suggestions[3a] and steric contributions to the β effect are considered only small factors.[12] Representative values for limiting solvolyses are 1.22 for α-phenethyl chloride[13] and 1.48 for 2-methyl-2-adamantyl chloride.[14] As with the α effect, neighboring group participation decreases the β effect.[15,20]

Deuterated triflates **8b** and **9b** were prepared by variations of known procedures.[16] Reaction of methylmagnesium iodide-d_3 with 1,3-dichloroacetone followed by ethylmagnesium bromide and ferric chloride gave 1-methyl-d_3-cyclopropanol,[17] which was converted to triflate **8b**. Triflate **9b** was prepared



8a, R = CH_3 **9a**, R = CH_3
b, R = CD_3 **b**, R = CD_3

via the bromomethyl-d_3 ketone, cyclopentadiene adduct[18] as shown in Scheme II. Separation of the isomers **10** and **11** was accomplished by distillation and conversion of bromo ketone **10** to acid **12** was analogous to ring contraction of the chloro ketone.[19] Conversion of **12** to triflate **9b** was straightforward.

Scheme II

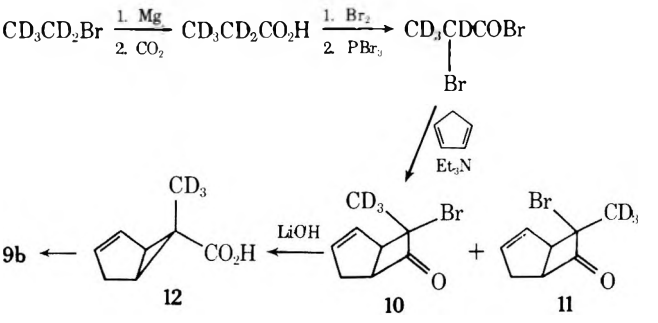
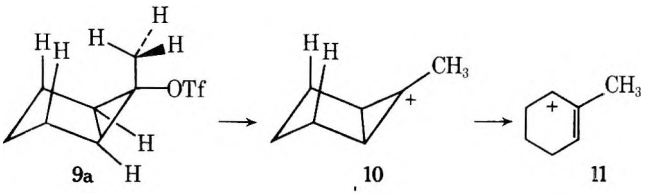


Table II gives β-deuterium isotope effects for solvolysis of triflates 8 and 9 in acetic acid. Previously, product and rate data did not allow assignment of a mechanistic pathway in the solvolysis of **8a**.[16] Only olefinic products were observed which could have arisen by stepwise or concerted processes. The magnitude of the β-deuterium isotope effect in the solvolysis of 8 is relatively small. This small value (1.12) supports a sigma assisted, concerted ionization, ring opening mechanism in preference to the formation of the 1-methylcyclopropyl cation as a discrete intermediate. Sigma assistance in 8 should be greatly reduced relative to the unsubstituted cyclopropyl system, **1**, even though allylic cations are the first intermediates produced in both cases. Apparently even a small amount of participation by the fragmenting cyclopropane bond gives a reduction in the β-deuterium isotope effect. The important feature is that the β effect of 1.12 is not consistent with a discrete cyclopropyl cationic intermediate.

Product studies have implicated the unopened 6-methylbicyclo[3.1.0]hex-6-yl cation (**10**) in the solvolysis of **9**.[16] The ring opened products obtained support a stepwise process in which the initially formed cation **10** rapidly opens to the 2-methylcyclohexenyl cation **11**. The measured β isotope effect



9a **10** **11**

is 1.42, a value significantly larger than the value for 1-methyl cyclopropyl triflate (**8**). A question arises concerning the normalcy of this value. We believe that this value is quite small in view of the system under consideration. Firstly, the unopened cyclopropyl cation, which is involved in the solvolysis of **9**, is quite unstable and hence should demand an unusually large amount of hyperconjugative stabilization. A standard system such as 2-methyl-2-adamantyl chloride, which gives a β effect of 1.48,[14] would not reflect the true demand of cation **10**. One of the largest β-deuterium isotope effects (1.86–2.33) has been observed in the solvolysis of 7-methyl-7-norbornyl tosylate.[14,20,21] This large value was presumed to result from the large demand for stabilization by the relatively unstable 7-norbornyl cation. More recently, Shiner and Sunko[14,22] have analyzed this effect in terms of α-methyl/α-hydrogen rate ratios. Their conclusion, in light of a "predicted" β isotope effect of 1.49, was that the measured isotope effect was unusually large and may be a result of partial rate determining elimination at an ion pair stage. Regardless of which value is a "normal" isotope effect in the 7-methylnorbornyl system, the demand for hyperconjugative stabilization in a cyclopropyl cation should certainly be larger than in the 2-adamantyl or the 7-norbornyl system.

Secondly, consider the relative solvolysis rates of **8a** and **9a**. Rates are approximately the same. The implication on the basis of the β effect is that the rate of **8a** is enhanced by σ participation. If this is true then **9a** must also be enhanced to account for the similarity in rate. Examination of molecular models suggests that steric factors are responsible for this rate enhancement in **9a**. Although steric factors are considered, in general, to contribute little to the β effect,[3a,12] we feel that a solvolytic steric isotope effect cannot be ruled out in very congested systems. That such effects can operate has been shown recently in solvolysis of 2-*tert*-butyl-2-adamantyl *p*-nitrobenzoate.[24] We can only speculate as to the magnitude of a steric isotope effect in **9**, but clearly it should complement the hyperconjugative effect.

Considering the demand for stabilization by the cyclopropyl cation **10**, and the possibility of an enhancing steric isotope effect, the measured β-deuterium isotope effect of 1.42 in triflate **9** must be considered quite small. Moreover, this value conforms to the implication[2b] that the solvolysis of cyclopropyl triflates leads to an early transition state. The β-deuterium isotope effect is not as large as one might naively expect since, in such a transition state, charge development is relatively small. Hence there is decreased demand for hyperconjugative stabilization relative to a later transition state, and a decreased β effect.

Experimental Section

Base-Catalyzed Exchange of Cyclopropyl Methyl Ketone. Cyclopropyl methyl ketone (Aldrich Chemical Co.) (3.0 g) was dissolved in 3 ml of methanol-d_1 and 10 ml of deuterium oxide containing 1.7 g of sodium methoxide. The mixture was refluxed for 40 h and extracted with two portions of pentane. The extracts were washed with a portion of water and solvents were removed by distillation through a glass helice packed column. The residue was distilled through a short-path condenser and the distillate was recycled under the same conditions. After an identical workup, the residue was isolated by distillation through a short-path condenser to give 0.781 g of tetradeuterated cyclopropyl methyl ketone. Mass spectral analysis showed complete exchange of the cyclopropyl proton.

Base-Catalyzed Exchange of Polycyclic Methyl Ketones. 7-Acetylbicyclo[4.1.0]heptane, 6-acetylbicyclo[3.1.0]hexane, and *exo*-3-acetyl-*endo*-tricyclo[3.2.1.$0^{2,4}$]octane (**5**) were prepared by reaction of the corresponding carboxylic acids with methyllithium. The exchange reaction of ketone **5** was representative. A mixture of 0.68 g of ketone **5**, 0.17 g of sodium methoxide, 27 ml of methanol-d_1, and 20 ml of deuterium oxide was refluxed for 4 h. After an aqueous workup, 0.63 g of ketone **6** was isolated by distillation through a short-path condenser. Mass spectral and NMR data indicated no deuterium incorporation of the cyclopropyl proton and complete exchange of the methyl protons. Treatment of a 1.5-g sample of ketone **5** with 12 ml of deuterium oxide, 15 ml of methanol-d_1, and 2.6 g of sodium methoxide at 120–130 °C in sealed tubes for 10 h gave deuterated ketone **7**. Mass spectral data indicated complete exchange of the cyclopropyl proton. Infrared spectra of ketones **5**, **6**, and **7** show substantial differences.

Treatment of 1.55 g of *exo*-7-acetylbicyclo[4.1.0]heptane with 2 g of sodium methoxide in 20 ml of methanol-d_1 and 20 ml of deuterium oxide at reflux for 18 h gave complete exchange of the methyl protons but only about 50% exchange of the cyclopropyl proton. The ketone was recycled for 44.5 h at 100 °C in sealed tubes under the same conditions. Mass spectral analysis showed complete exchange of the cyclopropyl proton.

Treatment of 1.7 g of *exo*-/*endo*-6-acetylbicyclo[3.1.0]hexane with 2.4 g of sodium methoxide in 24 ml of methanol-d_1 and 22 ml of deuterium oxide for 18 h at reflux gave incomplete exchange of the cyclopropyl proton. Recycling at 100 °C for 42 h gave complete exchange.

Conversion of Cyclopropyl Methyl Ketones to Triflates. Conversion of deuterated methyl ketones to the corresponding acetates was accomplished by oxidation with peroxytrifluoroacetic acid in methylene chloride[25] using procedures analogous to oxidation of the protio analogues. Treatment of the acetates with methyllithium in ether followed by reaction of the resulting alcohol with trifluoromethanesulfonic anhydride in pyridine gave the triflate derivative. The following procedure was typical. A mixture of 1.0 g of *exo*-7-acetylbicyclo[4.1.0]heptane-d_4 and 13.8 g of dibasic potassium phosphate in 18 ml of methylene chloride was treated with peracid prepared from 0.52 g of 90% hydrogen peroxide and 4.87 g of trifluoroacetic anhydride in 5 ml of methylene chloride. The mixture was refluxed for 1 h and 45 min. After an aqueous workup, distillation gave 0.912 g (82%) of *exo*-7-acetoxybicyclo[4.1.0]heptane-d_4.

A solution of 0.8 g of acetate in 6 ml of ether was cleaved with 7 ml of 1.8 M methyllithium in ether. After cooling to −78 °C, water was added and the mixture was warmed to about 15 °C. The organic phase was separated, washed with water, and dried, and the solvent was removed by rotary evaporator. The crude alcohol was converted directly to triflate **2b** by treatment with a solution of 2.5 g of trifluoromethanesulfonic anhydride in 10 ml of pyridine at 0 °C. After 5 h at 0 °C, an aqueous workup gave 1.059 g (85%) of triflate **2b**, bp 58 °C (1.2 mm).

Preparation of 1-Methyl-d_3-cyclopropanol. The procedure was analogous to the procedure of DePuy[26] using methylmagnesium iodide-d_3 prepared from 10.0 g of methyl iodide-d_4 (Aldrich Chemical Co.; 99+ atom % D). The yield of product was 1.7 g (42%), bp 56–60 °C (80 mm).

Preparation of 2-Bromopropionyl Bromide-d_4. Ethyl bromide-d_5 (10.0 g) (Merck and Co., Inc., 99 atom % D) was converted to ethylmagnesium bromide-d_5 with 2.7 g of magnesium in 60 ml of ether. Carbonation by addition to excess carbon dioxide gave 4.64 g (68%) of propionic acid-d_5. Conversion to 2-bromopropionic acid-d_4 was accomplished by treatment with 10.0 g of bromine and 0.5 ml of phosphorus trichloride at 80–95 °C for 6 h. The crude bromo acid was treated with 15.9 g of phosphorus tribromide and the mixture was refluxed for 30 min. The crude product was distilled through a Vigreux column. After a small forerun of propionyl bromide, 16.2 g of a mixture of 2-bromopropionyl bromide-d_4 and an unknown impurity was obtained, bp 55–61 °C (16 mm).

Preparation of Bromo Ketones 10 and 11. The procedure was essentially that of Brady and Roe.[18] The 2-bromopropionyl bromide mixture obtained above in 30 ml of hexane was added over a 1.5-h period to a solution of 9.5 g of triethylamine in 65 ml of cyclopentadiene and 70 ml of hexane at room temperature. After filtration and an aqueous workup, the crude residue was distilled through a Vigreux column. The first fraction, bp 69.5–73 °C (1.3 mm), 1.69 g, was about 77% exo bromo ketone **10**. The second fraction, bp 73–80 °C (1.3 mm), 2.83 g, was about 70% endo bromo ketone **11**.

Preparation of *endo*-6-Methyl-d_3-*exo*-bicyclo[3.1.0]hex-2-enecarboxylic Acid (12). A 1.69-g sample of the bromo ketone mixture enriched in exo bromo ketone **10** was vigorously stirred for 2 h at room temperature with a solution of 1.13 g of lithium hydroxide in 11.5 ml of water. The solution was extracted with ether and the aqueous phase was added to a cold hydrochloric acid solution. The precipitate was collected and air dried giving 0.879 g (75%) of acid **12**, mp 65–70 °C. Conversion of **12** to triflate **9b** was completely analogous to the preparation of **9a**.[16]

Kinetic Procedure. The procedure was followed as previously described.[2a] For runs at 25 °C, the time was recorded when the end points of the titrations were reached. The rate constants reported represent the average of a minimum of two determinations.

Registry No.—**5**, 56552-97-7; **10**, 60153-89-1; **11**, 60208-18-6; **12**, 60184-59-0; trifluoromethanesulfonic anhydride, 358-23-6; 1-methyl-d_3-cyclopropanol, 60153-90-4; 2-bromopropionyl bromide-d_4, 60153-91-5; ethyl bromide-d_5, 3675-63-6; propionic acid-d_5, 60153-92-6; 2-bromopropionic acid-d_4, 60153-93-7; cyclopropyl methyl ketone, 765-43-5; 7-acetylbicyclo[4.1.0]heptene, 10330-36-6; *exo*-6-acetylbicyclo[3.1.0]hexane, 10330-37-7; *endo*-6-acetylbicyclo[3.1.0]-hexane, 60153-94-8.

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Thianaphthen-2-one Chemistry. 2. The Benzylidene Thiolactone Rearrangement: Synthesis of 2-Arylthianaphthene-3-carboxylic Acids and Esters

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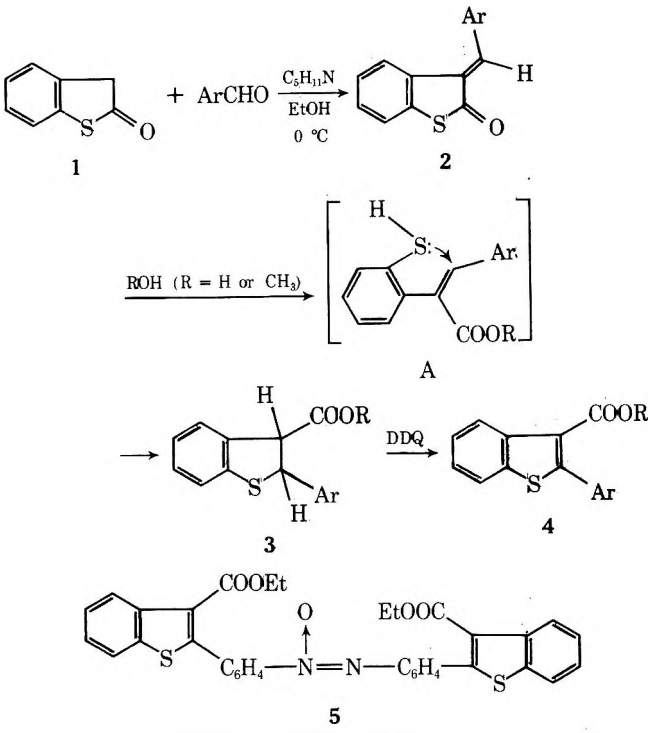
The condensation of thianaphthen-2-one and aromatic aldehydes gave the corresponding 3-benzylidenethianaphthen-2-ones (**2**). Treatment of the benzylidene derivatives with ethanolic potassium hydroxide followed by acidification gave 2-aryl-2,3-dihydrothianaphthene-3-carboxylic acids (**3a–c**), while refluxing the benzylidene derivatives with methanol gave the methyl 2-aryl-2,3-dihydrothianaphthene-3-carboxylates (**3d, 3e**) (benzylidene thiolactone rearrangement). Oxidation of the dihydro acids and esters with DDQ (2,3-dichloro-5,6-dicyano-1,4-quinone) gave the corresponding 2-arylthianaphthene-3-carboxylic acids and esters (**4a–d**).

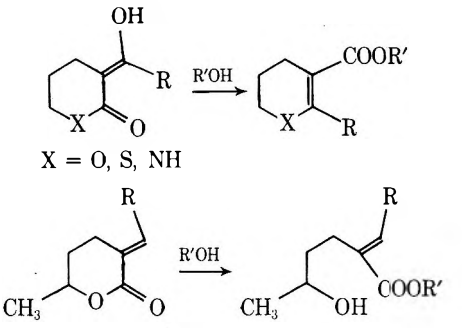
Earlier studies in these laboratories on the condensation of thianaphthen-2-one (**1**) with salicylaldehydes[1,2] led us to investigate the condensation of simple aryl aldehydes with **1** as a route to 3-benzylidenethianaphthen-2-ones (**2**). In the only prior report on such derivatives, Marschalk synthesized (Scheme I) 3-(2-methoxybenzylidene)thianaphthen-3-one (**2a**) which he claimed underwent hydrolytic scission to the mercaptostilbenecarboxylic acid (**A**) (Ar = o-$CH_3OC_6H_4$).[3] Having previously established the facile internal Michael addition of thiols to similarly activated double bonds,[1,2] we have reinvestigated Marschalk's claim and have found that the actual product is 2-(2-methoxyphenyl)-2,3-dihydrothianaphthene-3-carboxylic acid (**3a**).[4] This transformation of **2** to **3** resembles the well-known α-acyllactone rearrangement. However, there is no precedent for an α-benzylidenelactone undergoing this rearrangement, and other related α-exocyclic unsaturated lactones apparently experience only ring cleavage to hydroxy acid derivatives[5] (Scheme II). The enhanced nu-

Scheme I



Scheme II

Acyllactone rearrangement



cleophilicity of a thiol (or thiolate) apparently accounts for this special reaction of benzylidene thiolactones.

We wish to report a general procedure for the preparation of 3-benzylidenethianaphthen-2-ones (**2**), their unique rearrangement to 2-aryl-2,3-dihydrothianaphthene-3-carboxylic acids and esters (**3**) (benzylidene thiolactone rearrangement), and the subsequent oxidation of these dihydro derivatives to 2-arylthianaphthene-3-carboxylic acids and esters (**4**).

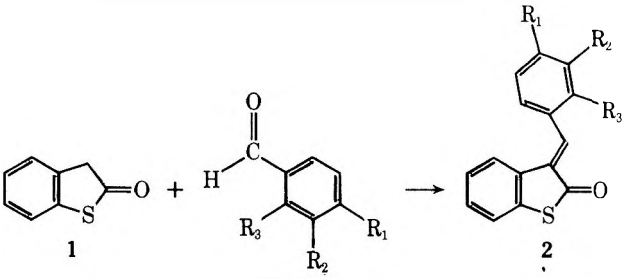
Benzylidene Derivatives (2a–g). 3-Benzylidenethianaphthen-2-ones were readily prepared by condensation, at ice bath temperatures, of **1** and an aryl aldehyde in ethanol containing a catalytic amount of piperidine. Reactions effected by heating did not yield pure products and sometimes led to mixtures of the rearranged 2-aryl-2,3-dihydrothianaphthene-3-carboxylates and other anomalous products.

The benzylidenes obtained (Table I) were yellow to red in color and displayed characteristic carbonyl absorptions at $1685 \pm 5\ cm^{-1}$. In the NMR, the vinylic protons appear within the aromatic complex and the downfield position of these vinyl resonances implies the more thermodynamically favored trans configuration (vinyl proton cis to carbonyl). Previous reports in closely related systems indicated a greater anisotropic deshielding for trans vinyls than for similar cis isomers.[6,7,8]

Benzylidene Thiolactone Rearrangement. Conversion of 3-Benzylidenethianaphthen-2-ones to 2-Aryl-2,3-dihydrothianaphthene-3-carboxylic Acids and Esters (3a–e). The hydrolytic ring opening of 3-benzylidenethianaphthen-2-ones with alcoholic potassium hydroxide followed by acidification provided a convenient high-yield synthesis of the previously unknown 2-aryl-2,3-dihydrothianaphthene-3-carboxylic acids (**3a–c**). These dihydro acids (Table II) were readily identified by their NMR spectra, the methinyl protons appearing as downfield doublets with J = 6–9 Hz.[9] 2-(4-Nitrophenyl)-2,3-dihydrothianaphthene-3-carboxylic acid could not be obtained by the benzylidene thiolactone rearrangement. The reaction of 3-(4-nitrobenzylidene)thianaphthen-2-one (**2g**) with ethanolic potassium hydroxide gave a large amount of carbonaceous material from which was isolated, in low yield (33%), a compound identified as **5**. The azoxy compound apparently arises from the ethanolysis of the thiolactone to the dihydro ester which undergoes concomitant oxidation–reduction. In retrospect, the formation of the azoxy compound seems reasonable since alcohols readily open thiolactones (vide infra) and nitrobenzene is readily converted to azoxybenzene by refluxing in ethanolic potassium hydroxide.[10,11]

The benzylidene thiolactone rearrangement was further extended to the preparation of the previously unknown methyl 2-aryl-2,3-dihydrothianaphthene-3-carboxylates (**3d, 3e**) by refluxing the corresponding 3-benzylidene thiolactones in methanol with a catalytic amount of piperidine. The dihydro esters (Table II) were also easily identified by their

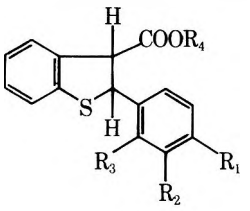
Table I.[a] 3-Benzylidenethianaphthen-2-ones



Registry no.	Compd	R_1	R_2	R_3	% yield	Mp, °C
55757-17-0	2a	H	H	OCH_3	65	96.5–98.5 (lit. 96–98)[b]
55757-19-2	2b	$-OCH_2O-$		H	54	162.0–162.5
60224-05-7	2c	OCH_3	H	OCH_3	83	146.5–148.0
60224-06-8	2d	$N(CH_3)_2$	H	H	75	160.0–163.0 (lit. 164–165)[b]
60224-07-9	2e	OH	H	OCH_3	84	173.0–175.0
60224-08-0	2f	Cl	H	H	86	137.0–138.0
60224-09-1	2g	NO_2	H	H	80	155.0–157.0

[a] Satisfactory analytical data [±0.3% for C, H, S (N)] were obtained on all new compounds listed. [b] C. Marschalk, *J. Prakt. Chem.*, **88**, 227 (1913).

Table II.[a] 2-Aryl-2,3-dihydrothianaphthene-3-carboxylates

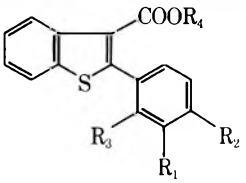


3

Registry no.	Compd	R_1	R_2	R_3	R_4	% yield	Mp, °C
55757-18-1	3a	H	H	OCH_3	H	84	139.0–140.0 (lit. 134–136)[b]
55757-21-6	3b	$-OCH_2O-$		H	H	78	186.0–187.5
60224-10-4	3c	OCH_3	H	OCH_3	H	77	163.0–164.0
60224-11-5	3d	$N(CH_3)_2$	H	H	CH_3	85	111.5–112.5
60224-12-6	3e	$-OCH_2O-$		H	CH_3	60	104.0–105.0

[a] Satisfactory analytical data [±0.3% for C, H, S (N)] were obtained on all new compounds listed. [b] C. Marschalk, *J. Prakt. Chem.*, **88**, 227 (1913).

Table III.[a] 2-Arylthianaphthene-3-carboxylates



4

Registry no.	Compd	R_1	R_2	R_3	R_4	% yield	Mp, °C
60224-13-7	4a	H	H	OCH_3	H	66	227.5–229.0
60224-14-8	4b	OCH_3	H	OCH_3	H	46	226.0–227.0
60224-15-9	4c	$N(CH_3)_2$	H	H	CH_3	55	130.5–131.5
60224-16-0	4d	$-OCH_2O-$		H	CH_3	82	85.0–86.0
6774-41-0	4e	H	H	H	H	33[b]	185.5–189.0 (lit. 188–189)[c]

[a] Satisfactory analytical data [±0.3% for C, H, S (N)] were obtained on all new compounds listed. [b] Prepared directly without isolation or purification of intermediate; see text for experimental method. [c] A. Chow et al., *J. Med. Chem.*, 9, 551 (1966).

NMR spectra which showed the methinyl protons, as in the case of the dihydro acids, as characteristic downfield doublets.

2-Arylthianaphthene-3-carboxylic Acids and Esters (4a–e). The 2-aryl-2,3-dihydrothianaphthene-3-carboxylic acids and esters obtained from the benzylidene thiolactone rearrangement were oxidized with DDQ in benzene to the corresponding 2-arylthianaphthene-3-carboxylic acids and esters (**4a–d**). The fully oxidized products (Table III) were characterized by the disappearance of the methinyl protons in the NMR and a shift of carbonyl frequencies in the infrared. The combined rearrangement and oxidation sequence represents a new and general two-step synthesis of these acids and esters. Previous syntheses of these compounds have involved multistep reactions.[12,13]

Finally, as further evidence for the structure of the rearrangement products, a literature compound, 2-phenylthianaphthene-3-carboxylic acid (**4e**), was prepared.[13] This involved the direct condensation and rearrngement of 1 and benzaldehyde to methyl 2-phenyl-2,3-dihydrothianaphthene-3-carboxylate. The crude ester was oxidized and subsequently hydrolyzed to 2-phenylthianaphthene-3-carboxylic acid.

Experimental Section

Infrared spectra were recorded on a Beckman IR 33 spectrophotometer as Nujol mulls or in solution using 0.1-mm sodium chloride liquid cells. NMR spectra were obtained on a Hitachi Perkin-Elmer R-20A spectrometer with tetramethylsilane as the internal standard.

Microanalyses were performed by Dr. G. I. Robertson, Jr., Florham Park, N.J. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected.

Procedure for the Preparation of 3-Benzylidenethianaphthen-2-ones (2a–g). A solution or slurry of 1.00 g (6.6 mmol) of thianaphthen-2-one[14,15] and the aromatic aldehyde (6.6 mmol) in 5 ml of absolute ethanol was cooled in an ice bath. Piperidine (3–7 drops) was added and stirring with ice bath cooling was continued for 3–8 h. The reaction mixture was then refrigerated overnight. Filtration and washing with cold 95% EtOH gave the crude product. Recrystallization from 95% EtOH gave the analytically pure benzylidene with the exception that **2e** was recrystallized from CH_3CN.

Procedure for the Preparation of 2-Aryl-2,3-dihydrothianaphthene-3-carboxylic Acids (3a–c). A solution or slurry of 3–4 mmol of the requisite benzylidene (**2a–c**) in 60 ml of absolute ethanol was treated with 10 ml of ethanolic KOH (0.7 g/10 ml). Any undissolved solid was soon solubilized and the initially intense orange to red color of the solution lightened. The solvent was removed in vacuo and the crude white potassium salt of the product was dissolved in a minimum of cold distilled water (10–25 ml) and acidified by dropwise addition of concentrated HCl to an oil which solidified on scratching.

2-(2-Methoxyphenyl)-2,3-dihydrothianaphthene-3-carboxylic Acid (3a). Recrystallization of the crude material, prepared as above, from benzene–petroleum ether (60–110 °C) gave 84% of white solid, mp 138.0–139.0 °C (lit. 134–136 °C).[3] An additional recrystallization gave 57%: mp 139.0–140.0 °C; NMR ($CDCl_3$) δ 3.82 (s, 3 H, OCH_3), 4.50 (d, 1 H, J = 6 Hz, CHCO), 5.75 (d, 1 H, J = 6 Hz, CHS), 6.62–7.80 (m, 8 H, ArH), 11.02 (s, 1 H, OH); ir ($CHCl_3$) 3400–2400 (br), 1700 cm^{-1}.

2-(3,4-Methylenedioxyphenyl)-2,3-dihydrothianaphthene-3-carboxylic Acid (3b). The crude product was recrystallized from benzene–petroleum ether (60–110 °C) to yield 78% of a white, fluffy solid, mp 185.5–187.0 °C. Recrystallization from benzene–petroleum ether gave a fluffy, white analytical sample: mp 186.0–187.5 °C; NMR (acetone-d_6) δ 4.48 (d, 1 H, J = 9 Hz, CHCO), 5.40 (d, 1 H, J = 9 Hz,

CHS), 5.95 (s, 2 H, OCH_2O), 6.58–7.48 (m, 7 H, ArH), 8.20–9.10 (broad, 1 H, OH, exchangeable with D_2O); ir (Nujol) 3400–2400 (br), 1695 cm^{-1}.

2-(2,4-Dimethoxyphenyl)-2,3-dihydrothianaphthene-3-carboxylic Acid (3c). Recrystallization from ethanol–water gave 77% of fine, yellow crystals: mp 163.0–164.0 °C; NMR (Me_2SO-d_6) δ 3.73 and 3.82 (two singlets of equal intensity, 6 H, OCH_3), 4.55 (d, 1 H, J = 6 Hz, CHCO), 5.57 (d, 1 H, J = 6 Hz, CHS), 6.30–6.70 (m, 2 H, ArH), 6.90–7.70 [m, 6 H, ArH, one proton (COOH) exchangeable with D_2O]; ir ($CHCl_3$) 3400–2400 (br), 1700 cm^{-1}.

Preparation of Methyl 2-Aryl-2,3-dihydrothianaphthene-3-carboxylates. Methyl 2-(4-Dimethylaminophenyl)-2,3-dihydrothianaphthene-3-carboxylate (3d). A slurry of 1.00 g (6.6 mmol) of **1** and 0.99 g (6.6 mmol) of *p*-dimethylaminobenzaldehyde in 5 ml of absolute ethanol was cooled in an ice bath prior to the addition of 10 drops of piperidine. A deep red solution resulted after approximately 20 min and at the end of 3 h blood red crystals of the benzylidene (**2d**) had separated. The reaction mixture was evaporated and the benzylidene was suspended in 30 ml of MeOH containing 2 ml of piperidine. After 20 h of reflux, an orange solution had formed which upon evaporation gave a light orange solid. Recrystallization from MeOH yielded 1.75 g (85%) of white crystals (**3d**): mp 109–110 °C; NMR ($CDCl_3$) δ 2.87 [s, 6 H, $N(CH_3)_2$], 3.68 (s, 3 H, OCH_3), 4.48 (d, 1 H, J = 9 Hz, CHCO), 5.42 (d, 1 H, J = 9 Hz, CHS), 6.43–7.52 (m, 8 H, ArH); ir ($CHCl_3$) 1730 cm^{-1}. An analytical sample of **3d** was prepared by recrystallization from MeOH: 1.40 g (68%) of stout, white needles, mp 111.5–112.5 °C.

Methyl 2-(3,4-Methylenedioxyphenyl)-2,3-dihydrothianaphthene-3-carboxylate (3e). Five drops of piperidine was added to a chilled solution of 1.00 g (6.6 mmol) of **1** and 1.00 g (6.6 mmol) of piperonal in 5 ml of absolute ethanol. A gummy orange solid was evident at the end of 2.5 h of stirring. Rotary evaporation gave the crude benzylidene (**2b**) which was dissolved in 20 ml of MeOH containing 1 ml of piperidine. After 5 h of reflux, rotary evaporation gave a yellow solid which was recrystallized from MeOH and air dried to 1.25 g (60%) of white crystals (**3e**): mp 102.0–103.0 °C; NMR ($CDCl_3$) δ 3.73 (s, 3 H, OCH_3), 4.38 (d, 1 H, J = 9 Hz, CHCO), 5.37 (d, 1 H, J = 9 Hz, CHS), 5.87 (s, 2 H, OCH_2O), 6.53–7.50 (m, 7 H, ArH); ir ($CHCl_3$) 1730 cm^{-1}. Recrystallization from methanol gave the analytical sample, mp 104.0–105.0 °C.

Procedure for the Preparation of 2-Arylthianaphthene-3-carboxylic Acids (4a, 4b). A solution of equimolar amounts (2.0–2.5 mmol) of the dihydro acid, either **3a** or **3c**, and DDQ in 20 ml of benzene was refluxed with stirring for 22 h. The hydroquinone was removed by hot filtration and the filtrate evaporated to approximately 10 ml. Chilling gave the dehydrogenated product which was recrystallized once from benzene to analytical purity, see Table III. **4a**, ir (Nujol) 3200–2400, 1665 cm^{-1}; **4b**, ir (Nujol) 3200–2400, 1670 cm^{-1}.

Procedure for Preparation of Methyl 2-Arylthianaphthene-3-carboxylate (4c, 4d). Equimolar amounts (3.5 mmol) of DDQ and either **3d** or **3e** were refluxed with stirring in 15 ml of anhydrous benzene for 18 h. The hydroquinone which had precipitated was filtered from the hot solution and rotary evaporation yielded a gummy oil. Trituration and subsequent recrystallization from MeOH gave the title compounds.

Methyl 2-(4-Dimethylaminophenyl)thianaphthene-3-carboxylate (4c). Recrystallization from methanol gave 55% of yellow solid (**4c**): mp 130.5–131.5 °C; NMR ($CDCl_3$) δ 2.90 (s, 6 H, NCH_3), 3.78 (s, 3 H, OCH_3), 6.50–8.40 (m, 8 H, ArH); ir ($CHCl_3$) 1705 cm^{-1}.

Methyl 2-(3,4-Methylenedioxyphenyl)thianaphthene-3-carboxylate (4d). Recrystallization from methanol gave 82% of fluffy cream-colored solid (**4d**), mp 84.0–85.0 °C. A second recrystallization from methanol yielded 63% of cream solid: mp 85.0–86.0 °C; NMR ($CDCl_3$) δ 3.82 (s, 3 H, OCH_3), 5.98 (s, 2 H, OCH_2O), 6.90–8.50 (m, 7 H, ArH); ir ($CHCl_3$) 1710 cm^{-1}.

Preparation of 2-Phenylthianaphthene-3-carboxylic Acid (4e). A solution of 1.00 g (6.6 mmol) of thianaphthen-2-one and 0.70 g (6.6 mmol) of benzaldehyde with 1 ml of triethylamine in 10 ml of methanol was refluxed for 6 h. Evaporation in vacuo gave the crude methyl dihydro ester as a brown oil: NMR ($CDCl_3$) δ 3.62 (s, 3 H, OCH_3), 4.43 (d, 1 H, J = 8 Hz), 5.42 (d, 1 H, J = 8 Hz), methinyl characteristic of the 2,3-dihydro system; ir (neat) 1735 cm^{-1}. The crude dihydro ester was then refluxed with 1.47 g (6.5 mmol) of DDQ in 20 ml of benzene for 14 h. The brown hydroquinone was removed by hot filtration through a sintered glass funnel and the filtrate was rotary evaporated to give the crude methyl 2-phenylthianaphthene-3-carboxylate as a red oil: NMR ($CDCl_3$) δ 3.68 (s, OCH_3), methinyls lacking; ir (neat) 1710 cm^{-1}. The crude ester was then saponified by refluxing with a potassium hydroxide solution (2.0 g KOH/125 ml) for 2.5 h. Acidification, filtration, and recrystallization from 50/50 ethanol–water gave 0.55 g (33% overall yield) of off-white acid: mp 185.5–189.0 °C (lit. 188–189 °C);[13] ir (Nujol) 3200–2400, 1660 cm^{-1}.

Preparation of 4,4′-Bis(3-carboethoxy-2-benzothienyl)-azoxybenzene (5). Ten milliliters of a hot ethanolic potassium hydroxide solution (0.7 g/10 ml ethanol) was added to a yellow-orange slurry of 1.00 g (3.5 mmol) of 3-(4-nitrobenzylidene)thianaphthen-2-one (**2g**) forming a dark black solution. The color slowly faded and a solid precipitated. The reaction mixture was evaporatgd to a black solid and this was slurried with 25 ml of distilled water. Acidification with concentrated HCl and filtration gave a dark green-black solid. Recrystallization of this material from benzene–petroleum ether (60–110 °C) produced 0.50 g of dark black carbonaceous solid, mp ≈300 °C, NMR (Me_2SO-d_6) only broad aromatic region. Evaporation of the filtrate from the recrystallization and digestion of the residue with hot acetone gave 0.35 g (33%) of the golden azoxy compound (**5**): mp 192.0–194.0 °C; NMR ($CDCl_3$) δ 1.18 (t, 3 H, J = 7 Hz, OCH_2CH_3), 4.27 (q, 2 H, J = 7 Hz, OCH_2CH_3), 7.20–8.60 (m, 8 H, ArH); ir ($CHCl_3$) 1700 cm^{-1}. Recrystallization from acetonitrile–chloroform gave golden-colored crystals of the analytical sample, mp 193.0–194.0 °C.

Anal. Calcd from $C_{34}H_{26}N_2O_5S_2$: C, 67.31; H, 4.32; N, 4.62; S, 10.57. Found: C, 67.56; H, 4.50; N, 4.79; S, 10.36.

Acknowledgments. R.A.C. (Lehigh University, Ph.D., 1974) was a recipient of the Horner and Buch Graduate Research Fellowships which, in part, supported this work.

Registry No.—**1**, 496-31-1; **4e** methyl dihydro ester, 60224-17-1; **5**, 60224-18-2; benzaldehyde, 100-52-7; benzaldehyde (R_1R_2 = H; R_3 = OCH_3), 123-11-5; benzaldehyde (R_1R_2 = $-OCH_2O-$; R_3 = H), 120-57-0; benzaldehyde (R_1R_3 = OCH_3; R_2 = H), 613-45-6; benzaldehyde (R_2R_3 = H; R_1 = $N(CH_3)_2$), 100-10-7; benzaldehyde (R_1 = OH; R_2 = H; R_3 = OCH_3), 18278-34-7; benzaldehyde (R_2R_3 = H; R_1 = Cl), 104-88-1; benzaldehyde (R_2R_3 = H; R_1 = NO_2), 555-16-8.

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Photoisomerization of Selected Oxiranes. Intermediacy of Carbonyl Ylides[1]

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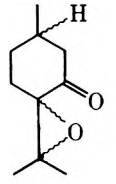
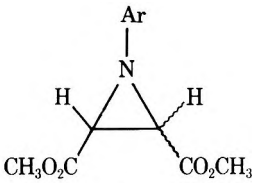
Several α-cyano β-arylglycidates were synthesized and their trans–cis photoisomerizations were studied. At elevated temperature (110 °C), a clean reaction occurred, providing a synthetically useful route to cis isomers. The isomerization proceeds via ylides, which may in turn be formed from a triplet excited state of a parent oxirane. The reaction in a matrix (77 K) was also studied and the mechanisms are discussed. A photorearrangement of the ylide was found in the case of a β-methyl-β-phenyl analogue.

While the photoequilibration of cyclopropanes has been studied extensively[2] this aspect of the photochemistry of the analogous oxiranes has been accorded only limited attention.[3,4a,b] Although photoinduced isomerizations of α,β-epoxy ketones, including *trans*-dypnone oxide[4c] and β-pulegone oxide (**1**),[4d] are known, such substrates for the most part have lowest energy n,π* singlet and triplet states.[4a] In such cases it has generally been assumed that cis–trans photoisomerization occurs by initial C–O bond cleavage and that the chemically significant excited state has n,π* character;[3] however, C–C bond cleavage has been invoked to explain the photointerconversion of epimers of epoxy ketone **1**.[4d]



1



2

Aziridines bearing stabilizing substituents such as **2** constitute another class of small-ring compounds known to photointerconvert to their epimers. It has been demonstrated that such substrates, which are thermo- as well as photolabile, equilibrate in the absence of dipolarophiles by way of azomethine ylides formed by thermal or photoinduced C–C bond scission.[5]

The present study was initiated to investigate the photointerconversion of a class of oxiranes known to undergo reversible C–C bond photolysis to carbonyl ylides[6] and to assess the extent to which constraints imposed by orbital symmetry restrictions apply. The isomeric methyl α-cyano-β-phenylglycidates, **3a** and **4a**, respectively, were synthesized from (*E*)- and (*Z*)-methyl α-cyanocinnamate (**5** and **6**), respectively.[7,8] (*E*)-Methyl α-cyanocinnamate (**5**) was prepared by condensation of benzaldehyde with methyl cyanoacetate using potassium fluoride.[7a] The requisite *Z* alkene **6** was obtained from the *E* isomer **5** by irradiation (254 nm)[9] of the latter in benzene in a quartz vessel. The resulting mixture was difficult to resolve by chromatographic methods into the alkenes **5** and **6** and thus conversions to **3a** and **4a** were conducted prior to separation of these precursors.

Epoxidation[8] of the mixture of (*E*)- and (*Z*)-methyl α-cyanocinnamates gave **3a** and **4a**. These trans and cis glycidates **3a** and **4a**, respectively, were separated by silica gel column chromatography and purified by recrystallization. Since the homogeneous *E* alkene precursor, unlike its *Z* counterpart, is available by direct condensation, the oxidation to **3a** in this case may be conducted on pure samples in the manner described for the mixture of **5** and **6**.

The stereochemical relationships assigned to **3a** and **4a** rest on the method of preparation and NMR data. The chemical shifts observed for the methyl protons of the carbomethoxy group of **4a** are shielded relative to those of **3a** as expected from the stereochemical relationship and proximity of the phenyl and carbomethoxy groups in **4a**.[10] Furthermore, the thermal equilibration of the neat epimers **3a** and **4a** (120 °C in benzene) demonstrates that **3a** is the more stable epimer (~7:1 and 5:1, respectively) although complete equilibration was not achieved even after 48 h. This result is in accord with the proposed assignments.

Contrary to expectations, based on the results of previous experience with vicinal diaryl oxides, the oxirane **3a** (0.2 M)[9] undergoes facile photoequilibration (254 nm, 3 h, eight lamps) in benzene to give a 1:1.8–2.0 mixture of **3a** to **4a**, presumably by way of carbonyl ylide intermediates **3b** and **4b**. The epimer ratio is readily determined by NMR analysis based on the differences in spectra. When **4a** is irradiated under the same conditions the ratio of **3a** to **4a** is 1:6.7. Clearly a true photoequilibrium is not established in either case due to the intervention of competing side reactions. Nevertheless this process is of synthetic utility (60% recovery of **3a** and **4a**) and may provide the only convenient route to the less stable epimeric oxirane in many cases. For example, the thermal equilibration described above favors the trans isomer and the requisite cis alkene is unavailable and/or may not be oxidized stereospecifically without interfering side reactions which is also the case for the cis epimer of **10** (see below). To our knowledge the photoequilibration of oxiranes such as **3a** and **4a** was without precedent in what are believed to be π,π* systems prior to the discovery of the reactions under discussion.[3]

A pronounced effect of temperature on the formation of by-products in the photolysis of **3a** and **4a** in benzene or toluene is apparent, which if general may enhance the synthetic utility of oxirane photoisomerization processes. Surprisingly, the complexity of the product mixtures decreases markedly when the photoisomerizations of both **3a** and **4a** are conducted

Scheme I. Summary of Possible Interconversions Contributing to Oxirane Photoisomerizations

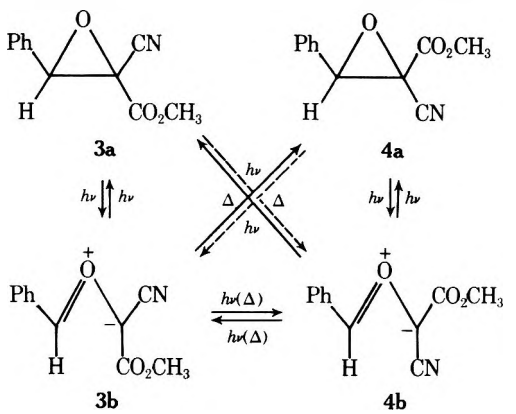


Table I. Effects of Temperature and Light Flux on the Photoequilibration of 3a and 4a [a]

	Temp, °C	No. of lamps	Ratio (3a:4a)
b	140	16	1:0.37
b	110	16	1:1.1
b	80	16	1:1.1
b	40	16	1:1.3
c	110	16	1:2.2[d]
c	110	12	1:1.8
c	110	8	1:1.6
c	110	4	1:09

[a] Irradiated for 3 h; 0.5 mmol in 5 ml of toluene (0.1 M). [b] Conducted in a decalin bath. [c] Conducted under conditions of reflux. [d] Irradiation for 2.5 h gave essentially the same values.

at 80 °C (benzene at reflux, 6 h). A much cleaner photoequilibration is observed with both the trans and cis glycidates (**3a** and **4a**, 1:2.1 and 1:3.6, respectively) under conditions where these substrates are thermally stable. It is also evident from the isomer ratios that the oxirane isomerization in this case is not thermally induced since the cis rather than trans isomer predominates regardless of whether **3a** or **4a** is photolyzed.

To assess the role of temperature and light flux on the equilibration rate and ratio, a series of experiments were designed to evaluate the effect of variations in these parameters with time (see Table I). Clearly increasing temperature has little effect upon the rate of attainment or position of equilibrium until the temperature is elevated to a point where thermal equlibration begins to compete with the photoprocesses as evidenced by the onset of an increase in the trans isomer **3a** and its ultimate emergence as the dominant epimer, i.e., 140 °C where C–C thermolysis competes with photolysis.

In contrast, variations in light flux as expected have a marked effect upon the rate of photoequilibration. It is apparent from Table I that the photoisomerization of **3a** to **4a** is optimized upon irradiation for 2.5 h with 16 lamps[9] in toluene at reflux. The products **3a** (30%) and **4a** (60%) may be recovered (90%) by preparative TLC and were identified by TLC and NMR. The product ratios reported were verified spectroscopically (NMR) prior to separation.

The results appear to relegate thermal mechanisms for ylide isomerization to a minor role in the photoisomerization process, at least within the limited temperature range studied. Possible alternative explanations may be envisaged for the photointerconversion of **3a** and **4a**. Experiments conducted at lower temperatures (7 °C) indicate that the reaction complexity increases substantially, in fact to the point where photoequilibration data are no longer accessible by NMR spectroscopy.

Strict adherence to the principles of orbital symmetry constraints requires that isomerization is obligatory if disrotatory photoinduced opening of the oxiranes **3a** and **4a** to carbonyl ylides **3b** and **4b** precedes conrotatory thermal cyclization in a two-step photoinitiated process.[11a] The conclusions regarding the modes of cleavage and cyclization are based upon the isoelectronic interrelationships which exist between aziridines and oxiranes. Both are 4n systems, and in this respect are analogous to the cyclopropyl anion which, it is argued, should undergo disrotatory opening in the excited state to the allyl anion.[11b,c]

Evidence has been presented that azomethine ylides generated photolytically may undergo photoisomerization.[5a] Thus the carbonyl ylides formed photochemically at 25 °C may also be photolabile and subject to secondary photoisomerization prior to cyclization, particularly in view of their stability and high absorbance (Scheme I).[6b] In this temperature range as noted ylide thermal equilibration cannot play a significant role.

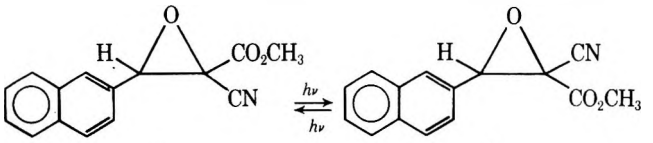
Recent evidence indicates, however, that orbital symmetry restrictions may apply less stringently to oxiranes than aziridines in ground state reactions.[5c,11b,c] Kinetic thermolysis studies of α-cyano-*cis*-stilbene oxide confirm that isomerization in the ground state must occur by dis- as well as conrotatory modes (36 and 64%, respectively).[5c] In this case the conclusion is inescapable that "orbital symmetry rules are violated". On the basis of this departure from symmetry restrictions, it is not unreasonable to conclude that similar deviations from expected behavior could be encountered in excited state processes as well, leading, for example, to photoinduced conrotatory oxirane opening. If indeed such is the case, then photoisomerization could be expected regardless of the recyclization mode. Isomerization could only be avoided in the unlikely event that the individual isomeric carbonyl ylides formed by concurrent con- and disrotatory electrocyclic opening undergo recyclization at precisely those relative rates and modes required to regenerate the initial oxirane in the absence of its epimer.

Several other factors may be significant in determining the photostationary equilibrium composition established between **3a** and **4a**, including the relative differences in oxirane as well as carbonyl ylide absorbtivities in the region of the source emission. The magntudes of the decay constants for **3a** and **4a** are also relevant as are the values for intermediates such as the ylides if photointerconversion in contrast to thermal equilibration plays a dominant role in the photoisomerization process. It is clear from this discussion that a complete mechanistic analysis is beyond the scope of this communication; however, it is not uncommon that the less stable isomer is the major isomer present at equilibrium in solution upon irradiation of alkenes and cyclopropanes[2] as is the case in these oxirane studies; i.e., the less stable isomer predominates.[11d]

Certain mechanistic aspects of the photoequilibration of **3a** and **4a** may be explained, however. The unique role of benzene or toluene as a solvent in the isomerization of **3a** and 4a prompted us to investigate the possibility that the triplet state may be implicated in the isomerization processes. Quenching studies were conducted on the trans oxirane **3a** (0.1 M) using a series of cyclohexane solutions containing incremental amounts of *trans*-1,3-pentadiene (E_t = 59 kcal mol^{-1})[11d] over a concentration range of 0.2–1.2 M. The solutions were irradiated for 2 h and NMR analyses of the photolysates were conducted. The extent of isomerization to the epimer **4a** was found to be suppressed when the quencher concentration exceeds 0.2 M. In the absence of quencher, however, ~15% conversion has occurred in cyclohexane as solvent, cf. benzene as a solvent. This suggests that a long-lived triplet intermediate might intervene at some stage in the reaction. Unfortunately [3 + 2 → 5] cycloaddition(s) of the ylide to the conjuated diene quencher competes with photoisomerization. This complicates the quenching studies substantially by introducing potentially photolabile by-products which interfere and alter the light absorbed by the oxirane at 254 nm. Sensitization experiments were therefore performed to supplement the dubious quenching results and ensure that the photoisomerization is triplet rather than singlet in character.

Sensitization of the photoequilibration of **3a** and **4a** could not be achieved with common high-energy solvent sensitizers employed, with the possible exception of benzene.[6a] *trans*-Methyl α-cyano-β-(2-naphthyl)glycidate (**7**) was selected for preliminary sensitization studies and was synthesized in high yield (90%) by base-catalyzed *m*-chloroperbenzoic acid oxidation of (*E*)-methyl α-cyano-β-(2-naphthyl)acrylate (**9**).

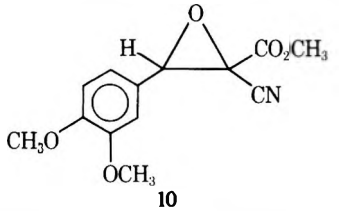
Direct irradiation (350 nm)[9] of a benzene solution of the trans oxirane **7** (6 h) in a Pyrex vessel, in the absence of added sensitizer, induces isomerization to a mixture of trans and cis oxiranes whose composition is 1:2.6, respectively. That the photoisomerization of **7** to **8**, and presumably the photo-



7 **8**

equilibration of **3a** and **4a** as well, may proceed through the triplet state was confirmed by irradiation of **7** in the presence of the sensitizeranthraquinone (62 kcal mol^{-1}) with a visible source.[12a] The results proved similar to those obtained upon direct irradiation of **7** (350 nm)[9] in the absence of a low-energy triplet sensitizer. Benzophenone (60 kcal mol^{-1}) is also effective as a sensitizer (350 nm)[9] for the photoequilibration of **7**. A filter composed of naphthalene (saturated) in benzene as a solvent or a uranyl glass filter was employed to ensure that direct absorption due to tailing at long wavelength in the spectrum of **7** is excluded and that the sensitizer is the sole absorbing species. In fact, insignificant isomerization occurs with the filter until sensitizer is added.

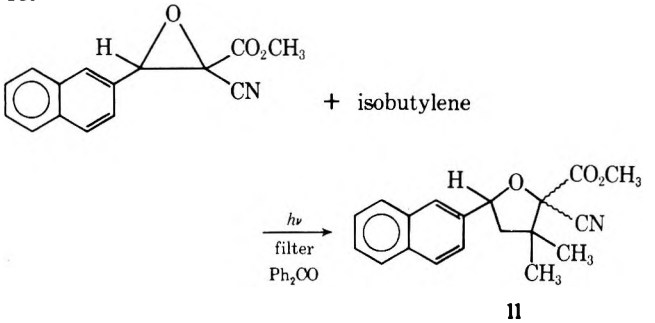
It was found that triplet sensitization also may be extended to *trans*-methyl α-cyano-β-(3,4-dimethoxyphenyl)glycidate (**10**); however, a sensitizer with a higher triplet energy, i.e., acetophenone (74 kcal mol^{-1}), is required in this case. The method employed for the preparation of **7** also proved successful for the synthesis of the substituted trans glycidate **10.**



10

Irradiation (350 nm)[9] of a benzene solution of the trans oxirane **10** (0.2 M) containing acetophenone (0.4 M) for 14 h results in significant interconversion to the cis isomer with the cis/trans ratio approaching 2.0. Acetone proved to be a less effective sensitizer; however, significant amounts (~11%) of the cis isomer are apparent in the NMR spectrum of the photolysate (350 nm, 12 h) when this ketone is used as a solvent sensitizer.

Our contention that the photointerconversion observed for the oxiranes **3a** and **4a** as well as **7** and **8** and the reported [3 + 2]cycloaddition reactions exhibited by these oxiranes probably involve common intermediates, namely carbonyl ylides, was also investigated.[6] A solution of **7** in benzene saturated with isobutylene was irradiated (350 nm)[9] for 5 h with a naphthalene filter. A 20% decrease in the concentration of **7** was observed in a 5-h time span under these conditions. A similar experiment was then performed after addition of benzophenone and essentially complete conversion of the oxirane **7** (>95%, NMR) occurs with formation of the adducts **11.**



11

By-products of the type observed with **3a, 4a,** and **7** in benzene are absent in cases where the dipolarophile is present, which suggests that side reactions are slower than cycloaddition. In fact isobutylene is sufficiently active as a dipolarophile in benzene that concomitant cis–trans isomerization is markedly suppressed. Since benzophenone undergoes intersystem crossing with unit efficiency to the triplet state and exerts such a dramatic effect on the conversion of **7** to **11** it is concluded that oxirane ring opening must be triplet in character and the nascent ylide is formed in the triplet excited state. Interception of the intermediate ylides by the dipolarophile is thought to occur in the ground state because of the observe regioselectivity and stereospecificity where dipolarophile cofiguration permits.[6a,13] Regardless of the mechanism of cycloaddition, the results cited for **7** are consistent with initial disrotatory opening of the oxirane in the excited triplet state with formation of a triplet ylide intermediate which is intercepted, after deactivation to the singlet ground state, by the dipolarophile or recyclizes after spin-inversion in a conrotatory fashion with overall net isomerization.[6] Thus common intermediates, carbonyl ylides, are invoked for both the isomerization and cycloaddition processes; however, as noted above for **3a** and **4a,** thermal and/or photoequilibration of the ylide and/or "violations of orbital symmetry" in the course of ring opening may contribute to oxirane isomerization. Furthermore, homolytic C–O bond photocleavage is advanced in the case of certain oxiranes to explain cis–trans isomerization[4] and this process may also contribute to photoequilibration here.

At this time it has not been determined if the reversible isomerization of **3a** and **4a** observed upon direct irradiation occurs in the singlet manifold; however, at least two explanations may be used to rationalize the results of unsensitized reactions in terms of triplet mechanisms. Direct excitation of the oxirane to the singlet state followed by intersystem crossing to the oxirane triplet may occur with subsequent electrocyclic opening to the triplet ylide and recyclization, after spin-inversion and relaxation to the singlet ground state. Alternatively, ring opening may precede intersystem crossing and in this manner the triplet oxirane would be circumvented.

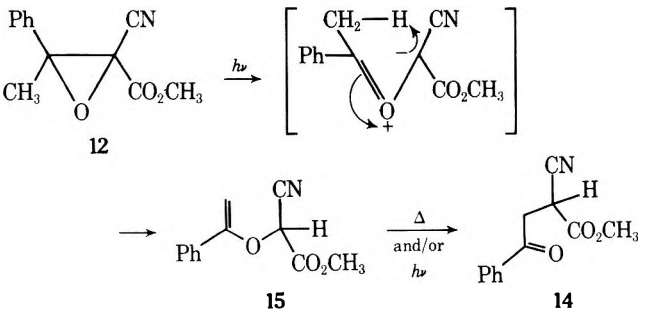
Photochemical experiments were performed at subambient temperature (77 K) to provide further insight into the mechanism by which the isomerization of **3a** to **4a** (and **7** to **8**) occurs. Reversible color formation in matrices at 77 K induced by light is a phenomenon characteristic of a variety of oxiranes including **3a, 4a, 7,** and **10** which has been attributed to C–C bond cleavage with formation of carbonyl ylides (λ_{max} 547 and 535 nm for **3b** and **4b,** respectively).[14]

It is evident from rigid matrix spectral data that the absorbtivities of the colored ylides produced upon irradiation (254 nm)[9] at 77 K are significantly greater than the parent oxirane. Thus ylide formation is restricted to the immediate region of the cell surface exposed to ultraviolet light. The resulting shielding effect must be overcome to increase photoefficiency, and techniques have been devised for maximizing the exposure and utilization of radiation, particularly in matrices, and are discussed elsewhere.[6b]

The behavior exhibited by **3a** at 77 K in an inert matrix upon photolysis utilizing the double-irradiation technique described earlier[6b] contrasts markedly with that observed for **4a,** which undergoes complete conversion to **3a.** Simultaneous illumination of **3a,** on the other hand, at 77 K with both ultraviolet (254 nm)[9] and visible (400–600 nm) sources,[12b] for a period of 3 h and subsequent analysis of the irradiated sample confirms that unlike **4a** no *detectable* photoconversion to the alternate isomer **4a** occurs (NMR, etc.) despite the fact that the colored ylide is obviously formed.

The absence of isomerization after photogeneration and

Scheme II



irradiation of the ylide derived from **3a** is in accord with expectations based on orbital symmetry arguments, if only allowed processes are considered.[11a] Significant thermal processes should be arrested under the matrix conditions and the isomerization of **3a** may be attributed to photoinduced recyclization of a relatively stable ylide which is not without precedent.[15] It remains to be explained why isomerization of **4a** to **3a** is complete under identical conditions. One possible reason for the disparate results obtained in the low-temperature photochemistry observed between **3a** and **4a** is the ionic interaction between the "cationic" center of the ylide and the carbomethoxy group which constrains **3b** from undergoing isomerization in the matrix while providing driving force for the observed photoconversions of **4b** to **3b** and ultimately **3a**. It is reported[16] that β-cyano-β-acetylstyrene oxide as well as other such α,β-epoxy ketones rearrange thermally to afford 1,3-dioxolenes through a mechanism involving C–C bond cleavage and subsequent cyclization of the resulting ylide; however, no such products are isolable in the case of **3a** and additional studies are required to validate or refute our proposal.

Unexpected results were obtained when an attempt was made to extend the photoequilibration process to *trans*- and *cis*-methyl α-cyano-β-methyl-β-phenylglycidate (**12** and **13**, respectively) separated from the oxidation mixture obtained from (*E*)- and (*Z*)-methyl α-cyano-β-methylcinnamate.[8] While both **12** and **13** develop blue colors upon irradiation (254 nm)[9] at 77 K, which attests to ylide formation, neither undergoes photoequilibration in benzene solution (254 nm, 40–80 °C), which is circumvented by an intramolecular photorearrangement. Upon irradiation of **12** and **13** in benzene (254 nm, 12 h), the product is methyl α-cyano-β-benzoylpropionate (**14**). Structural identification of **14** was achieved by independent synthesis.[17] It is believed that the enol ether **15** is implicated in the transformation of **12** (and/or **13**) to **14** and is formed by 1,4-proton transfer from the activated methyl to the carbanionic center of the ylide (Scheme II). Precedent exists for photoinduced 1,3-sigmatropic rearrangements such as **15** to **14**.[18] In addition, it is reported that this reaction may be induced thermally (180 °C).[8] Thus each step in the conversion **12** → **15** → **14** may be thermal in nature. Under milder conditions (120 °C), however, the formation of **15** together with **14** was observed by NMR. It is significant that no thermal equilibration of **12** to **13** is detectable below 120 °C. While isolation of the sensitive enol ether **15** was not attempted, evidence for its presence in solution was obtained by acid hydrolysis to acetophenone[6a] and conversion to **14** at higher temperature (130 °C). The signals for the enol ether **15**, present in the crude pyrolysate obtained from **12**, upon photolysis (254 nm, 40 °C) appear to decrease in intensity which suggests that in this system the conversion of **15** → **14**, as well as the formation of **15**, may also be induced photochemically.[18]

Experimental Section

General. Infrared spectra were determined on Perkin-Elmer Model 337 and 257 infrared spectrophotometers. ^{1}H NMR spectra were obtained on a Varian A-60 or Hitachi Perkin-Elmer R-20B spectrometer with 1% tetramethylsilane as an internal standard. A Hitachi Perkin-Elmer RMU-6E spectrometer was used for mass spectral analyses. Ultraviolet absorption spectra were recorded on a Cary Model 17 spectrophotometer. All melting points were established on a Büchi melting point apparatus and are uncorrected. Silica gel PF_{254} on microscope slides or glass plates was used for thin and thick layer chromatographic separation. Visualization was achieved by exposure of the chromatogram to short-wavelength ultraviolet light (Blak-Ray UVL-21) and/or developed in iodine vapor. A Griffin-Worden pressure vessel (Kontes Glass Co., Vineland, N.J.) was used for pressurized reactions. All combustion analyses for C, H, and N fell within acceptable limits of theoretical values and were performed by Galbraith Laboratories, Inc.

Preparation of (*E*)-Methyl α-Cyanocinnamate (5). The alkene **5** was synthesized (87%) by condensation of benzaldehyde (10.5 g, 0.1 mol) with methyl cyanoacetate (12 g, 0.12 mol) in methanol according to the procedure described by Rand and co-workers[7a] using potassium fluoride (2 g) as a catalyst.

Preparation of (*Z*)-Methyl α-Cyanocinnamate (6). The *E* isomer **5** (4 g, 0.02 mol) was dissolved in benzene (200 ml) and irradiated in a quartz vessel for a period of 12 h with a 254-nm source.[9] The photolysate was concentrated to a mixture containing **5** and **6** (1.5:1.0, respectively) which was not readily resolvable by chromatographic methods and was converted to the desired oxiranes **3a** and **4a** after preliminary purification, but without prior separation.

Photoisomerization of **5** to **6** may also be accomplished in cyclohexane in a Pyrex vessel using a 275-W cosmetic sunlamp as a light source; however, the ratio of **5**:**6** is only 4:1 after irradiation for 8 h under these conditions. The NMR spectrum, determined on the unseparated alkenes, differs significantly from tlhat reported earlier: NMR (CCl_4) δ 3.84 (s, 3 H, $-OCH_3$), 7.58 (s, 1 H, –CH).[7c]

Synthesis of the Isomeric Methyl α-Cyano-β-phenylglycidates (3a and 4, Respectively). A minor modification of the method of Robert and Pommeret[8] was utilized for the preparation of phenylglycidates **3a** and **4a**. To a solution of 4 g (0.021 mol) of the unresolved mixture of **3a** and **4a** dissolved in 50 ml of acetonitrile containing 4 ml of 1 M sulfuric acid was added dropwise 30 ml of aqueous sodium hypochlorite (household bleach, ~0.75 M) at 5 °C. The mixture obtained was allowed to stir (25 °C, 30 min) and was then diluted with water and the organic components isolated in the usual manner. The separation and purification of the oxiranes **3a** and **4a** were achieved by chromatography on silica gel. Oxirane **4a** (1.2 g) emerges first: mp 57–58 °C [$(C_2H_5)_2O$–C_6H_{14}]; ir (Nujol) 2240 (–CN), 1764 cm^{-1} (–CO); NMR ($CDCl_3$) δ 3.63 (s, 3 H, $-OCH_3$), 4.65 (s, 1 H, –CH); mass spectrum *m/e* 203 (M^+). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.59. Found: C, 65.17; H, 4.47; N, 6.68. Elution of the isomer **3a** follows (~1.9 g): mp 55–56 °C [$(C_2H_5)_2O$–C_6H_{14}]; ir (Nujol) 2259 (–CN), 1735 cm^{-1} (–CO); NMR ($CDCl_3$) δ 3.91 (s, 3 H, $-OCH_3$), 4.60 (s, 1 H, –CH); mass spectrum *m/e* 203 (M^+). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.59. Found: C, 64.87; H, 4.40; N, 6.82.

The trans isomer **3a** may be obtained directly from the *E* cinnamate using the method described above (78%) or by base-catalyzed oxidation using *m*-chloroperbenzoic acid (see below). The latter method is not adequate for epoxidation of mixtures of **5** and **6** because stereochemistry is not maintained (**3a**:**4a**, 4.6:1).

Preparation of (*E*)-Methyl α-Cyano-β-(2-naphthyl)acrylate (9). The acrylate **9** was prepared (93%) by condensation of 2-naphthaldehyde (15.6 g, 0.1 mol) with methyl cyanoacetate (12 g, 0.12 mol) according to the procedure described for **5**: mp 143 °C (CH_2Cl_2–C_6H_{14}); ir (Nujol) 2210 (–CN), 1738 cm^{-1} (–CO); NMR ($CDCl_3$) δ 3.94 (s, 3 H, $-OCH_3$), 8.30 (s, 1 H, –CH); mass spectrum *m/e* 237 (M^+). Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 76.09; H, 4.51; N, 5.87.

Oxidation of 9 to *trans*-Methyl α-Cyano-β-(2-naphthyl)glycidate (7). To a suspension of 2.4 g (0.01 mol) of α-cyanoacrylate **9** in 30 ml of methanol at 0 °C was added 2.1 g (0.012 mol) of 85% *m*-chloroperbenzoic acid and 2 ml of 1 N sodium methoxide. The mixture was then stirred at room temperature for 1 h at which time the alkene **9**, monitored by TLC, was consumed. Sufficient sodium bicarbonate was added and the reaction mixture was worked up in the conventional manner. The glycidate **7** was obtained in high yield after recrystallization of the crude product from a methylene chloride–hexane mixture (90%): mp 98–99 °C; ir (Nujol) 2250 (–CN), 1755 cm^{-1} (–CO); NMR ($CDCl_3$) δ 3.83 (s, 3 H, $-OCH_3$), 4.61 (s, 1 H, –CH); mass spectrum *m/e* 253 (M^+). Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 70.90; H, 4.48; N, 5.47. The NMR spectrum of the cis glycidate formed upon photolysis of **8** is consistent with the assigned structure[10]: δ 3.53 (s, 3 H, $-OCH_3$) and 4.76 (s, 1 H, –CH).

Preparation of *trans*-Methyl α-Cyano-β-(3,4-dimethoxy-

phenyl)glycidate (10). The method described for the preparation of **7** also proved useful for the conversion of (*E*)-methyl α-cyano-β-(3,4-dimethoxycinnamate) to **10** (87%): mp 118 °C (CH_2Cl_2–C_6H_{14}); ir (Nujol) 2280 (–CN, weak), 1770 cm^{-1} (–CO); NMR ($CDCl_3$) δ 3.84 (br s, 6 H, $ArOCH_3$), 3.88 (s, 3 H, $-OCH_3$), 4.41 (s, 1 H, –CH); mass spectrum *m/e* 263 (M^+). Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32 Found: C, 59.44; H, 4.89; N, 5.27. The requisite cinnamate was prepared (94%) by condensation of veratraldehyde with methyl cyanoacetate according to the procedure described earlier for the synthesis of the *E* cinnamate **5**: mp 123 °C (CH_2Cl_2–C_6H_{14}); ir (Nujol) 2210 (–CN), 1737 cm^{-1} (–CO); NMR ($CDCl_3$) δ 3.92 (br s, 6 H, $ArOCH_3$), 3.90 (s, 3 H, $-OCH_3$), 8.08 (s, 1 H, –CH); mass spectrum *m/e* 247 (M^+). Anal. Calcd for $C_{13}H_{13}NO_5$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.35; H, 5.23; N, 5.60.

The NMR of the cis dimethoxyglycidate formed upon sensitized photoequilibration of **10** is consistent with the assigned structure:[10] NMR ($CDCl_3$) δ 3.40 (s, 3 H, $-OCH_3$), 3.70 (br s, 6 H, $ArOCH_3$), 4.62 (s, 1 H, –CH).

Irradiation of the Trans Cyanonaphthylglycidate 7 in Isobutylene–Benzene Solution. A solution of **7** in benzene (0.03 M) saturated with isobutylene was irradiated for 5 h at 40 °C using a 350-nm source.[9] A filter was introduced consisting of a saturated solution of naphthalene in benzene or a uranyl glass sleeve. Both were sufficiently opaque to reduce direct absorption by **7** to an insignificant level. Upon addition of benzophenone (0.05 M) as a sensitizer, however, essentially complete conversion (>95%) to the adduct(s) **11** occurs as evidenced by NMR data. NMR ($CDCl_3$, major isomer) δ 1.08 (s, 3 H, CH_3–), 1.52 (s, 3 H, CH_3–), ~2.2 (m, 2 H, $-CH_2$–), 3.80 (s, 3 H, OCH_3), and ~5.4 (m, 1 H, –CH); ($CDCl_3$, minor isomer) 1.17 (s, 3 H, CH_3–), 1.49 (s, 3 H, CH_3–), ~2.2 (m, 2 H, $-CH_2$–), 3.80 (s, 3 H, OCH_3), and ~5.4 (m, 1 H, CH).

Preparation of the Isomeric Methyl α-Cyano-β-methyl-β-phenylglycidates (12 and 13). A mixture of (*E*)- and (*Z*)-methyl β-methylcinnamates was prepared by the conventional ondensation utilizing ammonium acetate as a catalyst. The isomeric products were isolated by distillation, bp 130–131 °C (0.4 mm) [lit.[19] 150–165 °C (0.9 mm)]. The NMR spectrum is in agreement with reported values.[7c]

A sample of the mixtures of cinnamates (2.1 g, 0.01 mol) was oxidized in the manner described for **3a** and **4a**, and the resulting oxiranes **12** and **13** resolved by column chromatography. The cis oxirane **13** (0.81 g, 3.7 mmol, 37%) eluted first and was obtained as an oil: ir (liquid film) 2260 (–CN), 1776 and 1740 cm^{-1} (–CO); NMR ($CDCl_3$) δ 1.94 (s, 3 H, CH_3) and 3.43 (s, 3 H, OCH_3); mass spectrum *m/e* 217 (M^+). Elution of the trans isomer **12** (1.17 g, 5.4 mmol, 54%) follows: mp 74–75 °C [$(C_2H_5)_2O$–C_6H_{14})]; ir 2260 (–CN), 1738 cm^{-1} (–CO); mass spectrum *m/e* 217 (M^+).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.14; H, 5.11; N, 6.37.

Preparation of an Authentic Sample of Methyl α-Cyano-α-benzoylpropionate (14). A solution of 2.0 g (0.01 mol) of phenacyl bromide was added dropwise to 10 ml of a 1 N solution of sodium methoxide containing 1.0 g (0.01 mol) of methyl cyanoacetate. The resulting mixture was allowed to stand for 2 h at room temperature and quenched with water. The organic products were then extracted with ethyl acetate and worked up in the conventional manner.

The crude residual product was purified by chromatography on silica gel and recrystallized from ether–hexane mixtures to give 0.68 g (30%) of the propionate **14**: mp 58–59 °C; ir 2250 (–CN), 1748 (–COOR), 1668 cm^{-1} (PhCO–); NMR ($CDCl_3$) δ 3.78 (s, 3 H, $-OCH_3$) and 3.5–4.2 (m, 3 H, $-CH_2$, –CH–); mass spectrum *m/e* 217 (M^+).

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.50; H, 5.12; N, 6.41.

Pyrolysis of *trans*-Methyl α-Cyano-β-methyl-β-phenylglycidate (12). A solution of 200 mg of the oxirane **12** was heated in benzene at 120 °C for 12 h. The NMR spectrum of the crude pyrolysate revealed new signals at δ 4.42 (d, 1 H), 4.97 (d, 1 H), and 5.29 (s, 1 H), which are attributed to the enol ether **15** together with peaks of **12** and **14**.

Acknowledgment. The authors are indebted to the National Science Foundation (Grant MPS75-14831) and the Army Research Office, Durham (Grant ARO-D-31-124-73-G4), for support of this work. We also wish to thank Dr. E. Elder and Ms. J. Thompson for aid in the preparation of the manuscript and Mr. Steve Spera for technical assistance.

Registry No.—**3a**, 60239-39-6; **4a**, 60239-40-9; **5**, 14533-86-9; **6**, 14533-85-8; **7**, 60239-41-0; **9**, 60239-42-1; **10**, 60239-43-2; *cis*-**10**, 60239-44-3; *cis*-**11**, 60239-46-5; *trans*-**11**, 60239-45-4; **12**, 0239-47-6; **13**, 60239-48-7; **14**, 22984-73-2; **15**, 60239-49-8; 2-naphthaldehyde, 42007-10-3; methyl cyanoacetate, 105-34-0; isobutylene, 115-11-7; (*E*)-methyl β-methylcinnamate, 3461-50-5; (*Z*)-methyl β-methylcinnamate, 26423-89-2; phenacyl bromide, 70-11-1.

References and Notes

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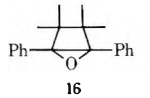
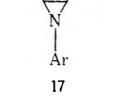


16



17

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The Unusually Mild and Facile Basic Hydrolysis of *N*-Nitroso-2-(methylamino)acetonitrile[1]

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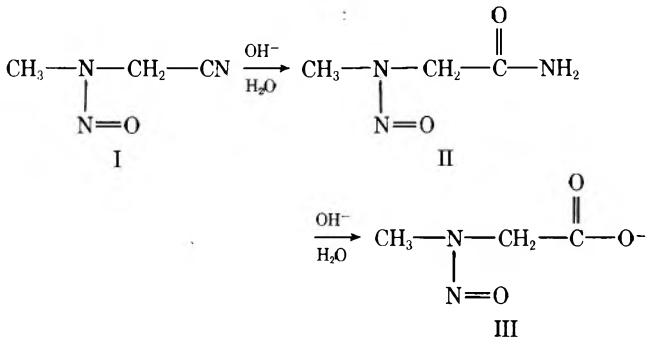
At pH 13 and room temperature, *N*-nitroso-2-(methylamino)acetonitrile (I) undergoes two unusually fast and successive hydrolytic changes that can be detected quantitatively by differential pulse polarography. The final hydrolysis product is *N*-nitrososarcosine (III), via the intermediate amide (II). The kinetics and activation parameters of the transformations have been determined. A mechanism has been proposed to account for these rapid reactions involving anchimeric assistance to the hydrolyses by the appropriately placed nitroso group. Isotopic labeling studies using ^{18}O enriched water and mass spectrometry confirm the proposed mechanism involving exclusive attack on carbon by hydroxide ion.

During the course of electroanalytical studies of a series of *N*-nitrosamines using differential pulse polarography,[2] one *N*-nitrosamine displayed unusual behavior. In aqueous solution at pH 13, *N*-nitroso-2-(methylamino)acetonitrile (I) displayed the anticipated current–potential peak at a negative potential vs. the saturated calomel electrode (SCE) but the expected peak was followed by a second peak, an unusual result for a *N*-nitrosamine.[2] In addition to the second peak, the situation was even more unusual by the observation that the peaks varied in height in some regular way as a function of time. A careful study yielded the results shown in Figure 1 where curves 1–5 are the results of repetitive scans on the same solution recorded over a period of approximately 200 min. Since the peak potential (E_p) of a *N*-nitrosamine is a function of pH and molecular structure, the results suggested that a chemical change was occurring resulting possibly in the formation of nitrosamines different from the original.

In this paper we report the results of an investigation to interpret the observed changes.

As Figure 1 shows, the initial scan yields two peaks at −1.26 and −1.42 V vs. SCE. The second scan taken about 5 min later shows a decrease in the first peak and an increase in the second with the suggestion of a third ill-defined peak at a more negative potential. Curve 5, recorded about 200 min after curve 1, shows that the species giving rise to the peaks at −1.26 and −1.42 V have completely disappeared; the only species left is that giving rise to the ill-defined peak at about −1.8 V.

Although it is well known that nitriles do not undergo basic hydrolysis rapidly at room temperature,[3] the most logical hypothesis to explain the polarographic results seemed to be the following sequence of hydrolytic reactions:



The final product (III) in the suggested sequence is the anion of *N*-nitrososarcosine. To establish the validity of the hydrolysis sequence, *N*-nitrososarcosine was prepared[4] and its properties were compared with those of the final hydrolysis product (III).

Figure 2, curve 1, shows the differential pulse polarogram obtained after acidifying (pH 1) the solution that yielded curve 5, Figure 1. The anodic shift of E_p with lower pH is characteristic of *N*-nitrosamines.[2,5] Curve 2, Figure 2, was obtained after addition of authentic *N*-nitrososarcosine to the solution that yielded curve 1. The increase in peak height without shift in potential strongly suggested that *N*-nitrososarcosine is the electroactive species in Figure 2, curve 1.

Since the polarograms were run on dilute solutions (ca. 10^{-4} M) and product isolation and identification would be difficult, reactions modeled after the polarographic runs were repeated on a preparative scale. The organic product was isolated by evaporation of the water and extraction of the residue with acetone. Evaporation of the acetone yielded a yellow oil which crystallized only after being held at 0 °C overnight. (In some cases the oil did not crystallize.) The crystals had a melting point of 66–67 °C. The melting point and crystallization behavior are those previously reported for nitrososarcosine.[4]

This result confirms the findings of Lijinsky et al. concerning the melting point of this compound as contrasted to the values of 73–74 °C reported by Hammick et al.[6] and 75–77 °C reported by Bergel et al.[7]

To confirm the identity of the hydrolysis product, the NMR, uv, and ir spectra of the final product were obtained; they were identical with those of authentic *N*-nitrososarcosine (Tables I and II). These results show unequivocally that the final product was, in fact, *N*-nitrososarcosine.

The unnitrosated parent amine, 2-(methylamino)acetonitrile, was subjected to the same alkaline reaction conditions as I. No change occurs over a period of 48 h, as would be expected for a simple nitrile. Thus, the *N*-nitroso group in I is clearly having an unusual activating effect on the nitrile group. To understand this effect, the kinetics of the reactions were determined using the rate of decay of the peak currents in the differential pulse polarograms. Both reactions (I → II and II → III) are second order overall, first order in nitrosamine and first order in OH^-. Rate constant data and calculated activation parameters are given in Table III. The most significant

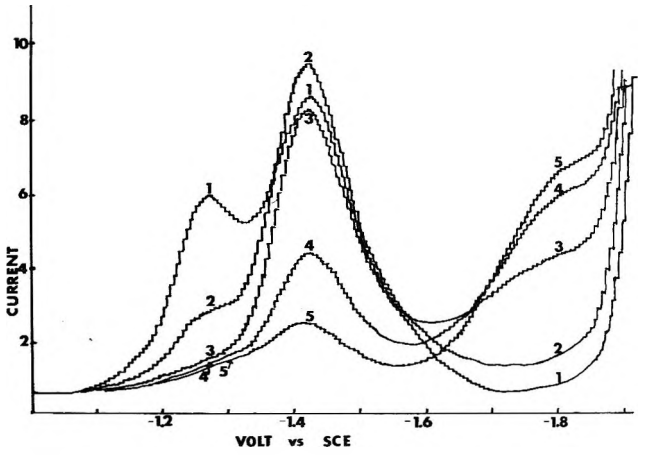


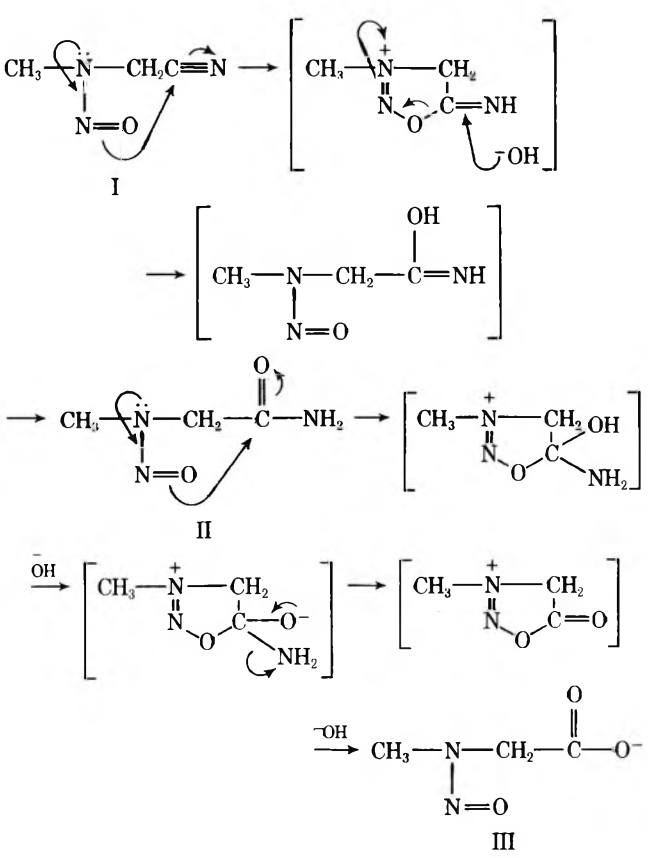
Figure 1. Differential pulse polarograms of *N*-nitroso-2-(methylamino)acetonitrile (I), pH 13.0, T = 25.3 °C: curve 1, 0 min; curve 2, 5 min; curve 3, 23 min; curve 4, 112 min; curve 5, 214 min. Scan 5 mV/s, pulse height 50 mV, drop time 1 s.

data in Table III are the large negative entropies of activation.

A mechanism that agrees with the experimental observations is shown in Scheme I. The activated complex, consisting of a five-membered ring, is consistent with the observed entropies of activation and the known polarities of the nitroso and nitrile groups. Two features of the hydrolytic mechanism are (a) the anchimeric assistance provided by the nitroso group and (b) the suggestion that the base attacks the cyclic complex at carbon.

Support for this mechanism involving a five-membered cyclic transition state is provided by comparing the kinetic results (Table IV) obtained for the analogous alkaline hydrolysis of $CH_3N(N{=}O)CH_2CH_2CN$ (IV) in which two methylene groups, rather than one, are between the *N*-nitroso

Scheme I



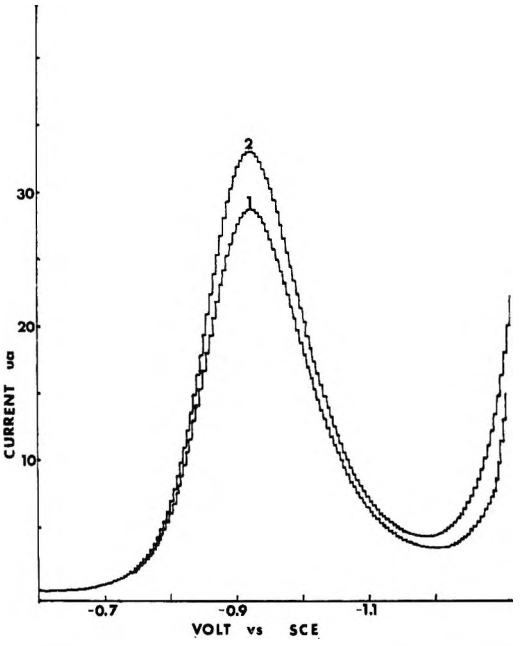


Figure 2. Curve 1: differential pulse polarogram of solution yielding curve 5, Figure 1, at pH 2.0 T = 25.3 °C. Curve 2: differential pulse polarogram resulting from addition of *N*-nitrososarcosine to solution yielding curve 1.

Table I. NMR Identification of Hydrolysis Product of *N*-Nitroso-2-(methylamino)acetonitrile (I)

	Hydrolysis product		*N*-Nitroso-sarcosine		
Solvent	ppm	Proton ratio	ppm	Proton ratio	Ref 4
Acetone-d_6	3.06	3:2	3.07	3:2	
	5.02		5.02		
	3.87	3:2	3.89	3:2	
	4.33		4.34		
Pyridine-d_5	3.22	3:2	3.21	3:2	*anti*-CH_3
	5.20		5.20		*anti*-CH_2
	3.88	3:2	3.89	3:2	*syn*-CH_3
	4.59		4.58		*syn*-CH_2

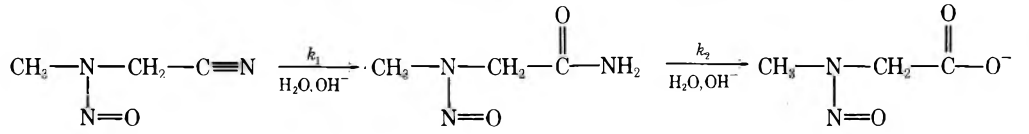
Table II. Uv Identification of Hydrolysis Product of *N*-Nitroso-2-(methylamino)acetonitrile (I)

	λ_{max}, nm			
Nitrososarcosine	340		229	
Hydrolysis product in H_2O (pH 7)	339	310	237	
Hydrolysis product in H_2O (pH 2)	335		230	
Lijinsky et al.[4] in H_2O (pH ?)	340		233	
Hydrolysis product in ether	372	361	351	235
Lijinsky et al.[4] in ether	373	361	352	234

and nitrile groups. The presence of the second methylene group results in a decrease in the overall rate by a factor of about 500. This decrease would be expected if a cyclic activated complex is the intermediate since a six-membered ring is required. The entropy of activation for the hydrolysis of IV is also in accord with such an activated complex.

Scheme I requires attack by OH^- to occur initially on the ring carbon associated with either the nitrile or the amide group. An alternative is attack on the ring nitrogen derived from the nitroso group, resulting in cleavage of the N–O bond rather than a C–O bond. To establish which pathway is, in fact, followed, the alkaline hydrolysis of I was conducted in

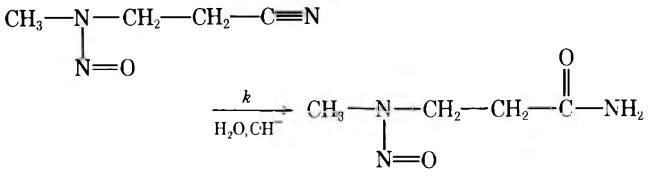
Table III. Hydrolysis of *N*-Nitroso-2-(methylamino)acetonitrile (I)



Temp, °C	k_1	k_2
0 ± 0.2	(3.73 ± 0.38) × 10^{-3}	
25.3 ± 0.2	(4.72 ± 0.59) × 10^{-2}	(1.15 ± 0.30) × 10^{-3}
37.3 ± 0.2	(1.10 ± 0.10) × 10^{-1}	(2.97 ± 0.24) × 10^{-3}
48.6 ± 0.2		(5.96 ± 0.27) × 10^{-3}
	$\Delta H^{\ddagger}$ = 13.3 ± 0.2 kcal/mol	$\Delta H^{\ddagger}$ = 11.3 ± 0.3 kcal/mol
	$\Delta S^{\ddagger}$ = −22.4 eu	$\Delta S^{\ddagger}$ = −35.8 eu

k_1, k_2 = average second-order rate constants (six concns), M^{-1} s^{-1}

Table IV. Hydrolysis of *N*-Nitroso-3-(methylamino)propionitrile. Kinetic Data



Temp, °C	k, M^{-1} s^{-1}
25.0	(5.28 ± 4.9) × 10^{-5}
34.8	(13.3 ± 1.2) × 10^{-5}
43.2	(27.8 ± 2.3) × 10^{-5}
$\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$
16.6 ± 0.7 kcal/mol	−24.8 eu

Table V. Mass Spectrometric Results for ^{18}O Incorporation

	Species	amu	Intensities	%
Expt A (see text)	M^+	120	133 120	16.2
		118	823 808	100.0
	M − NO	90	118 784	16.5
		88	720 896	100.0
	M − COOH	75	71 680	2.3
		73	3 021 824	100.0
Expt B (see text)	M^+	120	35 840	2.9
		118	121 246	100.0
	M − NO	90	17 920	2.1
		88	868 352	100.0
	M − COOH	75	34 304	1.0
		73	3 351 552	100.0

water containing about 8% ^{18}O. The hydrolysis product was then examined by mass spectrometry to determine the location of incorporated ^{18}O, if any (Table V). The results in Table V are from low-resolution semiquantitative studies.

The data in Table V contain only the results used to determine the location of the ^{18}O. *N*-Nitrososarcosine yields a very complex mass spectrum on electron impact due, apparently, to considerable self-protonation. This is noted by the presence of unusually large MH^+ peaks for all samples and is probably associated with the fact that the compound was run as an oil, hence it has a high vapor pressure.

Neglecting the chemical ionization effects noted above, *N*-nitrososarcosine yields a molecular ion (mass 118) and two fragments resulting from loss of NO and COOH. These fragments correspond to mass 88 and 73, respectively. The mass spectral data show that incorporation of ^{18}O has occurred in the hydrolysis of I but, of great significance, loss of NO does *not* result in loss of ^{18}O (experiment A). As seen in the table, the peak at mass 120 is 16.2% of the peak at mass 118. After losing NO the peak at mass 90 *is still* 16.5% of the peak at mass 88. This constancy in relative percentages would not have occurred if the NO group contained any ^{18}O. The fragment resulting from loss of COOH, however, *does* result in loss of ^{18}O as shown by the drop in relative percentage of the mass 75 peak compared to the mass 73 peak. The remaining 2% at mass 75 is probably due to chemical ionization effects coupled with normal isotope effects. Further corroboration is found in the relative intensity of the peak at mass 73 to that at mass 118. Loss of COOH (^{16}O) yields the peak at mass 73 and loss of COOH (^{18}O) should also yield a peak at mass 73 (i.e, 120 − 47 = 73).

Data are also given in the table (experiment B) that exclude the incorporation of ^{18}O by simple exchange between ^{16}O *N*-nitrososarcosine and a basic solution containing $H_2{}^{18}O$. If any exchange occurs it cannot exceed 1%. The peaks at mass 120 and 90 are again consistent with the conclusion that ^{18}O is absent in the NO group and, subtracting the 1% at mass 75 as due to chemical ionization and normal isotope effects, the incorporation due to simple exchange is about 1%.

The presence in the *N*-nitrososarcosine of about 16% ^{18}O from ^{18}O water agrees nicely with the percentage predicted by Scheme I. Incorporation can occur twice, I → II and II → III. Simple calculations predict approximately 14% incorporation when exchange effects are considered.

The mass spectral results show that the *N*-nitroso group is unmodified during the course of the reaction and that its role is to speed up hydrolysis of the nitrile by anchimeric assistance. Furthermore, the exclusive site of attack by OH^- in I is at carbon as opposed to nitrogen.

Experimental Section

Spectra. Uv spectra were obtained using a Cary Model 14 spectrophotometer. Infrared spectra were obtained on a Perkin-Elmer 225 or a Pye Unicam AP 1000 spectrophotometer. NMR were recorded on a Varian XL-100 spectrometer using Me_4Si as internal standard.

Differential Pulse Polarography. Differential pulse polarograms were obtained as previously described[2] except that a Princeton Applied Research Corp. (PAR) Model 174 electroanalyzer was used in place of the PAR Model 171. Temperature studies were performed in a PAR Model 9350 jacketed cell. Temperature was controlled by a Cole-Parmer proportional controller, No. 2163.

Kinetic Studies. Buffer solutions of constant ionic strength containing 0.2 N KCl and 0.2 N KOH were made at pH 13.2, 12.9, 12.6, 12.3, 12.0, and 11.7. The *N*-nitrosamine was dissolved in the solutions and placed in the electrochemical cell at specified temperatures (Table III). The potential was set at −1.26 V vs. SCE and the current recorded as a function of time. Since the II → III reaction was about 1/40 as fast as the I → II reaction, the kinetics of II → III could be studied independently after the I → II reaction was completed. After the I_p of I disappeared the potential was changed to −1.42 V to monitor the decay of II. In all cases log i_p vs. time (s) plots were linear indicating a first-order reaction with respect to *N*-nitrosamine. The slopes of these plots were obtained as pseudo-first-order rate constants (k'). Log k' vs. pH plots were made at each temperature and the slopes of these plots were determined yielding the order with respect to OH^-. The values were 1.00 ± 0.1 in all cases. The second-order rate con-

stants reported in the tables were then calculated by substituting OH^- concentration into the overall rate equation. Activation parameters were calculated in the usual fashion.[8]

Mass Spectrometry. Mass spectra were run by Battelle Memorial Laboratories, Columbus, Ohio.

***N*-Nitroso(2-cyanoethyl)methylamine (IV).** To a chilled, stirred solution of 3-(methylamino)propionitrile (20.0 g, 0.238 mol) (Aldrich) and concentrated HCl (25 ml) in H_2O (120 ml), $NaNO_2$ (19.7 g, 0.276 mol) in H_2O (30 ml) was added dropwise. After addition was complete, the solution was stirred near 0 °C for 0.5 h and then at room temperature for 1.5 h. The solution was concentrated to ~50 ml by rotatory evaporation, filtered (to remove the inorganic salts which precipitated during concentration), and extracted three times with methylene chloride (75 ml). The methylene chloride extracts were combined, dried ($MgSO_4$), and concentrated in vacuo leaving 23.0 g of a yellow liquid. Distillation gave 21.3 g (79%) of a light yellow liquid: bp 102–103 °C (0.04 Torr); ir (CH_2Cl_2) 2255 (C≡N), 1470 (N=O), and 1040 cm^{-1} (N–N). Anal Calcd for $C_4H_7N_3O$: C, 42.47; H, 6.24; N, 37.15; O, 14.14; Found: C, 42.37; H, 6.50; N, 37.28; O, 13.85. In the absence of information on the potential carcinogenicity of IV and I in humans, every precaution should be taken to protect laboratory investigators.

Synthesis of *N*-Nitroso-2-(methylamino)acetonitrile (I). To a stirred solution of 2-(methylamino)acetonitrile hydrochloride (10.0 g, 0.093 mol) (Aldrich) in H_2O (100 ml), $NaNO_2$ (6.9 g, 0.10 mol) in H_2O (15 ml) was added dropwise at room temperature. A few drops of concentrated HCl were added to ensure an excess, and the solution was then stirred for 3 h. The workup procedure was the same as that used in the previous preparation. Distillation gave 4.2 g (46%) of a light yellow oil: bp 52.5–53 °C (0.004 Torr) [lit.[9] 119 °C (13 Torr)]; ir ($CHCl_3$) 2260 (C≡N, 1470 (N=O), and 1025 cm^{-1} (N–N).

Basic Hydrolysis of *N*-Nitroso-2-(methylamino)acetonitrile (I) in ^{18}O-Enriched Water. Recovery of *N*-Nitrosarcosine for Mass Spectral Analysis. A preliminary experiment using the procedure described below except with nonenriched water gave a yellow oil which exhibited an ir spectrum (CH_2Cl_2) identical with that of an authentic sample of *N*-nitrososarcosine.

To ^{18}O-enriched water (5.0 ml) (ca. 8% enrichment) made alkaline to pH > 13 by 0.25 N NaOH solution was added *N*-nitroso-2-(methylamino)acetonitrile (56.1 mg, 0.567 mmol). The clear solution was stirred for 24 h at room temperature and the pH was then adjusted to ~1.5 with concentrated HCl. The water was evaporated under reduced pressure, and the residue was extracted with acetone (10 ml). The solution was filtered to remove NaCl and was evaporated under a stream of N_2. The resulting yellow oil was dried over P_2O_5; it weighed 66.1 mg (98.8%).

Recovery of Nitrososarcosine in Basic ^{18}O-Enriched Water for Mass Spectral Analysis. Attempted Exchange Experiment. To ^{18}O-enriched water (2.5 ml) made alkaline to pH >13 by 0.25 N NaOH solution was added *N*-nitrososarcosine (34.0 mg, 0.284 mmol). The clear solution was stirred for 24 h at room temperature and the pH was then adjusted to ~1.5 with concentrated HCl. The workup procedure was the same as that just described; the yield was 28.3 mg of a yellow oil.

Acknowledgments. This investigation was supported by PHS Research Grants CA-18618, 12227, and 05280 from the National Cancer Institute. The authors would also like to express their appreciation to Dr. David Dalton for his generous gift of ^{18}O-enriched water.

Registry No.—I, 3684-97-7; III, 60153-48-2; IV, 60153-49-3; 3-(methylamino)propionitrile, 693-05-0; 2-(methylamino)acetonitrile hydrochloride, 25808-30-4.

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The X-Ray Crystal and Molecular Structure of an Unusually Stable Cyclic Organic Peroxide

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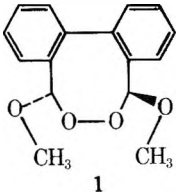
While the organic peroxides are an ubiquitous class of compounds whose chemical reactivity is relatively well known, the natural variations in peroxide structural parameters and resulting structure–reactivity correlations have yet to be fully enumerated. This paucity of structural data may reflect on their inherent thermodynamic instabilities as well as difficulties encountered in their handling.

In striking contrast to this reactivity norm is the thermally stable (e.g., mp 180–181 °C before decomposition) dimethoxy peroxide 1 produced in the acid-catalyzed methanolysis of phenanthrene ozonide.[1,2] Although dihydroxyalkyl peroxides have been isolated from equilibrium mixtures of aldehydes and hydrogen peroxide,[3] and dimethoxyalkyl peroxides have been prepared through alkene ozonolysis reactions in methanol,[4] no members of the two series exhibit the thermal stability characteristic of 3,8-dimethoxy-4,5,6,7-dibenzo-1,2-dioxacyclooctane (1). The structure of peroxide 1, exclusive of the stereochemical relationship between the methoxy groups, was initially proposed on the basis of its infrared spectrum, C–H analysis, and molecular weight determinations.[1] This proposal has recently been strengthened with natural abundance ^{13}C and ^{1}H NMR spectra as well as mass spectral data.[4,5] In order to confirm these conclusions, determine the stereochemistry of the methoxy groups, and gain insight into the unusual stability of peroxide 1 we have fully



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determined its molecular structure through a single-crystal x-ray diffraction study.

Experimental Section

3,8-Dimethoxy-4,5,6,7-dibenzo-1,2-dioxacyclooctane (1) was prepared through ozonolysis of phenanthrene in methanol at −30 °C as described by Bailey.[1,2] After recrystallization from chloroform, a needle-shaped crystal, 0.3 mm in length and 0.1 mm in diameter, was mounted on a glass fiber in air with the [*h*0*h*] direction coincident with the ϕ axis of a Picker FACS-I four-circle diffractometer. The reciprocal lattice showed $C2/m$ symmetry with systematic extinctions $l = 2n + 1$ for all reflections, which is consistent with space groups $C_{2/c}$ and C_c. The centrosymmetric $C_{2/c}$ was chosen and the choice was justified by the subsequent refinement. Lattice constants were determined at 25 °C by a least-squares fit of 12 carefully measured 2θ values of the Cu $K\alpha_1$ and $K\alpha_2$ doublet for reflections with $2\theta > 60°$. The resultant lattice constants and their estimated standard deviations are $a = 10.209\ (1)$, $b = 13.322\ (1)$, $c = 11.937\ (1)$ Å, and $\beta = 122.76\ (1)°$. The observed density, 1.31 g/cm^3 (by a flotation method using chloroform and 2-butanone), agrees with the calculated density, 1.32 g/cm^3, assuming four peroxide molecules per unit cell.

Intensity data were collected on a Picker FACS-I fully automated diffractometer using Ni-filtered Cu $K\alpha$ radiation. A θ–2θ scan rate of 2°/min, with a variable scan width (2.3° ± 0.4° tan θ) and 10-s background measurements at the extremities of the scan, were used to measure the 1093 unique reflections to a 2θ maximum of 125° (d = 0.87 Å). The intensities were corrected for Lorentz–polarization effects and absorption as a function of ϕ, with a transmission factor of 1.06:1.00 (linear μ = 7.9 cm^{-1} for Cu $K\alpha$ radiation). During the 28 h of actual x-ray exposure, the crystal exhibited an extreme intensity decay as monitored by three standard reflections measured hourly. Although the decay appeared anisotropic, the intensities were corrected for an isotropic linear decay of 40%. Structure amplitudes were calculated and a total of 891 (81%) reflections were considered statistically significant by the criterion $|F| > 3\sigma(F)$.

Structure Determination. The structure was solved by direct methods. After conversion to normalized structure magnitudes ($|E|$'s) with appropriate scaling using a k curve,[6] 130 reflections with $|E| \geq 1.50$ were obtained. An origin was selected by specifying the phases of two reflections. The phases of five other reflections were permuted resulting in 32 combinations, using the program MULTAN.[7]

An E map, calculated for the most consistent set, contained the ten unique nonhydrogen atoms among the top 12 peaks consistent with the expected structure. The molecule possesses a twofold axis of rotation (position e). Ten cycles of block-diagonal, least-squares isotropic refinement using $1/\sigma^2$ weights resulted in a value of the reliability index, R = 0.14.[8]

After conversion to anisotropic temperature factors, refinement was continued for ten more cycles, resulting in a value of R = 0.10. Since a difference electron density map at this stage showed no peaks greater than 0.3 e/Å^3, the coordinates of the five nonmethyl hydrogen atoms were calculated from expected geometry and included in future structure factor calculations but not refined. The refinement converged to a final value of R = 0.077 with the shifts in all parameters being significantly less than one-tenth of the estimated standard deviation of the respective parameter. The standard deviations of the bond distances, given in parentheses for the least significant figure, were calculated using the standard deviations of the xyz coordinates only.

Results and Discussion

Figure 1 shows the observed bond distances and angles as well as the atom labeling scheme. Figure 2 is an ORTEP[9] stereoscopic drawing of the complete molecule. The bond distances and bond angles in the aromatic rings are normal (1.398 ± 0.006 Å and 120.0 ± 0.9°, respectively). The dihedral angle between the aromatic rings is 61.9°. Figure 2 also clearly illustrates the fact that the methoxy groups are trans to one

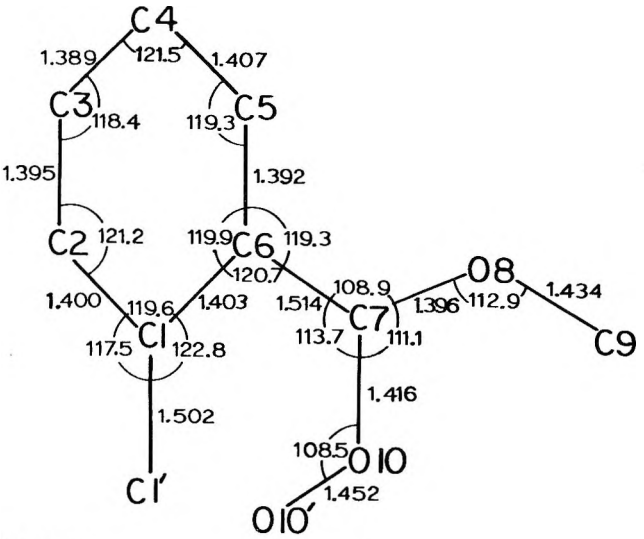


Figure 1.

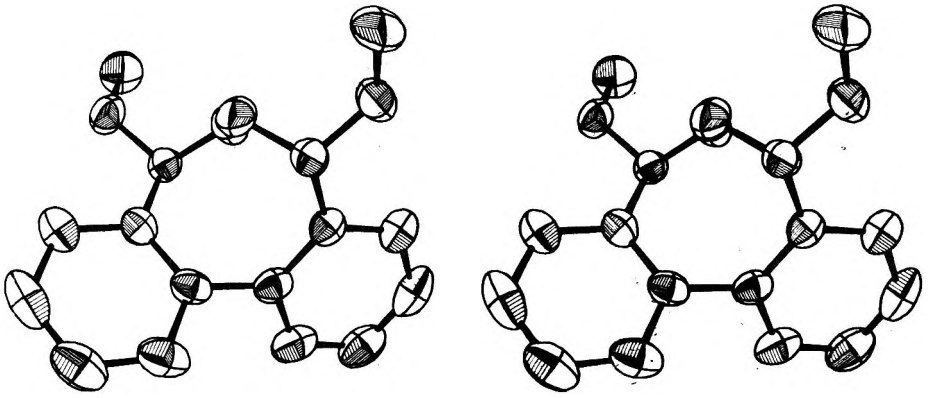
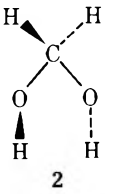


Figure 2.

another, a fact consistent with but not deducible from the spectroscopic studies.[2,5] The peroxide O10–O10′ bond [1.452 (18) Å] is shorter than those reported (1.48 Å) for dimeric and trimeric alkyl ketone peroxides[10–12] accounting, at least in part, for the unusual thermal stability of **1**. The C–O distance in the eight-membered ring is 1.416 (17) Å and is comparable to that observed in trimeric acetone peroxide.[10] The methyl C–O in the methoxy group compares with that observed in other studies,[13] but the Me–O–C angle (110°) is significantly compressed. The C–O–C angles within the eight-membered ring (108.5°) are consistent with those observed in the di- and trimeric alkyl ketone peroxides. The closest intermolecular contact distance is 3.37 Å observed between C3 and O10 in the molecule related by $\frac{1}{2} + x, \frac{1}{2} + y, z$.

The ab initio self-consistent field molecular orbital calculations carried out on methanediol by Radom, Hehre, and Pople[14] provide a useful theoretical framework for understanding the structural details of peroxide **1**.

Pople and co-workers found that of a series of 48 saturated molecules, methanediol possessed the largest "bond separation energy" (15.2 kcal mol^{-1}), or, in other words, the largest positive heat of reaction in its theoretical conversion along with 1 mol of methane to 2 mol of methanol. Therefore, since the bond separation energies evaluate the interactions between various bonds in terms of back-donating n → σ^* electron transfer, the Pople calculations[14] determined that this bond-strengthening interaction is strongest between the two C–O bonds of methanediol. It was further determined that this interaction has its greatest effect when the OCO plane is perpendicular to the COH plane. This leads to a favorable orientation of dipoles for the two OH groups within the preferred double gauche conformation, **2**.[14]



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Perhaps these same orbital interactions account for the unusual stability of peroxide **1** through strong n → σ^* back-donation of electron density into the peroxide bond from the geminal C–O bonds on the adjacent atoms (C7 and C7′). The double gauche conformation is indeed evident about C7 and C7′. The trends in bond lengths also strengthen the validity of the methanediol theoretical model: n → σ^* back-donation alternately lengthens C9–O8 [1.434 (10) Å], shortens O8–C7 [1.396 (12) Å], lengthens C7–O10 [1.416 (17) Å], and shortens O10–O10′ [1.452 (18) Å].

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Registry No.—**1**, 59645-79-3.

Supplementary Material Available. Tables of temperature and structure factors may be obtained upon request from the authors. The observed fractional coordinates for the unique atoms in the molecule have been retained as supplementary material for the microfilm edition (1 page). Ordering information is given on any current masthead page.

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A Novel Route to 1-Aminoalkylphosphonic Acids

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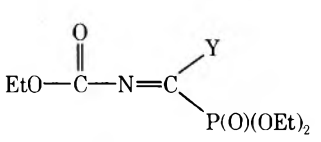
In view of the increasing interest in the biological[1] and chelating[2] properties of 1-aminoalkylphosphonic acids and 1-aminoalkylphosphine oxides we wish to report a convenient new route for the synthesis of these important classes of compounds. Recently we described a simple synthesis of *O,O*-diethyl 1-[*N*-ethoxycarbonylimino]-1-thioethyl methylphosphonate (**1a**) and its reaction with sulfuryl chloride to give **1b**.[3]

Table I. Spectral and Physical Characteristics of 1-Aminoalkylphosphonic Acids and 1-Aminoalkylphosphonoxides

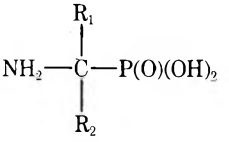
Ex.	Compd	Mp, °C	^{31}P NMR, δ, ppm	^{1}H NMR, δ	Yield, %	Lit. mp, °C
1	**2a**[a]	256–257	−16.8 (2 N KOH)	(2 N KOH/D_2O) 1.5 (6, d, J_{P-H} = 12 Hz)	45[b]	274–275[7] 258 (monohydrate)[8]
2	**2b**	272–273	−15.3 (H_2O)	(D_2O) 1.8 (3, pair of d, J_{H-H} = 7, J_{P-H} = 15 Hz), 3.8 (1, m)	58[b]	272–274[9]
3	**2c**	267–269	−14.5 (H_2O)	(D_2O) 1.4 (3, t, J_{H-H} = 7 Hz), 2.0–2.4 (2, m), 3.3–3.7 (1, m)	50[b]	264–266[9] 285–286[7]
4	**2d**	262–263	−22.2 2 N KOH)	(2 N KOH/D_2O) 1.5 (6, t, J_{H-H} = 6 Hz), 2.3–2.7 [1, m, CH(CH_3)$_2$], 2.9 (1, pair of d, CHP)	46[b]	274[10]
5	**2e**	268–270	−21.2 (2 N KOH)	(2 N KOH/D_2O) 2.7–3.7 (3, m, $CHCH_2$), 7.8 (5, s, aromatic protons)	41[b]	226[8] 276–277[11]
6	8	108–109	−34.5 ($CHCl_3$)	($CDCl_3$) 1.3 (3, pair of d, J_{H-H} = 7, J_{P-H} = 15 Hz), 3.4–3.9 (1, m), 7.3–8.1 (10, m, aromatic protons)	55[c]	

[a] Isolated as a monohydrate. [b] Yield calculated on the basis of starting **1a**. [c] Yield calculated for the conversion 7 → 8.

Because of the presence of the >P(O)C=N– unit in such compounds it was expected that they could be employed in a convenient synthesis of the important 1-aminoalkylphosphonic acids **2**.[4]



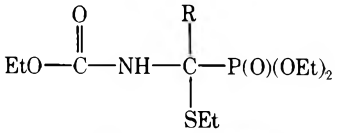
1a; Y = SEt
1b; Y = Cl



2a, R_1 = R_2 = Me
b, R_1 = H; R_2 = Me
c, R_1 = H; R_2 = Et
d, R_1 = H; R_2 = *i*-Pr
e, R_1 = H; R_2 = CH_2Ph

As expected, treatment of chloride **1b** with methylmagnesium iodide and subsequent hydrolysis by means of concentrated HBr gave 1-amino-1-methylethylphosphonic acid (**2a**).

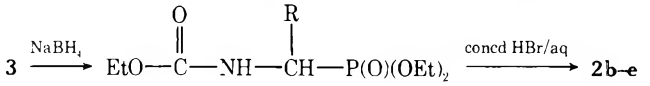
The dimethyl derivative **2a** was formed exclusively without regard to the molar ratio of methylmagnesium iodide used relative to chloride **1b**. However, its reaction with excess of isopropylmagnesium iodide gave only **2d** in 44% yield. On the other hand, reaction of **1a** with methylmagnesium iodide gave the thioethyl derivative *O,O*-diethyl 1-[*N*-ethoxycarbonylamino]-1-thioethylmethylphosphonate (**3b**). Other Grignard reagents (RMgX, R = Et, *i*-Pr, $PhCH_2$; X = I, Br) reacted similarly with **1a** to give the corresponding *O,O*-diethyl 1-[*N*-ethoxycarbonylamino]-1-thioethylalkylphosphonates (**3c–e**).



3b, R = Me **d**, R = *i*-Pr
c, R = Et **e**, R = CH_2Ph

Since distillation of the thioethylalkylphosphonates **3** caused partial decomposition, the compounds were identified by means of mass spectrometry and ^{1}H NMR spectroscopy without isolation.

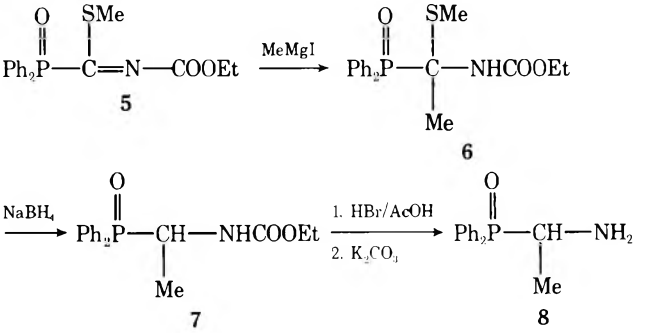
Conversion of the phosphonates **3** to the corresponding



4b, R = Me **d**, R = *i*-Pr
c, R = Et **e**, R = CH_2Ph

phosphonic acids **2** was achieved by reduction of **3** with sodium borohydride,[5] followed by hydrolysis of the desulfurated intermediate **4** by means of aqueous hydrogen bromide. The phosphonic acids were isolated and purified according to the procedure of Isbell.[6] Spectroscopic and physical data characteristic of the compounds obtained are collected in Table I.

The present synthetic method can also be applied to the preparation of 1-aminoalkylphosphine oxides. Treatment of [(ethoxycarbonylimino)(thiomethyl)methyl](diphenyl)-phosphine oxide (**5**)[3] with methylmagnesium iodide gave [1-(ethoxycarbonylamino)-1-(thiomethyl)ethyl](diphenyl)-phosphine oxide (**6**), which was reduced as usual by means of sodium borohydride to give intermediate **7**, which upon hydrolysis with 40% HBr in acetic acid gave 1-aminoethyl(diphenyl)phosphine oxide (**8**).



Experimental Section

Melting points and boiling points are uncorrected. ^{31}P NMR spectra were recorded at 24.3 MHz with H_3PO_4 as reference (negative chemical shift values for compounds absorbing at lower fields than H_3PO_4). ^{1}H NMR spectra were recorded at 80 MHz. Gas chromatography/mass spectrometric analyses were performed on an instrument (LKB 2091-PDP11) operated at 70 eV, ion source temperature 250 °C.

***O,O*-Diethyl 1-(*N*-Ethoxycarbonylimino)-1-thioethylmethylphosphonate (1a).** To a solution of ethoxycarbonyl isothiocyanate (13.1 g, 0.1 mol) in tetrahydrofuran (100 ml), triethyl phosphite (17.3 g, 0.11 mol) was dropped at a temperature of 30–40 °C. The reaction mixture was left for 6 h at room temperature, the solvent evaporated, and the residue distilled: bp 115 °C (0.05 mm); n^{20}D 1.4860; yield 18.5 g (62%); $\delta_{^{31}P}$ 1.2 ppm.

Anal. Calcd for $C_{10}H_{20}NO_5PS$: C, 40.40; H, 6.73; P, 10.43. Found: C, 40.71; H, 6.85; P, 10.69.

***O,O*-Diethyl 1-(*N*-Ethoxycarbonylimino)-1-chloromethylphosphonate (1b).** Sulfuryl chloride (14.8 g, 0.11 mol) was dropped into a solution of phosphonate **1a** (29.7 g, 0.1 mol) in methylene chloride (140 ml) without cooling. After 1 h at room temperature the solvent was evaporated and residue distilled: bp 102–103 °C (0.1 mm);

n^{20}D 1.4544; yield 19.3 g (71%); δ_{31P} 3.2 ppm. Anal. Calcd for $C_8H_{15}NO_5PCl$: C, 35.40; H, 5.54; P, 11.40. Found: C, 35.11; H, 5.89; P, 11.06.

***O,O*-Diethyl 1-(*N*-Ethoxycarbonylamino)-1-methylethylphosphonate (4a).** To a solution of phosphonate **1b** (13.6 g, 0.05 mol) in ethyl ether (300 ml) a solution of MeMgI (0.15 mol) in ether (100 ml) was dropped with vigorous stirring while maintaining the temperature at −10 °C. Stirring was continued until the temperature rose to 15 °C after which the mixture was cooled to −5 °C and a saturated solution of ammonium chloride in water (60 ml) was carefully added. The organic layer was separated and the aqueous phase extracted with chloroform (2 × 40 ml). The combined organic layers were dried over anhydrous magnesium sulfate, the solvent evaporated, and the oily residue distilled, bp 93–94 °C (0.05 mm), n^{20}D 1.4505, yield 8.4 g (63%).

Anal. Calcd for $C_{10}H_{22}NO_5P$: C, 44.90; H, 8.25; P, 11.61. Found: C, 45.22; H, 8.05; P, 11.40.

Reaction of Phosphonate 1b with Isopropylmagnesium Iodide. To a solution of isopropylmagnesium iodide (0.075 mol) in ethyl ether (150 ml) a solution of phosphonate **1a** (6.8 g, 0.025 mol) in ether (30 ml) was dropped with vigorous stirring while keeping the temperature at −10 °C. Stirring was continued until the temperature rose to 15 °C and after cooling to −5 °C the mixture was worked up as described for the case of **4a**. The crude phosphonate was identified as **4d** and was hydrolyzed without purification according to the procedure described by Chambers and Isbell, yielding 1.7 g (44%) of 1-aminoisobutylphosphonic acid **2d**.

***O,O*-Diethyl 1-(*N*-Ethoxycarbonylamino)-1-thioethylalkylphosphonates (3b–e).** To a solution of alkylmagnesium iodide (0.05 mol) (MeI, EtI, *i*-PrI, $PhCH_2Cl$) in ethyl ether (200 ml), a solution of phosphonate **1a** (7.5 g, 0.025 mol) in ether (30 ml) was dropped with vigorous stirring while keeping the temperature at −10 °C. Stirring was continued until the temperature rose to 15 °C and after cooling to −5 °C the mixture was worked up as described above for the case of **4a** except that the crude product obtained after the evaporation of solvent was used directly in the next step.

***O,O*-Diethyl 1-(*N*-Ethoxycarbonylamino)alkylphosphonates (4b–e).** Solutions of the crude phosphonates **3b–e** (prepared from 0.025 mol of **1a**) in THF (70 ml) were refluxed with sodium borohydride (1.5 g, 0.04 mol) for 2 h. After cooling to 20 °C, water (30 ml) was carefully added. The organic layer was separated, the water layer extracted with chloroform (3 × 30 ml), and the combined extracts dried over anhydrous magnesium sulfate. After evaporation of solvent the crude phosphonates **4b–e** were hydrolyzed without purification.

1-Aminoalkylphosphonic Acids (2a–e). Hydrolysis of phosphonates **4a–e** and isolation of the corresponding aminophosphonic acids **2a–e** was carried out according to the procedure described by Chambers and Isbell.[7] For the results see Table I.

1-(*N*-Ethoxycarbonylamino)ethyldiphenylphosphine Oxide (7). A solution of phosphine oxide **6**[3] (7.2 g, 0.02 mol) in THF (70 ml) was refluxed with sodium borohydride (1.5 g, 0.04 mol) for 2 h. After cooling to 20 °C, water (30 ml) was carefully added. The organic layer was separated and the aqueous phase extracted twice with chloroform (2 × 30 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent evaporated. The oily residue crystallized upon adding a small amount of ethyl ether. The product was filtered and recrystallized from benzene–petroleum ether (2:1) to give 5.5 g (87%) of **7**, mp 146–147 °C, δ_{31P} −35.0 ppm. Anal. Calcd for $C_{17}H_{20}NO_3P$: C, 64.30; H, 6.32; P, 9.78. Found: C, 64.37; H, 6.46; P, 9.84.

1-Aminoethyldiphenylphosphine Oxide (8). Phosphine oxide **7** (2.0 g, 0.0063 mol) was dissolved in a solution of HBr in acetic acid (40%, 20 ml). The reaction mixture was let stand at room temperature for 3 days. The crude 1-aminophosphine oxide hydrobromide separated as an oily liquid after addition of ethyl ether (about 100 ml). The oil was dissolved in 10 ml of water and the solution extracted twice with chloroform (2 × 10 ml) in order to remove unchanged **7**. The aqueous solution was neutralized with potassium carbonate and crude **8** extracted with chloroform (10 × 10 ml). The organic layer was dried ($MgSO_4$), the solvent evaporated, and the oily residue crystallized from benzene–petroleum ether (2:1) to give 0.7 g (55%) of pure **8**.

Anal. Calcd for $C_{14}H_{16}NOP$: C, 68.60; H, 6.53; P, 12.66. Found: C, 68.42; H, 6.31; P, 12.91.

Registry No.—**1a**, 60064-40-6; **1b**, 35156-57-1; **2a**, 5035-79-0; **2b**, 6323-97-3; **2c**, 14047-23-5; **2d**, 18108-24-2; **2e**, 6324-00-1; **3b**, 60064-41-7; **3c**, 60064-42-8; **3d**, 60064-43-9; **3e**, 60064-44-0; **4a**, 60064-45-1; **4b**, 60064-46-2; **4c**, 60064-47-3; **4d**, 60064-48-4; **4e**, 60064-49-5; **6**, 59766-64-2; **7**, 60064-50-8; **8**, 60064-51-9; ethoxycarbonyl isothiocyanate, 16182-04-0; triethyl phosphite, 122-52-1; sulfuryl chloride, 7791-25-5; isopropyl iodide, 75-30-9.

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A Convenient Synthesis of 25-Oxo-27-norcholesteryl Acetate

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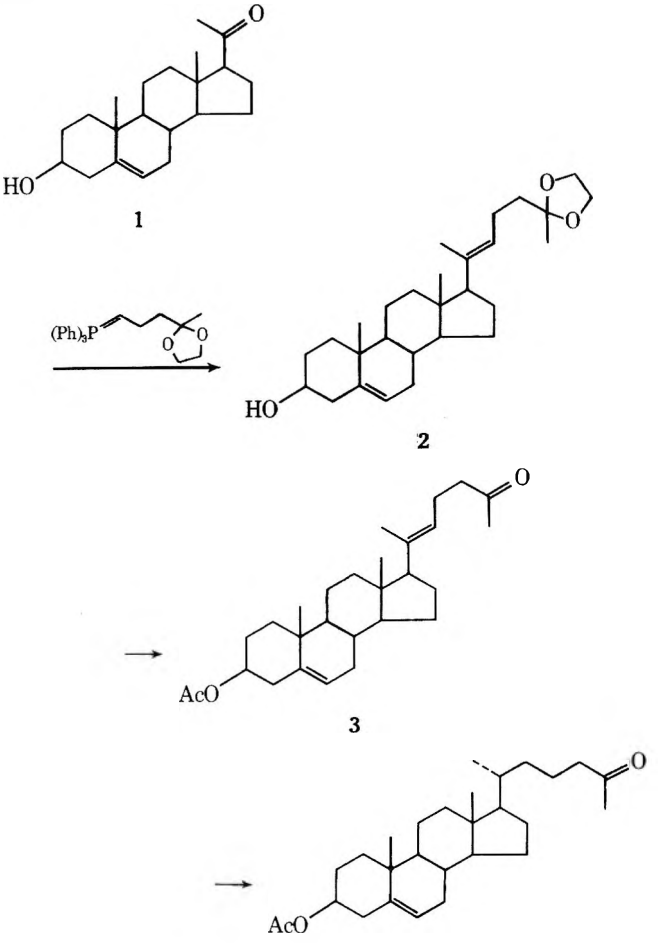
During an examination of the scope of the Wittig reaction with C-20 steroidal ketones as reported by Piraux and co-



workers[1] the synthesis of 25-oxo-27-norcholesteryl acetate, a key intermediate for the synthesis of 25-hydroxy vitamin D_3,[2-4] was undertaken. We wish to report an efficient preparation of this intermediate (4) starting from pregnenolone (1). The main steps are the Wittig reaction of pregnenolone with the ketal phosphorane shown below, and subsequent hydrogenation of the $\Delta^{20(22)}$ double bond of the product. A slightly higher overall yield can be obtained if the 3-hydroxyl is protected as the tetrahydropyranyl ether during the Wittig reaction.

The stereochemistry of the Wittig product (2) was found to be exclusively *E* as expected.[1] The NMR spectrum showed the 21-methyl as a singlet at δ 1.64 which is characteristic of the *E* isomer (lit. δ 1.65)[2] whereas the chemical shift in the *Z* isomer falls in the range δ 1.67–1.70. Deketalization and acetylation of 2 gave the keto acetate 3 which was identical with an authentic sample.[5] It was selectively hydrogenated in dioxane in the presence of acetic acid with platinum oxide as catalyst. A 90% yield of the 20*R* epimer (4) was obtained.[6] The 20*S* epimer was detected by NMR spectroscopy in the mother liquor from recrystallization of the hydrogenation product. The signal for the 21-methyl in this epimer appeared as a doublet centered at δ0.84 while that for the 20*R* epimer appeared at δ 0.94. The epimers could be separated by GLC. Their identity was confirmed by comparison with authentic samples.[5] The overall yield of 4 from pregnenolone was 62%.

Experimental Section

Melting points (uncorrected) were determined on a Köfler apparatus and NMR and ir spectra on Varian (220 MHz) and Beckman IR 18 A-X spectrometers, respectively. A Varian 2100 Aerograph was used for GLC analysis.

$\Delta^{5,20(22)}$-27-norcholestadien-3β-ol-25-one 25-Ketal (2). [3-(2-Methyl-1,3-dioxalan-2-yl)propyl]triphenylphosphonium bromide[7] (5.2 g, 11 mmol) in 5.7 ml of a benzene solution of potassium *tert*-amylate[8] (2.1M) was refluxed under argon for 45 min, then 500 mg of pregnenolone dissolved in 8 ml of hot benzene was added to the dark red solution. The combined solution was refluxed for 3 h, cooled, and poured into water and the resulting mixture extracted with ether. The ether extract was washed successively with 5% hydrochloric acid, 10% sodium bicarbonate solution, and water and dried over $MgSO_4$. Removal of the solvent and chromatography of the residue (silica gel, ethyl acetate–petroleum ether, 4:1) gave 470 mg (69%) of product: mp 139–140 °C; NMR ($CDCl_3$) δ 0.54 (s, 18-Me), 1.00 (s, 19-Me), 1.32 (s, 26-Me), 1.64 (s, 21-Me), 3.52 (m, 1 H, 3α-H), 3.97 (d, J = 1 Hz, 4 H, OCH_2CH_2O), 5.16 (t, J = 6.7 Hz, 1 H, 22-H), 5.33 (m, 1 H, 6-H). Cleavage of the ketal, by keeping a solution of the product in ethanol–water with toluenesulfonic acid for 12 h, followed by acetylation with acetic anhydride–pyridine overnight afforded $\Delta^{5,20(22)}$-27-norcholestadien-3β-ol-25-one acetate (3) in 98% yield: mp 115–118 °C (lit. 120–121 °C[2]); ir (KBr) 1740, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.53 (s, 18-Me), 1.02 (s, 19-Me), 1.64 (s, 21-Me), 2.03 (s, acetate), 2.14 (s, 26-Me), 4.59 (m, 1 H, 3α-H), 5.10 (t, J = 6.7 Hz, 22-H), 5.35 (m, 1 H, 6-H). The ir and NMR spectra were identical with those of an authentic sample.[5]

25-Oxo-27-norcholesteryl Acetate (4). The acetate 3 (300 mg) dissolved in 15 ml of dioxane–acetic acid (50:1) was hydrogenated in the presence of 30 mg of prereduced platinum oxide at room temperature and atmospheric pressure. After 4 h more platinum oxide (30 mg) was added. The reaction was complete after 7 h. The catalyst was separated by filtration and the solvent removed from the filtrate to give the crystalline product which was recrystallized from ethanol (yield 276 mg, 90%): mp 140–142 °C (lit. 139–140 °C);[2] ir (KBr) 1738, 1720 cm^{-1}; NMR ($CDCl_3$) δ 0.68 (s, 18-Me), 0.95 (d, J = 6 Hz, 21-Me), 1.02 (s, 19-Me), 2.02 (s, acetate), 2.13 (s, 26-Me), 4.61 (m, 3α-H), 5.39 (m, 6-H). The ir and NMR spectra were identical with those of an authentic sample.[5] The retention times on GLC (3% OV-17 on Gaschrom Q at 300 °C) were the same but differed from that of the 20*S* epimer.

Acknowledgment. This work was supported by Grant GM21350 from the National Institutes of Health.

Registry No.—1, 145-13-1; 2, 60065-10-3; 3, 53139-44-9; 20*R*-4, 7548-94-9; 20*S*-4, 55122-55-9; 3-(2-methyl-1,3-dioxolan-2-yl)propylidenetriphenylphosphorane, 3054-93-1.

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Approaches to the Synthesis of 1,2-Cyclooctatrienedione

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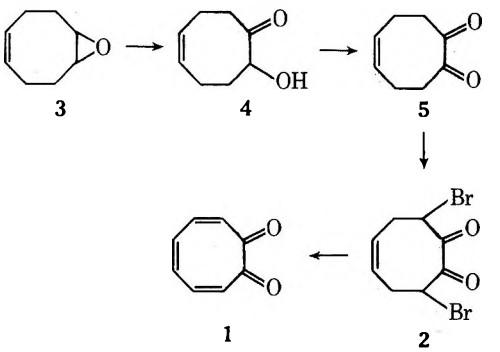
The recent interest[1-6] in the synthesis of the elusive 1,2-cyclooctatrienedione (1) and its isomers prompts this report of our successful synthesis of the quinoxaline derivative of 1 together with the chemistry of precursors to this potentially aromatic compound.

As a likely precursor to 1 a four-step synthesis of 3,8-dibromo-5-cyclooctene-1,2-dione (2) was undertaken. Epoxidation of 1,5-cyclooctadiene afforded the known[7] epoxy olefin 3 which was converted to keto alcohol 4 upon treatment with boron trifluoride in dimethyl sulfoxide. Cupric acetate oxidation of 4 gave 5-cyclooctene-1,2-dione (5) which has been prepared previously by another route.[1]

Cupric bromide dibromination of 5 resulted in the formation of 2 as a white, crystalline material. The infrared carbonyl absorptions of 2 at 1740 and 1727 cm^{-1} established[8] that the molecule exists in the trans diequatorial configuration. Confirmation of this assignment was obtained from the ^1H NMR spectrum ($CDCl_3$) which exhibits a single methine hydrogen absorption at δ 5.15 as an ABX doublet of doublets.[9]

Scheme I

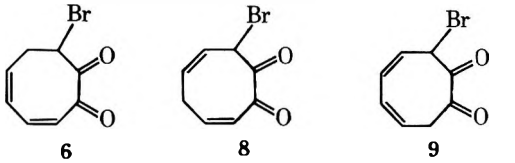


3 4 5 1 2

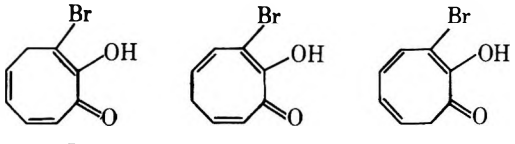
To date all efforts to convert 2 to 1 by direct dehydrobromination have proven unsuccessful. Numerous procedures have been attempted which result in either recovered starting material or a multitude of intractable products.

Treatment of 2 with warm hexamethylphosphoric triamide,[10] however, resulted in the formation of the monodehydrobrominated product 3-bromo-5,7-cyclooctadiene-

1,2-dione (**6**). Compound **6** exists predominantly as the enol **7** as evidenced by the infrared intramolecular hydrogen bonded hydroxy absorption at 3365 cm^{-1}. Corroboration of the structure **7** was derived from its ^1H NMR spectrum (Me_2SO-d_6) which showed, in addition to four olefin hydrogen absorptions, a doublet (J = 8.0 Hz) at δ 3.16 indicative of a pair of doubly allylic hydrogens coupled to a single olefinic hydrogen. The isomeric bromocyclooctadienediones **8** and **9** have been recently reported[11] and have been shown to exist as their enol tautomers **10** and **11**, respectively. Attempts to convert **6** to **1** have failed to produce an isolable product.



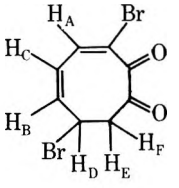
6 **8** **9**



7 **10** **11**

The reaction of **7** with *N*-bromosuccinimide efficiently produced 3,7-dibromo-3,5-cyclooctadiene-1,2-dione (**12**). The composition of **12** was established by elemental analysis and mass spectral data. The infrared carbonyl absorptions at 1677 and 1724 cm^{-1} suggested the presence of α,β-unsaturated ketone and saturated ketone moieties.

The ^1H NMR spectrum ($CDCl_3$) of **12** exhibits a doublet at δ 7.68 (H_A, $J_{H_A-H_C}$ = 6.0 Hz), a doublet of doublets at δ 6.55 (H_B, $J_{H_B-H_D}$ = 8.5 Hz), a doublet of doublets at δ 5.95 (H_C, $J_{H_C-H_B}$ = 12.0 Hz), a heptet at δ 5.23 (H_D, $J_{H_D-H_E}$ = 5.5 Hz), a doublet of doublets at δ 3.84 (H_E, $J_{H_E-H_F}$ = 13.5 Hz), and a doublet of doublets converged to a triplet at δ 3.22 (H_F, $J_{H_F-H_D}$ = 13.5 Hz).



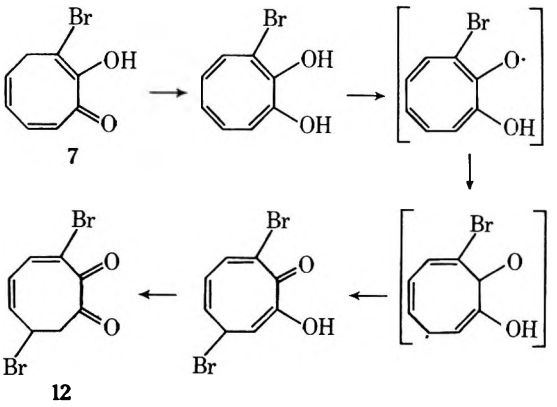
12

The coupling between H_A and H_C is lower than the expected 9–13 Hz.[12] The observed value of 6 Hz, however, is consistent with a conformation of **12** in which the angle between H_A and H_C is approximately 45 °. A molecular model of such a conformation shows that the angles between H_D and the methylene hydrogens H_E and H_F are approximately 80 and 170°, respectively. The H_D–H_E and H_D–H_F coupling constants of 5.5 and 13.5 Hz, respectively, are consistent with this conformation in accordance with the Karplus relationship.[13]

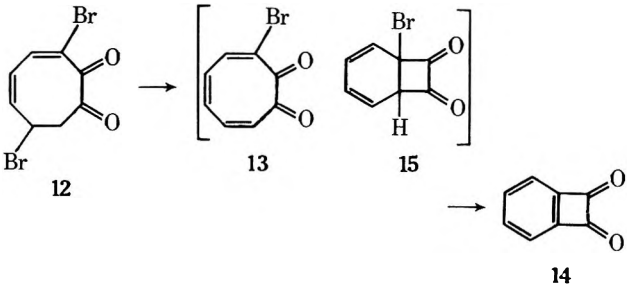
The formation of **12** from **7** may be envisioned as proceeding by a one-electron oxidation of the bis enol of **7** followed by rearrangement of the resultant radical and bromination as depicted in Scheme II.

Dehydrobromination of **12** was expected to lead to the formation of 3-bromocyclooctatriene-1,2-dione (**13**). Treatment of **12** with an excess of triethylamine in chloroform produced an immediate reaction. The infrared spectrum of the reaction mixture showed carbonyl absorption identical with that of benzocyclobutadienequinone (**14**) and lacked the carbonyl absorption of **12**. Use of a deficient quantity of base resulted in a mixture of **12** and **14**. Infrared and ^1H NMR spectra of this mixture failed to demonstrate the presence of additional identifiable components. The conversion of **12** to

Scheme II



Scheme III

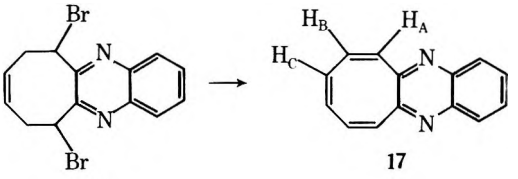


14

14, however, clearly implicates the intermediacy of **13** and its bicyclic tautomer **15**.

The failure to isolate a 1,2-cyclooctatrienedione by dehydrobromination of an appropriate precursor indicated that this system may be quite labile and suggested the selection of a carbonyl substituted derivative of **1** as a synthetic target. Toward this end quinoxaline **16** was prepared by the action of *o*-phenylenediamine on **2**. Dehydrobromination of **16** with 1,5-diazabicyclo[4.3.0]nonene-5 afforded **17**, the quinoxaline derivative of **1**.

Scheme IV



16 **17**

The ^1H NMR spectrum ($CDCl_3$) of **17** shows an aromatic AA'BB' pattern centered at δ 7.92 which corresponds to the benzenoid hydrogens. The α-imino hydrogen, H_A, appears at δ 6.88 as a doublet of an AB quartet (J = 11.5 Hz). The other half of the AB quartet at δ 6.43 arises from H_B and appears as a doublet of doublets (J = 1.5 Hz) due to coupling to H_C, the latter appearing as a doublet at δ 6.15. The small coupling constant between H_B and H_C indicates a nonplanar structure[12] for the eight-membered ring of **17**.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 237B spectrophotometer. The NMR spectra were obtained using a Varian T-60 spectrometer with chemical shifts reported as δ values measured from an internal standard of tetramethylsilane. The uv spectra were recorded on a Unicam Model SP-800 spectrophotometer using 1-cm quartz cells. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6 mass spectrometer. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., or Galbraith Laboratories, Inc., Knoxville, Tenn. Molecular models were constructed from Framework Molecular Models by Prentice-Hall, Englewood Cliffs, N.J.

5-Cyclooctene-1,2-dione (5). A three-neck, 1-l., round-bottom

flask equipped with a mechanical stirrer and a reflux condenser was charged with 52.7 g (0.375 mol) of 2-hydroxy-5-cyclooctenone, 168 g (0.84 mol) of cupric acetate monohydrate, 35 ml of methanol, and 420 ml of 50% aqueous acetic acid. The mixture was heated to reflux with stirring for 2 h. After cooling the solid material was filtered and washed with water and ether. The combined filtrate and washes were poured into 500 ml of saturated sodium chloride solution. The aqueous solution was then extracted with six 100-ml portions of ether. The combined extracts were washed with saturated sodium bicarbonate solution until neutral and then with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate the ether was removed. The resulting yellow oil was distilled under reduced pressure yielding 26.4 g (51%) of 5-cyclooctene-1,2-dione: bp 56–57 °C (0.5 mm); mp 35–36.5 °C; ir ($CHCl_3$) 3050 (C–H), 1723, 1708, and 1692 cm^{-1} (C=O); NMR ($CDCl_3$) δ 5.88 (m, 2, olefinic) and 2.53 (m, 8, allylic and α-carbonyl); uv max (cyclohexane) 230 nm (ϵ 99), 281 (35.6), 288 (33.3), and 345 (17.2); mass spectrum (70 eV) *m/e* 138 (parent), 110 (– CO), and 82 (– 2CO).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.62; H, 7.30. Found: C, 69.40; H, 7.16.

***trans*-3,8-Dibromo-5-cyclooctene-1,2-dione (2).** A three-neck, 500-ml, round-bottom flask equipped with a magnetic stirrer, a gas inlet tube, and a reflux condenser was charged with 6.9 g (0.05 mol) of 5-cyclooctene-1,2-dione, 44.6 g (0.2 mol) of cupric bromide, and 200 ml of a 1:1 ethyl acetate–chloroform solution. The mixture was stirred under nitrogen for 15 min at room temperature and then at 75 °C for 12 h. Upon cooling the cuprous bromide was filtered and washed with chloroform. The combined organic phases were washed with water until neutral followed by a wash with saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvents were removed giving a brown solid material. Trituration with cyclohexane removed the brown material affording white crystals. Recrystallization of the crude product from methylene chloride–cyclohexane provided 5.0 g (34%) of dibromide **2**, mp 136–139 °C. An analytical sample was obtained by sublimation: mp 138–141 °C; ir ($CHCl_3$) 3000, 2925 (C–H), and 1740, 1727 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.07 (m, 2, olefinic), 5.15 (ABX quartet, 2, CHBr), and 2.90 (m, 4, allylic); uv max (cyclohexane) 288 nm (ϵ 244), 280 (302), and 224 (742); mass spectrum (70 eV) *m/e* 298, 296, 294 (parent).

Anal. Calcd for $C_8H_8Br_2O_2$: C, 32.46; H, 2.73. Found: C, 32.71; H, 2.82.

3-Bromo-2-hydroxy-2,5,7-cyclooctatrienone (7). A solution of 3.0 g (0.01 mol) of 3,8-dibromo-5-cyclooctene-1,2-dione in 70 ml of dry hexamethylphosphoric triamide was maintained at 80 °C with stirring for 18 h. The yellow-red solution was poured into 500 ml of saturated sodium chloride solution and extracted with four 100-ml portions of cyclohexane. The extracts were washed with two 150-ml portions of water and then saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure provided 0.8 g of a red-brown semisolid which was chromatographed on silica acid eluting with carbon tetrachloride–benzene (10:2). Fractions 6–18 (20 ml) afforded 0.325 g (15%) of ketone **7**. Sublimation of the crude product afforded **7** as white crystals: mp 101–103 °C; ir ($CHCl_3$) 3365 (O–H), 1662 (C=O), 1622 and 1600 cm^{-1} (C=C); NMR ($CDCl_3$) δ 7.86 (s, 1, hydroxyl), 6.64 (m, 3, H_6, H_8), 6.73 (q, J = 8 Hz, 1, H_5), and 3.16 (br m, 2, allylic); uv max (cyclohexane) 297 nm (ϵ 5×10^3), 254 (1.27×10^4), 246 (1.23×10^4), 239 (1.04×10^4), and 198 (6.55×10^3); mass spectrum (70 eV) *m/e* 216, 214 (parent).

Anal. Calcd for $C_8H_7BrO_2$: C, 44.69; H, 3.28. Found: C, 44.65; H, 3.27.

3,7-Dibromo-3,5-cyclooctadiene-1,2-dione (12). A solution of 108.7 mg (0.5 mmol) of 3-bromo-2-hydroxy-2,5,7-cyclooctatrienone and a catalytic amount of benzoyl peroxide in 15 ml of carbon tetrachloride and 89.0 mg (0.5 mmol) of *N*-bromosuccinimide was heated to reflux with simultaneous irradiation with a sun lamp for 30 min. The succinimide was filtered upon cooling and the solvent removed under reduced pressure. The residue was purified by preparative thin layer chromatography on silicic acid eluting with benzene–methylene chloride (10:12). There was obtained 125 mg (85%) of dione **12** as a yellow, crystalline material. An analytical sample was obtained by sublimation: mp 106–109 °C; ir ($CHCl_3$) 1724, 1677 (C=O), and 1575 cm^{-1} (C=C); NMR ($CDCl_3$) δ 7.68 (d, 1, olefinic, H_A), 6.55 (d of d, 1, olefinic, H_B), 5.95 (d of d, 1, olefinic, H_C), 5.23 (heptet, 1, bromomethine, H_D), 3.84 (d of d, 1, α-carbonyl, H_E), and 3.22 (t, 1, α-carbonyl, H_F); uv max (cyclohexane) 299 nm (ϵ 7.5×10^3), 235 (3.83×10^3), and 212 (6.47×10^3); mass spectrum (70 eV) *m/e* 296, 294, 292 (parent).

Anal. Calcd for $C_8H_6Br_2O_2$: C, 32.65; H, 2.04. Found: C, 32.68; H, 2.11.

Reaction of 3,7-Dibromo-3,5-cyclooctadiene-1,2-dione (12) and Triethylamine (14). To a solution of 100 mg (0.47 mmol) of 3,7-dibromo-3,5-cyclooctadiene-1,2-dione in 0.4 ml of deuterated chloroform was added one drop of triethylamine. The solution immediately turned light brown. The NMR spectrum of the reaction mixture showed absorptions corresponding to the starting material and benzocyclobutadienedione. The ir spectrum of the reaction mixture exhibited the carbonyl absorptions characteristic of **14**. Thin layer chromatographic analysis of the reaction mixture on silicic acid eluting with chloroform demonstrated the presence of **14** as the only identifiable product.

2,7-Dibromo-10,11-benzo-9,12-diazabicyclo[6.4.0]-4,8,10,12-dodecatetraene (16). To a solution of 3.4 g (1.5 mmol) of 3,8-dibromo-5-cyclooctene-1,2-dione in 140 ml of glacial acetic acid was added a solution of 1.24 g (1.5 mmol) of freshly distilled *o*-phenylenediamine in 40 ml of glacial acetic acid. The resulting solution was stirred at room temperature for 24 h. The solution was poured into 500 ml of water and extracted with four 100-ml portions of ether. The extracts were washed with water, saturated sodium bicarbonate solution, water, and saturated sodium chloride solution and then dried over anhydrous sodium sulfate. Removal of the solvent gave 3.9 g (72%) of quinoxaline **16** as a white powder, mp 177–182 °C. An analytical sample was prepared by sublimation: mp 180–182 °C; ir ($CHCl_3$) 2975 cm^{-1} (C–H); NMR ($CDCl_3$) δ 8.00 (AA'BB' pattern, 4, aromatic), 5.93 (t, J = 9 Hz, 2, CHBr), 5.54 (t, J = 4 Hz, 2, olefinic), and 3.30 (m, 4, allylic); mass spectrum (70 eV) *m/e* 370, 368, 366 (parent).

Anal. Calcd for $C_{14}H_{12}Br_2N_2$: C, 45.69; H, 3.29. Found: C, 45.72; H, 3.28.

10,11-Benzo-9,12-diazabicyclo[6.4.0]-2,4,6,8,10,12-dodecahexene (17). To a solution of 3.68 g (10 mmol) of quinoxaline **16** in 85 ml of dimethyl sulfoxide was added a solution of 2.5 g (20 mmol) of 1,5-diazabicyclo[4.3.0]nona-5-ene in 25 ml of dimethyl sulfoxide and the resulting solution was stirred at room temperature for 18 h. The reaction mixture was poured into 500 ml of water and extracted with five 100-ml portions of methylene chloride. The extracts were washed well with water and saturated sodium chloride solution and then dried over anhydrous sodium sulfate. Removal of the solvent gave 1.6 g of a red powder which was chromatographed on neutral alumina eluting with benzene. The first three 20-ml fractions which were collected consisted of a mixture of starting material and product. Subsequent fractions upon removal of the solvent provided 1.0 g (48.5%) of quinoxaline **17** as a very light yellow powder. An analytical sample was prepared by recrystallization from pentane: mp 143–145 °C; NMR ($CDCl_3$) δ 7.94 (AA'BB' pattern, 4, aromatic), 6.88 (d of AB quartet, J = 11.5 Hz, 2, H_A), 6.43 (coupled d of AB quartet, J = 1.5 Hz, 2, H_B), and 6.15 (d, 2, H_C); uv max (cyclohexane) 354 nm (ϵ 3.09×10^4), 334 (5.15×10^3), 284 (4.12×10^3), 245 (227×10^4), and 205 (2.78×10^4); mass spectrum (70 eV) *m/e* 206 (parent).

Anal. Calcd for $C_{14}H_{10}N_2$: C, 81.62; H, 4.89. Found: C, 81.54; H, 4.84.

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Registry No.—**1**, 20665-78-5; **2**, 60183-99-5; **4**, 57858-30-7; **5**, 35353-89-0; **7**, 60184-00-1; **12**, 60184-01-2; **14**, 6383-11-5; **16**, 60184-02-3; **17**, 262-86-2; o-phenylenediamine, 95-54-5.

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Synthesis of Monosubstituted 1,3,4-Oxadiazolidine-2,5-diones

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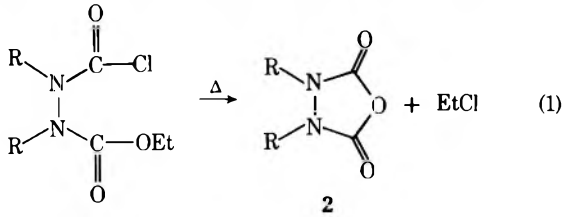
Monosubstituted 1,3,4-oxadiazolidine-2,5-diones **7** (diazasuccinic anhydrides), desired by us as precursors of cyclic diacylhydrazyl radicals, have never been reported. Although structurally simple, they cannot be prepared by the routes that suffice for the synthesis of disubstituted analogues **2**, themselves only recently prepared. Hurd and Cesark[1] found that pyrolysis of 2-carbethoxy-1,2-dialkylhydrazinecarbonyl chlorides **1** [R = CH_3, CH_3CH_2, $(CH_3)_2CH$] at 140–180 °C



(1)

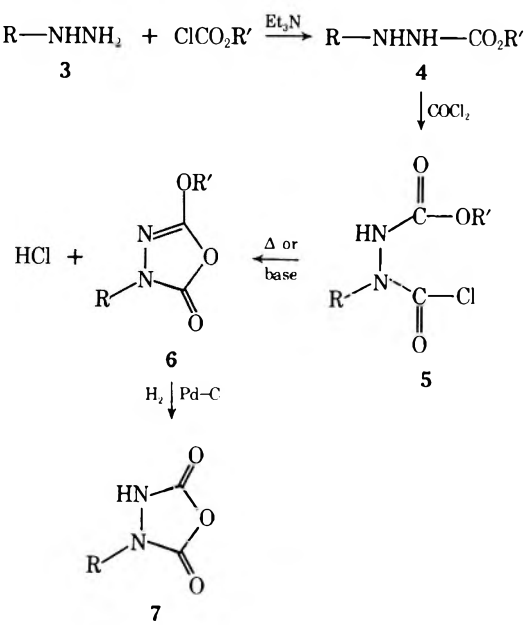
1 **2**

provides dialkyl diazasuccinic anhydrides (**2**) in quantitative yields (eq 1). Henderson and Zweig[2] reported that diphenyldiazasuccinic anhydride **2** (R = C_6H_5) could be made in 35% yield by the copper(II)-catalyzed pyrolysis of the corresponding hydrazinecarbonyl chloride (**1**).

Pyrolysis of 2-carbethoxy-1-phenylhydrazinecarbonyl chloride (**5d**) afforded, not the desired monosubstituted diazasuccinic anhydride, but Δ^2-1,3,4-oxadiazolin-5-one **6d**, via the loss of hydrogen chloride.[3] Unsurprisingly, attempts to remove the ethyl groups from this product by either acid- or base-catalyzed hydrolysis were unsuccessful, resulting instead in ring cleavage. Replacement of the ethyl group with benzyl, it was felt, would allow the latter to be removed under potentially mild conditions. Pyrolysis of carbobenzyloxyhydrazinecarbonyl chloride **5e** affords hydrogen chloride and a gum in which none of the desired oxadiazolinone could be detected (NMR). Base-induced cyclization of **5e** with ethyldiisopropylamine provides oxadiazolinone **6e** in high yield. Hydrogenolysis (palladium on carbon) occurs rapidly to give oxadiazolidinedione **7a** in good yield. Phenyldiazasuccinic anhydride **7a**, a crystalline solid, turns yellow and decomposes after a few months at room temperature. α-Cumylhydrazinecarbonyl chloride **5f** did not cyclize when treated with ethyldiisopropylamine. However, treatment of **5f** with lithium diisopropylamide affords, after workup, a brown semisolid product, from which analytically pure α-cumyloxadiazolinone **6f** was obtained chromatographically. Hydrogenolysis of **6f** affords oxadiazolidinedione **7b** (22%), as a white solid that began to decompose within a week at 25 °. Similarly, *tert*-butyloxadiazolinone **6g** was made by lithium diisopropylamide treatment of *tert*-butylhydrazinecarbonyl chloride **5g**. Hydrogenolysis of **6g** affords a white solid that was shown by NMR to be a 1:1 mixture of *tert*-butyloxadiazolidinedione **7c** and *tert*-butylhydrazine (**3c**). Presumably, hydrolytic decomposition of the diazasuccinic anhydride via loss of carbon dioxide gives rise to *tert*-butylhydrazine. A solid containing ca. 85% of oxadiazolidinedione **7c** was obtained by washing the impure solid with 1:1 benzene–pentane. Within a few days at room temperature, the diazasuccinic anhydride had partially decomposed as judged by an increase in relative size of the *tert*-butylhydrazine NMR signals.

These monosubstituted diazasuccinic anhydrides decompose on standing at room temperature. However, the benzyloxyoxadiazolinone precursors **6** are appreciably more stable to storage at room temperature.

Scheme I



a, R = Ph
b, R = PhC(Me)$_2$
c, R = *t*-Bu
d, R = Ph; R′ = Et
e, R = Ph; R′ = $PhCH_2$
f, R = PhC(Me)$_2$; R′ = $PhCH_2$
g, R = *t*-Bu; R′ = $PhCH_2$

Experimental Section

Benzyl 3-Phenylcarbazate (4e). After cooling a solution of phenylhydrazine (**3a**, 50.8 g, 0.471 mol) and triethylamine (49.6 g, 0.491 mol) in THF (960 ml) to −5 °C in an ice–acetone bath, a solution of benzyl chloroformate (82.15 g, 0.482 mol) in THF (480 ml) was added with mechanical stirring at a rate that maintained a temperature below 0 °C. When the addition was complete, the reaction mixture was allowed to warm to room temperature. Filtration and concentration of the filtrate in vacuo afforded 116.59 g of a brown-red solid. Recrystallization from ethanol provided 69.18 g (0.286 mol, 60.6%) of a white solid: mp 94.5–96.5 °C; ir ($CHCl_3$) 3420 and 3380 (NH), 3035 (CH), 1742 (C=O), 1607, 1500, 1482, 1240 (C–O), 1180, 790, and 700 cm^{-1}; NMR ($CDCl_3$) 5.08 (s, 2, OCH_2Ph), 5.51 (s, 1, PhNHN), and 6.4–7.6 ppm (m, 11, C_6H_5 and CONHN); mass spectrum (70 eV) *m/e* (rel intensity) 242 (15, M^+), 108 (6), 107 (61), 93 (5), 92 (12), 91 (100), 77 (17), 65 (14), 51 (7), and 39 (7).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.23; H, 5.76; N, 11.67.

Benzyl 3-α-Cumylcarbazate (4f). α-Cumylcarbazate **4f** was prepared from α-cumylhydrazine[4] (**3b**, 25.66 g, 0.171 mol) and benzyl chloroformate (30.2 g, 0.177 mol) in a manner similar to that used to prepare phenylcarbazate **4e**. The crude solid product was purified (three times) by dissolution in carbon tetrachloride and precipitation by pentane addition to afford a white solid: mp 51–52 °C; ir ($CHCl_3$) 3440, 3380, and 3320 (NH), 3020 and 2995 (CH), 1730 (C=O), 1455, 1380 (CMe_2), 1374 (CMe_2), 1255 (C–O), 1175, 1152, 788, and 705 cm^{-1}; NMR ($CDCl_3$) 1.42 [s, 6, $C(CH_3)_2$], 3.82 (s, 1, CNHN), 5.06 (s, 2, $PhCH_2O$), 5.84 (s, 1, NNHCO), and 7.1–7.6 ppm (m, 10, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 284 (4, M^+), 166 (9), 120 (12), 119 (100), 92 (8), 91 (77), 79 (7), 77 (8), 65 (9), 41 (13), and 28 (9).

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.59; H, 6.93; N, 9.87.

Benzyl 3-*tert*-Butylcarbazate (4g). *tert*-Butylcarbazate **4g** (14.52 g, 65.3 mmol) was prepared in 65% yield from *tert*-butylhydrazine[5] (**3c**, 8.82 g, 100 mmol) and benzyl chloroformate (17.10 g, 100 mmol) in a manner analogous to that used to prepare phenylcarbazate **4e**. The crude yellow product was washed with pentane to afford an off-white solid, mp 73.5–76.5 °C. An analytical sample was recrystallized from benzene: mp 74–76 °C; ir ($CHCl_3$) 3435, 3395, and 3210 (NH), 3025 and 2980 (CH), 1723 (C=O), 1470, 1442, 1395 (CMe_3), 1369 (CMe_3), 1258 (C–O), 1150, and 702 cm^{-1}; NMR ($CDCl_3$) 1.05 [s, 9, $C(CH_3)_3$], 5.11 (s, 2, $PhCH_2O$), and 7.32 ppm (s, 5, C_6H_5); mass spectrum (70 eV) *m/e* (rel intensity) 222 (9, M^+), 92 (9), 91 (100), 87 (41), 65 (8), 56 (69), 41 (9), 29 (5).

Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.59; H, 8.11; N, 12.66.

2-Carbethoxy-1-phenylhydrazinecarbonyl Chloride (5d). To a stirred solution of phosgene (37.7 g, 0.381 mol) in anhydrous ether (40 ml) at 0 °C was added a solution of ethyl 3-phenylcarbazate[6] (**4d**, 13.52 g, 0.075 mol) in anhydrous ether (100 ml), causing a solid to form. While being stirred at 30 °C overnight, this solid dissolved. Addition of pentane caused the product to precipitate as a white solid. Recrystallization from 1:1 benzene–cyclohexane afforded 14.76 g (0.061 mol, 81.1%) of a white solid: mp 96.5–98 °C; ir (KBr) 3270 (NH), 2990 (CH), 1755 (C=O), 1497, 1290, 1255, 1118, 1056, 819, 751, and 703 cm^{-1}; NMR ($CDCl_3$) 1.24 (t, 3, J = 7 Hz, OCH_2CH_3), 4.18 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), 7.2–7.5 (m, 5, C_6H_5), and 8.28 ppm (s, 1, CONHN); mass spectrum (70 eV) m/e (rel intensity) 244 (8, M + 2), 242 (26, M^+), 179 (9), 170 (11), 169 (8), 136 (5), 135 (25), 119 (12), 108 (8), 107 (100), 106 (11), 105 (19), 91 (17), 79 (8), 78 (11), 77 (81), 65 (5), 64 (9), 63 (6), 51 (22), 29 (62), 28 (5), and 27 (11).

Anal. Calcd for $C_{10}H_{11}ClN_2O_3$: C, 49.50; H, 4.57; Cl, 14.61; N, 11.54. Found: C, 49.72; H, 4.38; Cl, 14.91; N, 11.54.

2-Carbobenzyloxy-1-phenylhydrazinecarbonyl Chloride (5e). A solution of phenylcarbazate **4e** (52.56 g, 0.215 mol) in THF (150 ml) was treated with a solution of phosgene (63.3 g, 0.64 mol) in THF (300 ml) in a manner similar to that used to prepare carbethoxyhydrazinecarbonyl chloride **5d**. Removal of the solvent at reduced pressure gave 67.24 g of a light yellow solid. Recrystallization from carbon tetrachloride afforded 54.59 g (0.179 mol, 83.3%) of a white solid: mp 104–106 °C; ir ($CHCl_3$) 3410 (NH), 3040 and 2965 (CH), 1758 (C=O), 1495, 1283, 1240, and 700 cm^{-1}; NMR ($CDCl_3$) 5.16 (s, 2, $PhCH_2O$), 7.30 (s, 5, $C_6H_5CH_2$), 7.35 (s, 5, C_6H_5N), and 7.68 (s, 1, CONHN); mass spectrum (70 eV) m/e (rel intensity) 306 (1.2, M + 2), 304 (4.8, M^+), 224 (5), 197 (5), 92 (9), 91 (100), 77 (9), and 65 (7).

Anal. Calcd for $C_{15}H_{13}ClN_2O_3$: C, 59.12; H, 4.30; Cl, 11.63; N, 9.19. Found: C, 58.68; H, 4.32; Cl, 11.90; N, 9.17.

2-Carbobenzyloxy-1-α-cumylhydrazinecarbonyl Chloride (5f). A solution of α-cumylcarbazate **4f** (16.27 g, 57.2 mmol) in THF (115 ml) was treated with a solution of phosgene (13.2 g, 133 mmol) in THF (30 ml) in a manner similar to that used to prepare phenylhydrazinecarbonyl chloride **5d**. Removal of the solvent at reduced pressure gave a viscous brown oil which afforded, after vacuum drying, 23.60 g (119%) of a brown gum that could not be induced to crystallize or further purified: NMR ($CDCl_3$) 1.59 [s, $C(CH_3)_2$], 1.73 [s, $C(CH_3)_2$], 5.19 (s, $PhCH_2O$), 7.0–7.6 (m, C_6H_5), and 7.86 ppm (s, CONHN).

2-Carbobenzyloxy-1-*tert*-butylhydrazinecarbonyl Chloride (5g). A solution of *tert*-butylcarbazate **4g** (9.92 g, 44.6 mmol) in THF (45 ml) was treated with a solution of phosgene (9.4 g, 95 mmol) in THF (45 ml) in a manner analogous to that used to prepare **5d**. Concentration in vacuo and vacuum drying afforded 12.80 g (100.7%) of an off-white solid. Recrystallization from carbon tetrachloride afforded a white solid: mp 95–96.5 °C; ir ($CHCl_3$) 3410 (NH), 3035 and 2985 (CH), 1754 (C=O), 1483, 1398 (CMe_3), 1368 (CMe_3), 1246, 1200 (C–O), 1044, 1025, and 697 cm^{-1}; NMR ($CDCl_3$) 1.31 and 1.41 [2 s, 9, $C(CH_3)_3$], 5.15 (s, 2, $PhCH_2O$), and 7.09 ppm (s, 5, C_6H_5); mass spectrum 70 eV) m/e (rel intensity) 286 (weak, M + 2), 284 (weak, M^+), 228 (3), 92 (9), 91 (100), 65 (6), 57 (52), 41 (9), and 29 (6).

Anal. Calcd for $C_{13}H_{17}ClN_2O_3$: C, 54.84; H, 6.02; Cl, 12.45; N, 9.84. Found: C, 54.95; H, 5.92; Cl, 12.92; N, 9.81.

2-Ethoxy-4-phenyl-Δ²-1,3,4-oxadiazolin-5-one (6d). Phenylhydrazinecarbonyl chloride **5d** was heated at 150 °C until gas evolution ceased. The cooled melt was recrystallized from ethanol to afford oxadiazolinone **6d** as white needles: mp 67.5–69 °C; ir ($CHCl_3$) 3000 (CH), 1798 (C=O), 1662 (C=N), 1505, 1390, 1375, 1355, 955, and 888 cm^{-1}; NMR ($CDCl_3$) 1.46 (t, 3, J = 7 Hz, OCH_2CH_3), 4.43 (q, 2, J = 7 Hz, $CO_2CH_2CH_3$), and 7.05–7.85 (m, 5, C_6H_5); mass spectrum (70 eV) m/e (rel intensity) 207 (7, M^+), 206 (50), 178 (53), 134 (18), 105 (19), 92 (10), 91 (100), 77 (70), 64 (11), 51 (26), 29 (50), and 27 (17).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.08; H, 4.90; N, 13.60.

2-Benzyloxy-4-phenyl-Δ²-1,3,4-oxadiazolin-5-one (6e). A solution of carbobenzyloxyhydrazinecarbonyl chloride **5e** (54.59 g, 0.179 mol) and ethyldiisopropylamine (27.20 g, 0.21 mol) in THF (680 ml) was stirred at 30 °C. After 1 h, a solid had begun to form; stirring was continued for an additional 1.5 h. The reaction mixture was washed with 5% hydrochloric acid, 10% sodium bicarbonate, and saturated sodium chloride, and dried over anhydrous magnesium sulfate. Filtration and concentration provided 48.34 g of crude product as an off-white solid. Recrystallization from ethanol furnished 36.59 g (0.136 mol, 76.2%) of a slightly off-white solid: mp 86–88.5 °C; ir ($CHCl_3$) 3080, 3045, and 2965 (CH), 1798 (C=O), 1663 (C=N), 1508, 1377, 1359, 939, 909, and 701 cm^{-1}; NMR ($CDCl_3$) 5.29 (s, 2, $PhCH_2O$), and 7.0–7.9 ppm (m, 10, C_6H_5); mass spectrum (70 eV) m/e (rel intensity) 268 (3, M^+), 92 (10), 91 (100), 77 (5), and 65 (7).

Anal. Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 66.86; H, 4.38; N, 10.40.

2-Benzyloxy-4-α-cumyl-Δ²-1,3,4-oxadiazolin-5-one (6f). A solution of lithium diisopropylamide was prepared at 0 °C from a solution of diisopropylamine (7.05 g, 69.8 mmol) in anhydrous ether (75 ml) and ethereal methyllithium (33.4 ml of 2 M, 66.8 mmol). When the effervescence had stopped, the solution was stirred for 15 min at 0 °C and then cooled to below −60 °C in a dry ice–acetone bath. A solution of α-cumylhydrazinecarbonyl chloride **5f** (23.60 g, 68.1 mmol) in THF (150 ml) was added to the ethereal lithium diisopropylamide at a rate that maintained the temperature below −60 °C. When the addition was complete, the reaction mixture was allowed to warm to room temperature and then stirred for 2 h. This solution was washed with 5% hydrochloric acid, 10% sodium bicarbonate, and saturated sodium chloride, and dried over anhydrous magnesium sulfate. Filtration and concentration gave 18.85 g of a brown semisolid, that was chromatographed on silica gel with chloroform. Collection and concentration of the mobile yellow band afforded a light yellow solid. After vacuum drying, 13.79 g (44.4 mmol, 64.3%) of product was obtained: mp 57.5–60 °C; ir ($CHCl_3$) 3035 and 2995 (CH), 1790 (C=O), 1675 (C=N), 1423, 1396 (CMe_2), 1374 (CMe_2), 1355, 1322, 940, 902, and 700 cm^{-1}; NMR ($CDCl_3$) 1.95 [s, 6, $C(CH_3)_2$], 5.10 (s, 2, $PhCH_2O$), 7.25 and 7.29 (2 s, 10, C_6H_5); mass spectrum (70 eV) m/e (rel intensity) 119 (31), 92 (8), 91 (100), 65 (8), and 41 (9).

Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.87; H, 5.97; N, 9.25.

2-Benzyloxy-4-*tert*-butyl-Δ²-1,3,4-oxadiazolin-5-one (6g). A solution of *tert*-butylhydrazinecarbonyl chloride **5g** (2.85 g, 10.0 mmol) in anhydrous ether (20 ml) was treated with ethereal (15 ml) lithium diisopropylamide (10.2 mmol) as described for α-cumyloxadiazolinone **6f**. After workup, 2.43 g of a yellow solid was obtained. Washing with pentane afforded 2.33 g (9.4 mmol, 93.9%) of a white solid: mp 78–80 °C; ir ($CHCl_3$) 3035 and 2990 (CH), 1786 (C=O), 1653 (C=N), 1423, 1354, 1320, 932, 910, and 697 cm^{-1}; NMR ($CDCl_3$) 1.48 [s, 9, $C(CH_3)_3$], 5.22 (s, 2, $PhCH_2O$), and 7.38 ppm (s, 5, C_6H_5); mass spectrum (70 eV) m/e (rel intensity) 248 (1, M^+), 92 (8), 91 (100), 65 (7), and 57 (10).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 63.02; H, 6.35; N, 11.40.

3-Phenyl-1,3,4-oxadiazolidine-2,5-dione (7a). A solution of phenyloxadiazolinone **6e** (5.15 g, 19.2 mmol) in ethyl acetate (95 ml) was shaken with 5% palladium on carbon (100 mg) in a Parr apparatus under an atmosphere of hydrogen (20 psi). After 15 min, hydrogen uptake had ceased. Filtration and concentration of the filtrate at reduced pressure furnished 3.37 g of a tan solid. Recrystallization from ethyl acetate gave 2.92 g (16.4 mmol, 85.4%) of an off-white solid: mp 150–155 °C dec; ir (KBr) 3450 and 3170 (NH), 2940 (CH), 1853 and 1763 (C=O), 1510, 1365, 982, 957, 843, and 760 cm^{-1}; NMR (acetone-d_6) 7.1–7.7 (m, 5, C_6H_5) and 8.60 ppm (s, 1, CONHN); mass spectrum (70 eV) m/e (rel intensity) 179 (5), 178 (46, M^+), 135 (10), 134 (100), 106 (40), 105 (47), 92 (20), 91 (100), 78 (39), 77 (86), 65 (33), 64 (55), 63 (20), 52 (19), 51 (42), 50 (17), 44 (61), 39 (22), 38 (12), and 28 (18).

Anal. Calcd for $C_8H_6N_2O_3$: C, 53.94; H, 3.39; N, 15.72. Found: C, 53.89; H, 3.32; N, 15.95.

3-α-Cumyl-1,3,4-oxadiazolidine-2,5-dione (7b). A solution of α-cumyloxadiazolinone **6f** (1.56 g, 5.0 mmol) in ethyl acetate (25 ml) was shaken overnight with 5% palladium on carbon (25 mg) under an atmosphere of hydrogen (25 psi). Filtration and concentration under reduced pressure provided 1.17 g of a light yellow solid. When washed with carbon tetrachloride, 0.70 g of an off-white solid remained. Recrystallization from benzene afforded 0.24 g (1.1 mmol, 21.8%) of a white solid: mp 94–95 °C dec; ir ($CHCl_3$) 3370 (NH), 3030 and 3000 (CH), 1850 and 1780 (C=O), 1338, 962, and 708 cm^{-1}; NMR ($CDCl_3$) 1.84 [s, 6, $C(CH_3)_2$], 6.7 (s, 1, CONH), and 7.38 (s, 5, C_6H_5); mass spectrum (70 eV) m/e (rel intensity) 220 (weak, M^+), 120 (11), 119 (72), 118 (7), 117 (5), 103 (5), 91 (37), 79 (7), 77 (8), 51 (5), 44 (100, CO_2), 41 (15), 39 (5), and 28 (11).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.24; H, 5.59; N, 12.75.

3-*tert*-Butyl-1,3,4-oxadiazolidine-2,5-dione (7c). A solution of *tert*-butyloxadiazolinone **6g** (1.24 g, 5.0 mmol) in ethyl acetate (25 ml) was shaken overnight with 5% palladium on carbon (25 mg) under an atmosphere of hydrogen (20 psi). Filtration and concentration under reduced pressure afforded a yellow oil, which upon shaking with carbon tetrachloride formed a slurry. After filtration and washing (carbon tetrachloride) 0.48 g (3.0 mmol, 60%) of a white solid, mp ca. 91 °C, was obtained; NMR shows this solid to be contaminated by an

equal molar amount of *tert*-butylhydrazine. Repeated washing with 1:1 benzene–pentane afforded a solid that was 85% pure (NMR): mp 90–92 °C dec; NMR ($CDCl_3$) 1.11 (s, *tert*-butylhydrazine) and 1.40 ppm (s, 7c).

Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.57; H, 6.37; N, 17.71. Found: C, 46.17; H, 6.65; N, 18.69.

Acknowledgments. This work has been partially supported by the Alfred P. Sloan Research Foundation and the National Institutes of Health (GM 14518).

Registry No.—**3a,** 100-63-0; **3b,** 3178-39-0; **3c,** 32064-67-8; **4d,** 6233-02-9; **4e,** 40887-05-6; **4f,** 60103-93-7; **4g,** 60103-94-8; **5d,** 60103-95-9; **5e,** 60103-96-0; **5f,** 60103-97-1; **5g,** 60103-98-2; **6d,** 3711-77-1; **6e,** 60103-99-3; **6f,** 60104-00-9; **6g,** 60104-01-0; **7a,** 60104-02-1; **7b,** 60104-03-2; **7c,** 60104-04-3; benzyl chloroformate, 501-53-1; phosgene, 75-44-5; ethyldiisopropylamine, 7087-68-5; lithium diisopropylamide, 4111-54-0.

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New Syntheses of β,β-Dimethoxy Esters and Ketones by Conjugate Addition of Methanol to Some Activated Alkynes

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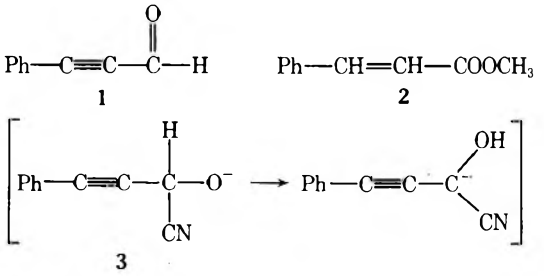
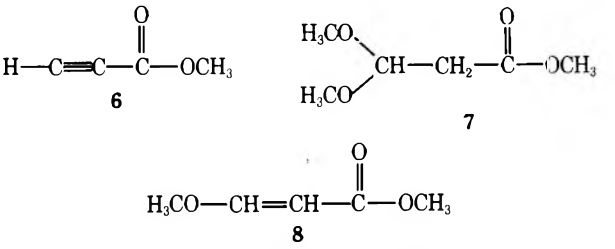
Received April 27, 1976

We have previously reported[2,3] that cyanide ion catalyzes the addition of the elements of one molecule of methanol to α,β-acetylenic aldehydes such as 3-phenyl-2-propynal (**1**), which yield a 1:1 mixture of *cis*- and *trans*-methyl 3-phenyl-2-propenoate (**2**). Others have also described[4,5] reactions of this type. A key step envisaged in the proposed[2] mechanism for this reaction is the prototropic shift of the aldehydic proton in the intermediate **3** (formed by nucleophilic attack of cyanide ion on the carbonyl group of **1**). A test of this mechanism might be made using α,β-acetylenic esters and ketones **4**, which possibly could provide the hydrocyanated product **5**. This report provides the answer to this query, at least for a few representative cases.

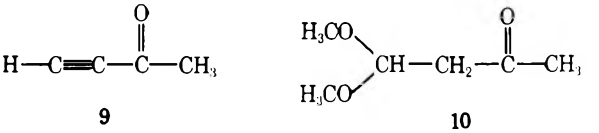


However, no product related to **5** was observed. Instead, the reaction of methyl 2-propynoate (**6**) with excess methanol using 1.2 molar equiv of sodium cyanide provided methyl 3,3-dimethoxypropanoate (**7**) as the major product (75%). When 0.1 molar equiv of sodium cyanide was used, a mixture was obtained that was predominantly ester **7** along with a lesser amount of methyl 3-methoxypropenoate (**8**). Relative yields were estimated from the infrared spectrum of the mixture. When the reaction was carried out in the presence of acetic acid, the ir spectrum of the crude reaction mixture showed the presence of a large amount of unsaturated ester **8** together with some ester **7**. The structure of ester **7** was established by comparison of boiling point and spectroscopic data with those of an authentic sample. Since the ester **7** is easily accessible by our method and has a potential aldehydic group present, it ought to be a useful bifunctional synthetic intermediate.

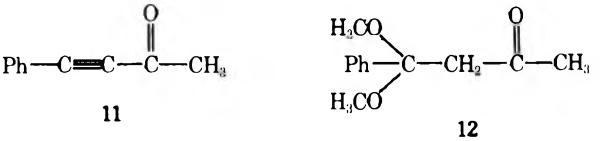


A possible mechanism for the conversion of ester **6** to **7** involves Michael addition of two molecules of methanol (presumably initiated by methoxide ion, generated by the reaction of sodium cyanide and methanol) in two steps via unsaturated ester **8**. The fact that olefinic ester **8** (prepared independently[6] by the reaction of **6** with methanol in the presence of triethylamine) on treatment with cyanide ion in methanol under these conditions also gives ester **7** supports the proposed mechanism.

It was of interest to investigate the extension of this reaction to α,β-acetylenic ketones. Treatment of commercially available 3-butyn-2-one (**9**) with 0.05 molar equiv of sodium cyanide in methanol at −10 °C for about 10 min gave 1,1-dimethoxy-3-butanone (**10**) in 88% yield; clearly, two molecules of methanol added to **9**. These reaction conditions are critical; increasing the amount of cyanide ion, temperature, and/or reaction time decreased the yield of **10**. The structure of ketone **10** was established by the identity of its ir spectrum with that of a commercial sample of 1,1-dimethoxy-3-butanone.

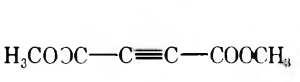


When the cyanide ion catalyzed addition reaction of methanol was carried out with 4-phenyl-3-butyn-2-one (**11**), a mixture of products was formed as indicated by the ir and NMR spectra of the crude product. Attempts to obtain a single product by variation of reaction conditions were not fruitful. It appeared that the nucleophilic nature of cyanide ion could have caused side reactions. We therefore tried next the poorly nucleophilic weak base, carbonate ion. It was gratifying to find that carbonate ion catalyzed addition of methanol to ketone **11** occurred smoothly at 0 °C to afford 1-phenyl-1,1-dimethoxy-3-butanone (**12**) in 86% yield. Expectedly, the carbonate ion also catalyzed the addition of methanol to methyl prop-2-ynoate (**6**), and 3-butyn-2-one (**9**)

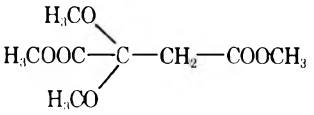


to afford ester **7** and ketone **10** in 74 and 84% yields, respectively.

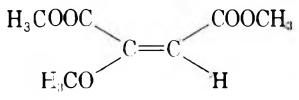
The carbonate ion catalyzed addition of methanol to dimethyl acetylenedicarboxylate (**13**) gave a 5:1 mixture of esters **14** and **15a.** A 1:2.5 mixture of cis and trans esters **15a** and



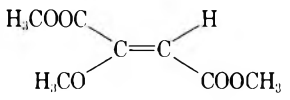
13



14



15a



15b

15b, prepared[6] by the triethylamine-catalyzed addition of methanol to **13,** on carbonate ion catalyzed addition of methanol gave results similar to those obtained with the acetylenic ester **13.** This further supports the mechanism suggested above.

Experimental Section

General. Boiling points are uncorrected. Infrared spectra were taken in chloroform solution, unless otherwise noted, with a Perkin-Elmer Model 237 infrared spectrophotometer. The NMR spectra were recorded on a Varian A-60 in chloroform-*d* solution with tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million (δ) and signals are described as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet).

Methyl 3,3-Dimethoxypropanoate (7). Method A. Cyanide Ion Catalyst. To a magnetically stirred ice-cooled solution of 8.4 g (0.1 mol) of methyl 2-propynoate (**6**) in methanol (100 ml) was added 6.4 g (0.13 mol) of sodium cyanide in 100 ml of methanol over a period of 15 min. The solution, which developed a light yellow color, was stirred at ambient temperature (about 23 °C) for 48 h. After most of the methanol was evaporated on a steam bath, the residue was diluted with ice–water, when oily globules separated. The oil was extracted with ether, and the ethereal layer washed twice with brine, dried over anhydrous Na_2SO_4, and concentrated to afford 11.1 g (75%) of crude yellow oil. Fractional distillation provided analytically pure methyl 3,3-dimethoxypropanoate (**7**): bp 79–80 °c)25 Torr) [lit.[7] bp 77 °C (20 Torr)]; ir (CCl_4) 1745 (saturated ester), 1130 (ether), transparent 2100–2300 cm^{-1} (absence of triple bond); NMR ($CDCl_3$) δ 2.67 (d, 2 H of CH_2, J = 6 Hz), 3.38 (s, 6 H of OCH_3), 3.75 (s, 3H of $-OCH_3$), 4.88 (t, 1 H of –CH, J = 6 Hz).

Method B. Carbonate Ion Catalyst. To a magnetically stirred, cooled solution (−5 to −6 °C) of 0.84 g (0.01 mol) of methyl 2-propynoate (**6**) in 12 ml of methanol was added a suspension of 0.41 g (0.003 mol) of potassium carbonate in 12 ml of methanol. After the addition no significant change in color was noticed. The solution was stirred at that temperature for an additional 24 h. The undissolved carbonate was filtered, methanol removed by heating, and the organic material extracted with ether. The dried (Na_2SO_4) ethereal extract after concentration and distillation gave 1.03 g (70%) of methyl 3,3-dimethoxypropanoate (**7**), bp 72–73 °C (18.5 Torr).

Conversion of methyl 3-methoxy-2-propenoate (8)[6] to methyl 3,3-dimethoxypropanoate (7) was carried out using conditions similar to those described above in method A. The usual workup gave crude methyl 3,3-dimethoxypropanoate (**7**) (62%) as a yellow-brown oil, the ir and NMR spectra of which were almost identical with those of pure ester **7.**

1,1-Dimethoxy-3-butanone (10). Method A. Cyanide Ion Catalyst. To a cooled (−10 °C) solution of 3-butyn-2-one (**9**, 1.36 g, 0.02 mol) in 15 ml of methanol was added dropwise a solution (0.049 g, 0.001 mol) of sodium cyanide in 8 ml of methanol. After the addition the solution developed a light yellow color and stirring was continued for an additional 8 min when the solution developed a light red color. Methanol was removed by heating, the residue extracted with ether, and the ethereal layer washed with brine, dried (Na_2SO_4), and concentrated to give 2.3 g (88%) of 1,1-dimethoxy-3-butanone (**10**). Fractional distillation gave 2.1 g (79%) of 1,1-dimethoxy-3-butanone (**10**): bp 67 °C (18 Torr) [lit.[8] bp 38 °C (2 Torr)]; ir (CCl_4) 1720 (C=O), transparent from 2100 to 2250 cm^{-1} (absence of triple bond); NMR ($CDCl_3$) δ 2.18 (s, 3 H of CH_3), 2.76 (2.18–2.71, d, 2 H of CH_2), 3.40 (s, 6 H of 2 OCH_3), and 4.86 (t, 1 H of CH). The structure was established by the superimposability of its ir spectrum on that of an authentic sample.

Method B. Carbonate Ion Catalyst. A suspension of 0.69 g (0.005 mol) of potassium carbonate in 75 ml of methanol was added to an ice-cooled solution of 3-butyn-2-one (6.8 g, 0.1 mol) in 75 ml of methanol. After a period of 15 min when the solution was very light yellow in color most of the methanol was removed on steam bath. The product was extracted with ether, and the ethereal layer washed with brine, dried over anhydrous sodium sulfate, and concentrated to afford 11.1 g (84%) of pale yellow oil. Fractional distillation gave pure product, bp 72 °C (19 Torr), the ir and NMR spectra of which were identical with those of ester **10** obtained by method A.

Reaction of 4-Phenyl-3-butyn-2-one (11) with Methanol in the Presence of Potassium Carbonate. To an ice-cooled solution of 2.88 g (0.02 mol) of 4-phenyl-3-butyn-2-one (**11**) in 30 ml of methanol was added 2.76 g (0.02 mol) of potassium carbonate in 30 ml of methanol over a period of 10 min; a deep yellow color developed. The solution was stirred in ice water for an additional 40 min; the color changed to yellowish red. The usual workup gave 3.69 g (89%) of reddish yellow oil, which upon fractional distillation afforded 3.08 g (77%) of 1,1-dimethoxy-1-phenyl-3-butanone (**12**): bp 90–96 °C (2 Torr); ir (CCl_4) 1710 cm^{-1} (ketone); NMR ($CDCl_3$) δ 1.68 (s, 3 H, CH_3 of $COCH_3$), 3.17 (s, 6 H, 2-CH_3 of OCH_3), 3.05 (s, 2 H of CH_2), and 7.40 (m, 5 H of phenyl).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.62; H, 7.54.

Reaction of Dimethyl Acetylenedicarboxylate (13) with Methanol in the Presence of Potassium Carbonate. To a solution of potassium carbonate (0.41 g, 0.003 mol) in 40 ml of methanol was added a solution of 4.26 g (0.03 mol) of dimethyl acetylenedicarboxylate in 40 ml of methanol over a period of 15 min at room temperature. After the mixture was stirred for 5 h, methanol was removed, the residue taken up in ether, and the ethereal layer washed twice with brine, dried over anhydrous sodium sulfate, and evaporated, leaving 4.85 g of light yellow liquid, which was fractionally distilled to yield 4.25 g of an oil: bp 129 °C (13 Torr); ir ($CHCl_3$) 1750 (s, –COOR), 1720 (m, unsaturated ester), 1620 (s, olefinic), and 1145 cm^{-1} (s, ether); NMR ($CDCl_3$) δ 3.0 (s, 2 H of $-CH_2$), 3.3 (s, 2 CH_3 of OCH_3), 3.68 (s, CH_3 of $COOCH_3$), and 5.28 (s, 1 H of CH). The value at δ 5.28 is assigned[6] to the olefinic proton in cis ester **15a,** while the signal at δ 3.0 is assigned to the methylene proton in methyl 3,3-dimethoxy-3-carbomethoxypropanoate (**14**). Integration showed the two esters **15a** and **14** to be present in the ratio of 1:5.

Reaction of Methyl *cis*- and *trans*-3-Methoxy-3-carbomethoxy-2-propenoate (15a and 15b)[6] with Methanol in the Presence of Potassium Carbonate. A solution of cis and trans esters **15a** and **15b** (4.35 g, 0.025 mol) was subjected to dropwise addition of potassium carbonate solution (0.33 g, 0.0025 mol in 40 ml of methanol) at room temperature. The resulting mixture was stirred for an additional 5 h. The usual workup gave 4.38 g of colorless, oily material which was fractionally distilled to yield 4.0 g of material, bp 128–129 °C (13 Torr). The ir and NMR spectra for this material were identical with those obtained above in the reaction of dimethyl acetylenedicarboxylate with methanol.

Acknowledgments. We thank Mr. Gordon G. Boudreaux, Southern Regional Research Laboratory, U.S. Department of Agriculture, for NMR spectra.

Registry No.—**6,** 922-67-8; **7,** 7424-91-1; **8,** 34846-90-7; **9,** 1423-60-5; **10,** 5436-21-5; **11,** 1817-57-8; **12,** 60084-52-8; **13,** 762-42-5; **14,** 2215-04-5; **15a,** 2509-14-0; **15b,** 2215-05-6; methanol, 67-56-1.

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Robinson Annelation by Reactions of 2-Methyl 1,3 Diketones with a β-Chloro Ketone

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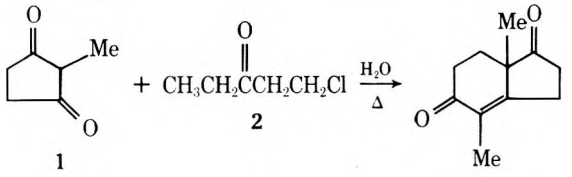
Recently we reported that octalones could be obtained by reaction of a β-chloro ketone[2] with 2-methylcyclohexanone in the presence of an acid in benzene. We now report that a Robinson annelation reaction can be achieved by reaction of 2-methylcyclopentane-1,3-dione (1) with 1-chloro-3-pentanone (2) in water to afford good yields of 7,7a-dihydro-4,7a-dimethyl-1,5(6*H*)-indandione[3] (3). In this method the 1,3



1 2 3

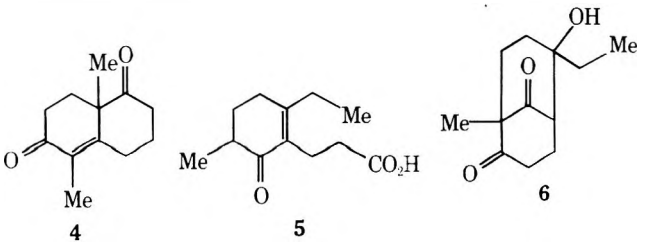
diketone serves as an acid catalyst in the in situ generation of the vinyl ketone, and the generated HCl acts as a catalyst in both the Michael and aldol steps of the reaction.

The results of the synthesis of 7,7a-dihydro-4,7a-dimethyl-1,5(6*H*)-indandione (3) using different molar ratios of 1 and 2 are summarized in Table I. As shown in Table I, the yields of 3 range from 73 to 78%.

Table I. Indandione Formation Using Different Molar Ratios

Molar ratio 1:2	% yield of 3	
	Distilled	Chromatographed
1:1	72.6	62.2
1:1.5	78.1	68

Although the indandione 3 was obtained in good yield as described above, an identical reaction employing 2-methylcyclohexane-1,3-dione and 1-chloro-3-pentanone afforded after column chromatography only 23% of 5,8a-dimethyl-3,4,8,8a-tetrahydro-1,6(2*H*,7*H*)-naphthalenedione[4,5] (4), the major compound being the keto acid[5,6] 5 (41% yield), mp 58–61 °C (known mp 59–61 °C). The keto acid 5 presumably results from opening of the bridged[7] aldol intermediate 6 followed by dehydration of the resulting β-hydroxy ketone.



4 5 6

Experimental Section

7,7a-Dihydro-4,7a-dimethyl-1,5(6*H*)-indandione (3). 2-Methylcyclopentane-1,3-dione (2.5 g, 0.022 mol) and 1-chloro-3-pentanone (4.0 g, 0.033 mol) were added to 20 ml of H_2O. The mixture was stirred at room temperature for 4 h and then refluxed for 16 h. The reaction mixture was poured into a 10% $NaHCO_3$ solution (50 ml); water (100 ml) was added and the resulting mixture was extracted with two 100-ml portions of chloroform. The chloroform extracts were washed with water, dried over anhydrous $MgSO_4$, filtered, and concentrated on a rotary evaporator. Distillation of the residue gave 3.1 g (78.1%) of 7,7a-dihydro-4,7a-dimethyl-1,5(6*H*)-indandione (3), bp 94–98 °C (0.01 mm). Chromatography of the oil (3.1 g) on silica gel and elution with ether–hexane afforded 2.7 g (68%) of pure 3: NMR (CCl_4) δ 1.30 (s, angular methyl, 3 H), 1.73 (s, 3 H), 1.78–3.09 (methylenes, 8 H); ir (neat) 1660 and 1745 cm^{-1}.

Registry No.—1, 765-69-5; 2, 32830-97-0; 3, 28255-09-6; 4, 28255-08-5; 5, 60065-15-8; 6, 60065-16-9; 2-methylcyclohexane-1,3-dione, 1193-55-1.

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(1) Undergraduate research participant.
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Air Oxidation of Cyclopentadecane

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Received November 25, 1975

The oxidation of hydrocarbons has been thoroughly studied[1-4] and it has been found that the hydroperoxide initially formed decomposes mainly by a nonchain process to yield the alcohol plus ketone.[5] It has been suggested that the alcohol is the initial product, and the ketone is formed by further oxidation. As the reaction proceeds, the alcohol and ketone are consumed with the formation of by-products (eq 1).

$$RH \xrightarrow{O_2} ROOH \rightarrow ROH \rightarrow \text{ketone} \rightarrow \text{by-products} \quad (1)$$

The selectivity of the oxidation of hydrocarbons to alcohol can be improved by the addition of boric acid[6] to the oxidation mixture. This increased selectivity was initially believed to be due to the formation of borate esters of the alcohols which retarded the oxidation of the alcohol and subsequent by-product formation.[4]

It has been proposed, however, that the function of boric acid (metaboric acid) is not solely to esterify the alcohols to protect them against oxidation, but to catalyze the decomposition of the hydroperoxides.[7-9] Indeed, it has been shown that the boric acid esters are as effective as boric acid itself in directing the oxidation of paraffins to alcohols in concentrations as low as 0.2% ester.[10]

In this note, we report our observations on the air oxidation of cyclopentadecane. The products are important precursors in musk synthesis.[11]

Results and Discussion

The results of some experiments on the air oxidation of cyclopentadecane are shown in Table I. The yields of alcohol and ketone from this cyclic hydrocarbon compare well with the yields of alcohol and ketone from the air oxidation of cyclododecane.[12] The results confirm previous observations that product yields and conversions in air oxidations are dependent on air flow rate, boric acid, and temperature among other variables.[4]

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Table I. Air Oxidation of Cyclopentadecane

Expt	Cyclopentadecane,[a] mol	Boric acid,[b] wt %	Flow rate, ml min^{-1} mol^{-1}	Time of rxn, h	Temp, °C	Convn, %	Yield, %[c,d] Cyclopentadecanone	Yield, %[c,d] Cyclopentadecanol
1	0.25	5	100	2	150	12.3	8.9	77.2
2	0.25	5	100	5	150	27.9	9.3	71.3
3	0.25	5	100	3	160	21.0	5.7	84.3
4	0.25	5	100	3	170	23.7	4.2	81.0
5	0.25	5	100	6	170	42.2	7.1	58.5
6	0.25	0	100	3	150	23.3	20.8	14.0
7	0.25	0	200	7	140	25.4	25.1	17.0
8	0.71	5	564	2	165	35.8	3.5	71.0
9	0.71	5	310	2	165	34.0	7.0	70.5
10	0.71	5	140	2	165	32.3	3.3	75.2
11	0.71	5	56	5	165	40.4	5.5	72.4
12	0.25	10	100	5	140	12.0	7.4	66.9
13	0.25	10	100	3	170	23.1	3.8	72.4

[a] 99%+ cyclopentadecane twice recrystallized from methanol. [b] Mallinckrodt AR. [c] Yield determined by VPC, 5 ft × 0.125 in. 1% Carbowax on Chromosorb W (180–120 mesh). Program run of 100–160 °C at 8 °C/min. Cyclododecanone and 16-hexadecanolide were used as internal standards. [d] We did not attempt to identify all by-products (except qualitatively by ir).

Table II. Various Workup Procedures for Cyclopentadecane Air Oxidation

No.	Procedure[a]	Yield, g[b] Cyclopentadecane	Cyclopentadecanone	Cyclopentadecanol	Material balance[c]
1	Dissolve in hexane, filter solid[d]	6.92	0.11	1.72	88
2	Dissolve in hexane, wash 10% NaOH, workup	6.74	0.11	1.66	85
3	Dissolve in hexane, wash 20% NaOH, workup	6.34	0.11	1.66	81
4	Stir with 20% NaOH 80 °C 15 min, workup	6.54	0.09	1.68	82
5	Stir with 20% NaOH 80 °C 30 min, workup	6.38	0.10	1.78	83

[a] Reaction conditions same as those of expt 3, Table I. [b] Yield determined by VPC. See footnote *c*, Table I. [c] From 10–15% by-products (acids, polyhydroxy compounds) also present. [d] The solid has mp 197–200 °C. Metaboric acid exists in three modifications having mp 236, 200.9, and 176 °C. Orthoboric acid has mp 170.9 °C. See ref 16.

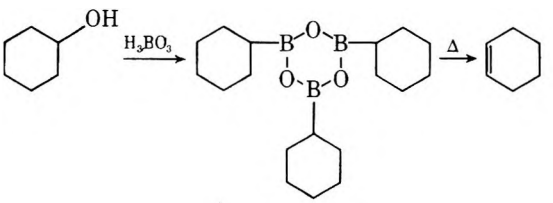
It is apparent from the table that (a) boric acid is necessary for good yields and high conversion to the alcohol; (b) an increase in concentration of boric acid over 5 wt % does not result in improved yields; (c) very high air flow rates are not necessary for good yields and high conversion (although conversion may be slightly faster).

We could detect no hydroperoxide (iodometric titration) when the air oxidation was carried out in the presence of boric acid at 150 °C. In the absence of boric acid (150 °C) a maximum of 6% (of theory) hydroperoxide is formed after 2 h. This rapidly decreases to less than 1% at 3 h. If the maximum of 6% hydroperoxide is added to the yields of products (Table I, expt 6), the total yield of products still falls short of the product yields for the air oxidation in the presence of boric acid.

The experiments were conducted according to the conditions in Table I and worked up by cooling to 80–90 °C, adding 20% sodium hydroxide or water, and refluxing for 1 h. Solvent was then added to the mixture, aqueous and organic phases were separated, and the organic phase was dried and weighed. The products were then determined by VPC.

One air oxidation mixture was split into equal portions and worked up according to the procedures shown in Table II. The yields were determined by VPC. It is immediately obvious that, for the air oxidation of cyclopentadecane under the conditions reported here, *the main portion of the alcohol is not present as a borate ester.* However, boric acid is necessary for high yields of alcohol. Also one cannot discard the possibility that *traces* of borate ester may be present.

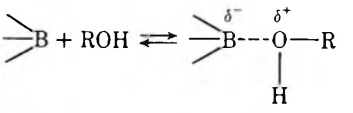
It may be reasonably argued that the borate ester cracks on the VPC column to yield the alcohol, but it is unlikely that this occurs. O'Connor and Nace have shown the borate esters decompose at high temperatures to give olefins in high yield (eq 2).[13,14]



(2)

The results presented here support the rationalization that the function of boric acid (or traces of borate ester[10]) is to catalyze the decomposition of the hydroperoxide to give mainly the alcohol.[15] Consequently, the hydroperoxide is never at a high concentration, and oxidation of the alcohol and ketone to by-products is suppressed. By-products may also arise from the hydroperoxide itself (at high concentration).[4]

We have noted in the air oxidation of cyclopentadecane that as the air oxidation progresses, the metaboric acid goes into solution. If a weak complex is formed (eq 3) or hydrogen



(3)

bonding occurs, this may help prevent oxidation of the alcohol.[17] Addition of a nonpolar solvent would precipitate the metaboric acid (Table II).

Experimental Section

A 100-ml resin flask was fitted with a heated water condenser (~65 °C), a mechanical stirrer (600 rpm), a fritted glass gas addition tube (25–50 μ pore size), and a thermometer. Cyclopentadecane (99%, 52.6 g, 0.25 mol) and 2.5 g of boric acid were placed in the flask and the reaction mixture heated slowly to 150–155 °C. The water present was driven off with the aid of air or nitrogen. The mixture was then heated to a given temperature (±2 °C) and air bubbled through the molten hydrocarbon for the required time. The reaction mixture was then cooled to ~95 °C and 25 ml of water added. (For the experiments in Table II only hexane was added.) After stirring at 95 °C for 1 h, the reaction mixture was cooled and hexane added. The mixture was transferred to a separatory funnel and the aqueous and organic layers separated. The organic phase was washed with water once more, weighed, and analyzed by VPC according to the conditions given in footnote *c*, Table I.

Registry No.—Cyclopentadecane, 295-48-7; cyclopentadecanone, 502-72-7; cyclopentadecanol, 4727-17-7.

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(14) A reviewer has suggested that the following reactions may occur on the VPC column:

$$(ROBO)_3 \rightarrow B_2O_3 + (RO)_3B$$
$$2(RO)_3B + H_3BO_3 \rightarrow (ROBO)_3 + 3ROH$$

We feel that these reactions are not significant here for the following reasons: (a) The metaboric acid (expt 1, Table II) was filtered before analysis. (b) No significant tailing of the alcohol peak was observed (which should occur if the above reactions take place on the column). (c) In the presence of boric acid, significant quantities of the olefin[13] should be observed, lowering the yield of the alcohol. Cyclopentadecene was not observed as a significant product.
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(17) See review for discussion of various suggested mechanisms: W. G. Woods and R. J. Brotherton, *Prog. Boron Chem.*, **3**, 1 (1970).

Synthesis of Authentic Tri-*O*-benzylphloroglucinol

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It is surprising that such a simple compound as the tri-*O*-benzyl ether of phloroglucinol, allegedly prepared first in 1900, has actually been synthesized as a pure, individual compound only in the present work.

The tribenzylphloroglucinol (mp 39–41 °C) reported by Kaufler[1] and quoted in the literature as such[2,3] is a mixture of several components as shown by repetition of the description[1] and TLC of the product.

Tri-*O*-benzylphloroglucinol (**1**), which is a promising intermediate in the synthesis of specially substituted flavonoids and *C*-methyl flavonoids, is obtainable by benzylation of phloroglucinol in the presence of sodium hydride. Separation from the by-product, *C*-benzyltri-*O*-benzylphloroglucinol (2,4,6-tribenzyloxydiphenylmethane) (**2**), has been achieved by TLC and column chromatography.

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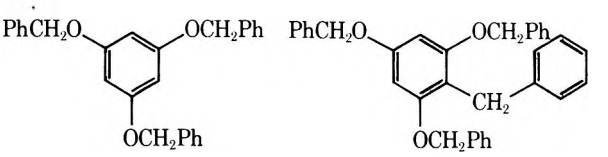

1 **2**

Rather simple spectra were obtained by NMR as evidence for the structures of **1** and **2**. These were verified by MS data.

Hydrogenation of the compound **1** in the presence of 10% Pd on carbon in glacial acetic acid yielded the starting material (phloroglucinol) which proved to be identical according to ir, TLC, and melting point with the authentic phloroglucinol.

Experimental Section

Benzylation of Phloroglucinol in the Presence of NaH. A 50% dispersion of sodium hydride in oil (1.44 g, 720 mg of NaH, 30 mmol) was gradually added to a stirred solution of anhydrous phloroglucinol (1.26 g, 10 mmol) in dimethyl sulfoxide (40 ml). After the evolution of hydrogen had ceased, benzyl chloride (3.6 ml, 30 mmol) was added to the reaction mixture. The temperature rose to about 50 °C. After stirring for about 40 min, the greenish suspension was then poured on ice (400 g), and allowed to stand overnight. The yellow powder (1.06 g) which precipitated was recrystallized from ethanol to give white needles (300 mg), mp 76–78 °C. This product was a mixture of two compounds (**1** and **2**) as shown by TLC in a 60:40 benzene–petroleum ether (bp 60–80 °C) mixture (R_f 0.6 and 0.7). Separation of this mixture by preparative TLC yielded pure tribenzylphloroglucinol, mp 96–97 °C (from ethanol), R_f 0.6, and *C*-benzyl-tri-*O*-benzylphloroglucinol, mp 101–103 °C (from ethanol), R_f 0.7. The two compounds were also separated on a silica gel column (0.05–0.20 mm) with the above solvent mixture.

$C_{27}H_{24}O_3$ (396) (compound **1**): *m/e* 396 (M^+), 91 (base); NMR ($CDCl_3$, Me_4Si) δ 5.13 (s, 6, OCH_2), 6.43 (s, 3, ArH), 7.57 (s, 15, ArH).

$C_{34}H_{30}O_3$ (486) (cmmpound **2**): *m/e* 486 (M^+), 91 (base); NMR ($CDCl_3$, Me_4Si) δ 4.21 (s, 2, $ArCH_2$), 5.16 (s, 2, OCH_2), 5.18 (s, 4, OCH_2), 6.49 (s, 2, ArH), 7.37–7.57 (m, 20, ArH).

Catalytic Debenzylation of Tri-*O*-benzylphloroglucinol. Pd/carbon (10%, 114 mg) in glacial acetic acid (20 ml) was prehydrogenated, then a solution of tribenzylphloroglucinol (63 mg, 0.16 mmol) in glacial acetic acid (10 ml) was added and the hydrogenation was continued at room temperature; 11 ml of hydrogen was absorbed (theoretical 11.5 ml). The catalyst was removed and the solution evaporated to dryness to obtain a product (18 mg), mp (after drying at 110 °C) 211–216 °C (lit. 219 °C) (anhydrous phloroglucinol), which proved to be identical with authentic phloroglucinol (TLC, ir).

Registry No.—**1**, 59434-20-7; **2**, 59434-21-8; phloroglucinol, 2041-15-8.

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A Simple Method for Converting Nitriles to Amides. Hydrolysis with Potassium Hydroxide in *tert*-Butyl Alcohol

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Many years ago it was reported that nitriles could easily be converted into amides by heating them in weakly basic medium in the presence of hydrogen peroxide.[1-3] Treatment of a nitrile with sodium hydroxide and hydrogen peroxide in aqueous ethanol has become a standard synthetic[4] and qualitative analytical procedure.[5]

Table I. Conversion of Nitriles to Amides

Nitrile	g	Registry no.	Base	g	Solvent	ml	Reaction time, min	Yield of amide, % Crude	Yield of amide, % Pure	Registry no.
Phenylacetonitrile	5	140-29-4	KOH	10	*tert*-Butyl alcohol	50	30	93.6	90.1[a]	103-81-1
Butyronitrile	5	109-74-0	KOH	10	*tert*-Butyl alcohol	50	30		53.9	541-35-5
Capronitrile	5	628-73-9	KOH	10	*tert*-Butyl alcohol	50	60	89.5	84.4[a]	628-02-4
Benzonitrile	5	100-47-0	KOH	10	*tert*-Butyl alcohol	50	20		90.3	55-21-0
3-Nicotinonitrile	5	100-54-9	KOH	10	*tert*-Butyl alcohol	50	40		51.1	98-92-0
Butyronitrile	5		KOH	10	Butyronitrile	18.5	30	42.8	25.3[b]	
Benzonitrile	5		KOH	10	Benzene	50	30		3.4	
Benzonitrile	10		KOH	10	Methyl alcohol	50	60	78.3	51.1[a]	
Benzonitrile	10		NaOH	6	Methyl alcohol	50	120	71.6	55.4[a]	
Benzonitrile	10		NaOH	12	Methyl alcohol	50	15		77.5	
Benzonitrile	5		NaOH	8	*tert*-Butyl alcohol	50	60	95.4	90.2[a]	

[a] The crude amide was washed with a few milliliters of cold petroleum ether. [b] Recrystallized from benzene.

Our interest in this reaction was stimulated when we observed that benzamide was not hydrolyzed when refluxed in *tert*-butyl alcohol containing powdered solid potassium hydroxide. Subsequently, we found that benzonitrile, when refluxed for 20 min in *tert*-butyl alcohol containing powdered potassium hydroxide, gave a 94% yield of benzamide.

Several other nitriles were also converted into amides. The data are given in Table I. In those cases where the amide was relatively water insoluble (workup was in aqueous media) yields of 85–95% were realized.

Since the potassium hydroxide is insoluble in *tert*-butyl alcohol we also tried potassium hydroxide in methyl alcohol. However, going to homogeneous solutions gave lower yields of amides and more hydrolysis to the carboxylic acid. Potassium hydroxide in benzene gave little amide. Sodium hydroxide in methanol gave moderate yields, but sodium hydroxide in *tert*-butyl alcohol proved as effective as potassium hydroxide in *tert*-butyl alcohol, giving a 95% yield of benzamide.

It is clear from this work that the addition of hydrogen peroxide to the reaction is not necessary for high yields. Although some participation of peroxide as an impurity in our potassium or sodium hydroxide cannot be excluded, the stoichiometry of the reaction precludes this being a major pathway.

Roberts and Whitney, who did a brief kinetic study on the basic hydrolysis of benzonitrile in dimethyl sulfoxide, reported that benzamide was the only product. They suggested that the reaction might be made synthetic by using massive amounts of sodium or potassium hydroxide.[6] In our work, we used a four- to fivefold excess of base, in order to increase the surface area and reduce reaction time.

The most likely explanation as to why the hydrolysis stops at the amide stage in the *tert*-butyl alcohol is that the amide is tied up at the end of the reaction as the insoluble sodium or potassium salt, precluding further nucleophilic attack.

Experimental Section

General Procedure for Hydrolysis of Nitriles. To a stirred solution of 5 g (0.0485 mol) of benzonitrile in 50 ml of *tert*-butyl alcohol was added 10 g of finely powdered potassium hydroxide. The reaction mixture was refluxed for 20 min while stirring. The mixture was cooled and poured into 100 ml of an aqueous sodium chloride solution. The mixture was extracted three times with chloroform (total volume 200 ml). The chloroform solution was dried over magnesium sulfate. Removal of the solvents under vacuum gave 5.3 g (90.3%) of pure benzamide, mp 132 °C.

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Generation and Trapping of Methylenecyclopropene

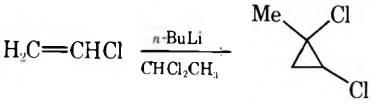
Summary: Evidence is presented for the intermediacy of methylenecyclopropene as a reactive intermediate.

Sir: Methylenecyclopropene (**1**) is of considerable interest both from a preparative and theoretical standpoint. This

1

elusive hydrocarbon is predicted to possess only minor resonance stabilization,[1] and the high index of free valency at the exocyclic position is expected to facilitate polymerization, a process favored additionally by release of strain. Although numerous derivatives of the methylenecyclopropene family have been reported,[2] only two attempts to prepare the parent hydrocarbon can be found in the literature.[3] We report here the generation and trapping of this hydrocarbon.

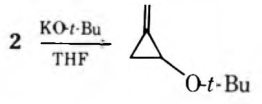
The starting material **2** was prepared in low yield by addition of chloromethyl carbene (CH_3CHCl_2, *n*-BuLi)[4] to vinyl chloride. Compound **2** was separated from several unidentified



2

products by preparative GLC (Carbowax 20M on Chromosorb W). Preliminary results from a study of the microwave spectrum of **2** suggest that the chlorines bear a cis relationship.[5] Other spectral data follow: NMR (CCl_4) δ 1.12–1.43 (m, 2 H), 1.60 (s, 3 H), and 2.70–2.99 (m, 1 H); mass spectrum calcd for $C_4H_6Cl_2$ 123.9846, found 123.9836.

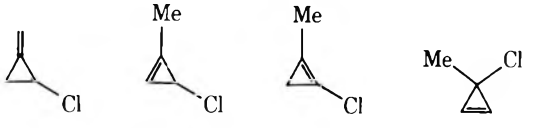
Reaction of **2** (1 equiv) with KO-*t*-Bu (8 equiv) in THF at −30–40 °C for 1 h gave **3** in 37% isolated (preparative GLC) yield. In Me_2SO at 18–20 °C **3** was produced in 33% yield.



3

Compound **3** was characterized by its NMR spectrum which shows a multiplet at δ 1.19–1.40 overlapping a singlet at 1.20 (11 H total) with other signals at 3.35–3.62 (m, 1 H) and 5.23–5.57 (m, 2 H). Elemental composition was provided by mass spectroscopy: calcd for $C_8H_{14}O$ 126.1044, found 126.1042.

The formation of **3** is rationalized in terms of **1** as a reactive intermediate. Possible intermediates in the conversion of **2**

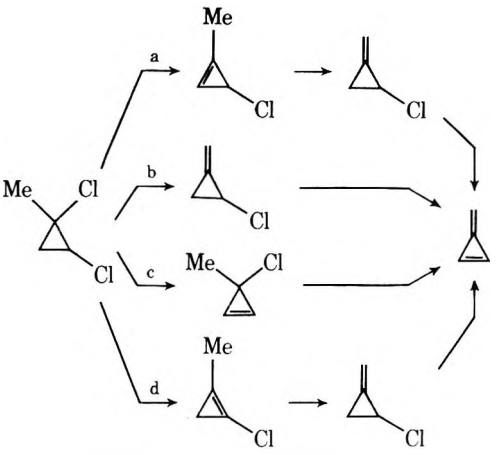


4 **5** **6** **7**

→ **1** → **3** are compounds **4–7**. Four paths (a–d) which utilize these intermediates are summarized in Scheme I.

Intermediate **4** appears in paths a, b, and d and would be expected to undergo dehydrochlorination to give **1**. One might escape postulating **4** (and thus methylenecyclopropene) by assuming addition of *t*-BuO^- to cyclopropenes **5** and **6** prior to isomerization to **4**, although the previous observation that

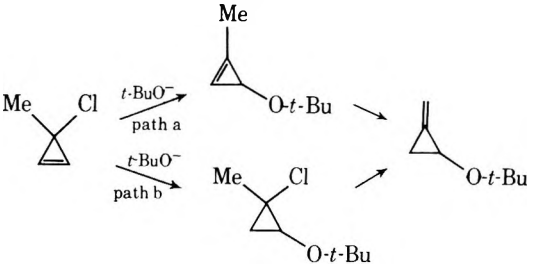
Scheme I



alkylcyclopropenes undergo double-bond isomerization to the exocyclic position rather than add *t*-BuO^- would seem to undermine this assumption.[6]

Such an option is not available for intermediate **7** (path c). While the facile conversion of **7** to **1** would be expected, nevertheless, two additional routes (paths a[7] and b) for **2** → **3** via **7** which bypass methylenecyclopropene are shown in Scheme

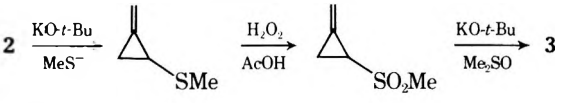
Scheme II



II. These routes cannot be eliminated on the basis of the data that are available.

Much more compelling evidence which supports the intermediacy of methylenecyclopropene is found in the reaction sequence of Scheme III. Thus, reaction of **2** with KO-*t*-Bu (6

Scheme III



9 **8**

equiv) in Me_2SO in the presence of MeS^- (2 equiv) yielded, in addition to **3** (12%), the sulfide **9** in 34% yield. Spectral data: NMR (CCl_4) δ 0.93–1.73 (m, 2 H), 2.10 (s, 3 H), 2.20–2.58 (m, 1 H), and 5.27–5.53 (m, 2 H); mass spectrum calcd for C_5H_8S 100.0346, found 100.0342. When 4 equiv of MeS^- was used, **9** was produced in 51% yield. Oxidation of **9** with 30% H_2O_2 in glacial acetic acid gave the sulfone **8** in 72% yield. When **8** was treated with KO-*t*-Bu (8 equiv) in Me_2SO, **3** was produced as the only volatile product in 11% yield.

Since sulfones are well known to give alkenes via β elimination,[8] this result provides the most compelling evidence for the intermediacy of methylenecyclopropene. Another possible interpretation, e.g., SN2 displacement in **8** or **4** seems unlikely, since cyclopropyl systems normally fail to undergo SN2 reactions.

Acknowledgment. We gratefully acknowledge The Robert A. Welch Foundation and Eli Lilly and Co. for support of this work.

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(7) The sequence shown in path a could proceed via a cyclopropenium ion or an S_N2' process.
(8) J. E. Hofmann, T. J. Wallace, P. A. Argabright, and A. Schriesheim, *Chem. Ind. (London)*, 1243 (1963).
(9) Alfred P. Sloan Foundation Fellow, 1973–1975.

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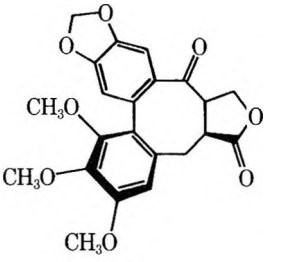
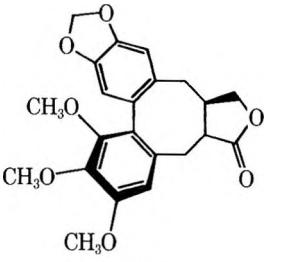
A Short Synthesis of (±)-Isostegane[1]

Summary: (±)-Isostegane has been prepared in a three-step sequence utilizing sequential substitution of the β and α positions of an electron-deficient olefin followed by nonphenolic oxidative coupling.

Sir: Kupchan and coworkers recently described an unusual and highly cytotoxic class of dibenzocyclooctadiene lactones exemplified by the ketone lactone steganone (1).[2] Two total syntheses of 1 have been reported and another group has described synthetic efforts in this area.[3] Our retro-synthetic analysis of 1 suggested that the dibenzocyclooctadiene skeleton might be efficiently constructed by sequential substitution of the β and α positions of an electron-deficient olefin using a conjugate addition alkylation sequence followed by nonphenolic oxidative coupling to yield a tetracyclic debenzocyclooctadiene structure.[4] Herein, we wish to describe a three-step construction of isostegane (2)[1] which demonstrates the validity of this strategy and which proceeds in 55% overall yield.


1


2

Compound 2 was prepared in the following manner. The carbonyl anion equivalent 3 was generated from piperonal dithiomethyl acetal[5] (1 equiv, 1 M in THF, −78 °C) by treatment with *n*-butyllithium (1 equiv). After stirring for 40 min at −78°C, the butenolide 4[6] (1 equiv, 1 M in THF) was slowly added over a period of 30 min. The resulting white suspension was stirred for 3 h at −78 °C whereupon the bromide 5[7] (1 equiv, 1 M in THF) was rapidly added followed immediately by tetramethylethylenediamine (1 equiv).[8] The temperature of the reaction mixture was then raised to −20 °C and stirring continued for 10 to 12 h. Standard workup gave the adduct 6 as an amorphous yellow solid in 99% crude yield.[9] Without purification, adduct 6 (2.5 g) was treated with a suspension of W-4 Raney Nickel (25 g) in acetone (100 ml) at reflux for 30 min. Vacuum filtration of the crude desulfurized product through silica gel gave compound 7 as a clear oil in 85% overall yield from 3.

Cyclization of 7 into 2 was accomplished by slowly adding (10 min) compound 7 (1 equiv, 0.02 M in methylene chloride) to VOF_3 (3 equiv.) suspended in a 2:1 mixture of methylene chloride and trifluoroacetic acid (0.16 M) at −45 °C.[10] The reaction mixture was stirred at −45 °C for 7 h and then worked up by addition of saturated sodium carbonate solution. The crude dark yellow product was purified by vacuum filtration through silica gel followed by crystallization from chloroform–methanol to give pure isostegane (mp 172–172.5 °C) as the sole reaction product in 65 to 70% yield.[11]

The spectral characteristics of compound 2 (uv, ir, NMR, and mass spectrum) clearly indicated it to be a tetracyclic dibenzocyclooctadiene lactone. However, the stereochemical configuration of 2 could not be assigned from these data. As a result, the bromide 8 was prepared[12] and an x-ray structure determination undertaken.

The crystals of compound 8 were monoclinic, space group $P2_1/a$, with a = 22.699 (9), b = 7.433 (6), c = 11.984 (5) Å; β = 95.16 (2)° and d_{calcd} = 1.574 g cm^{-1} for Z = 4. The intensity data were measured on a Hilger-Watts diffractometer (Ni filter Cu Kα radiation, θ-2θ scans,

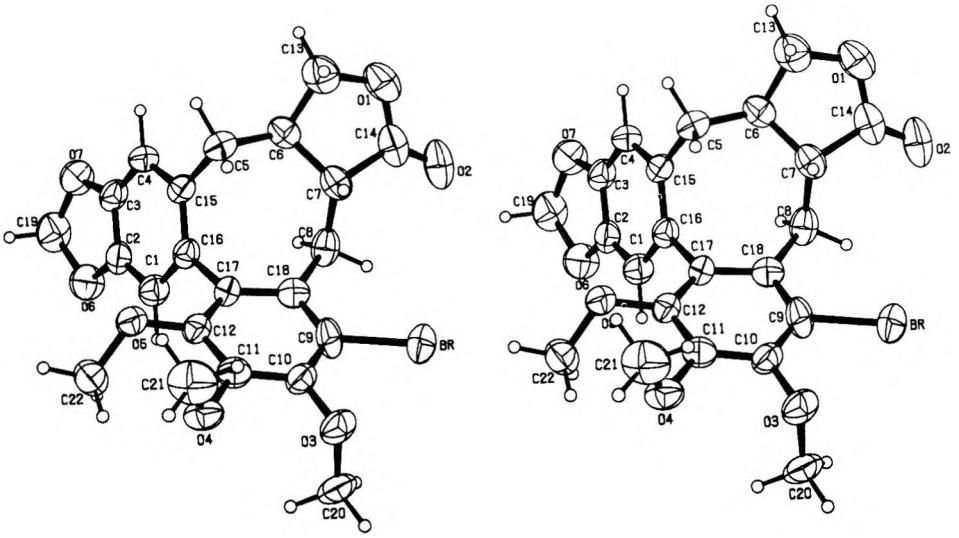
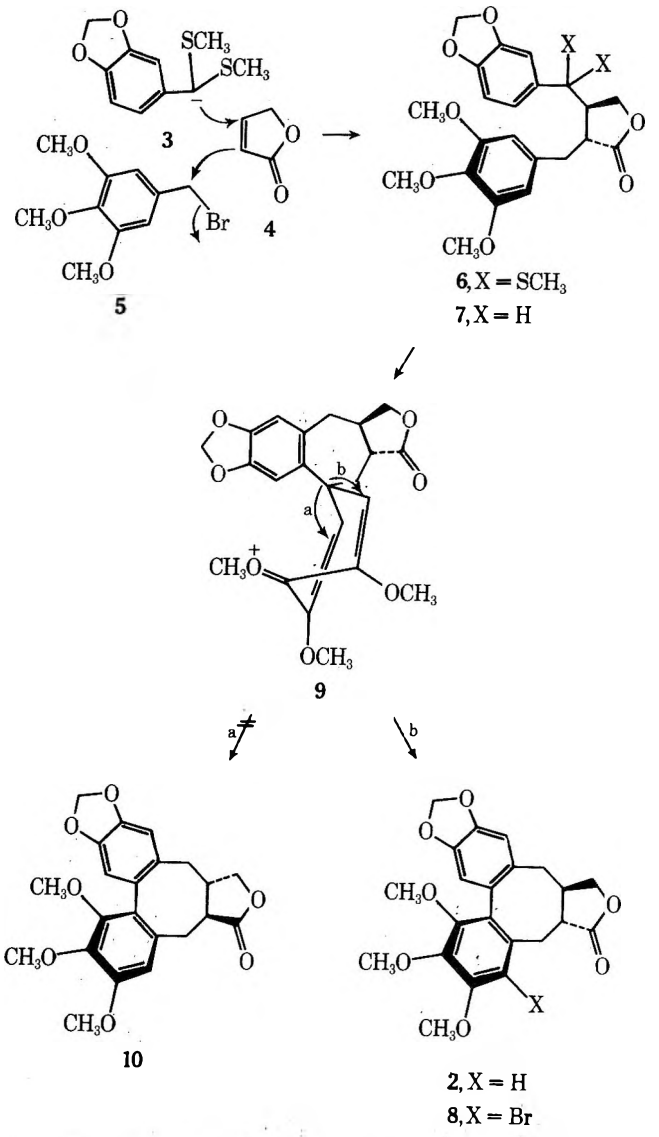


Figure 1.



pulse height discrimination). The size of the crystal used for data collection was approximately 00.2 × 0.25 × 0.30 mm; the data were corrected for absorption (μ = 34.5 cm^{-1}). Of the 2706 independent reflections with $\theta < 57°$, 1859 were considered to be observed. The structure was solved by a multiple solution procedure[13] and was refined by full matrix least squares. In the final refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations but their parameters were not refined. The final discrepancy indices are R = 0.059 and wR = 0.056 for the 1859 observed reflections. The final difference map has no peaks greater than ±0.4 e A^{-3}. The computer drawing of compound 8 (Figure 1) clearly indicates that 8, and therefore compound **2**, possess the unnatural biphenyl configuration.[14]

The exclusive formation of **2** as opposed to compound **10** (the natural biphenyl configuration) must occur during the VOF_3 cyclization of compound **7**. One possible explanation for this stereochemical result involves the intermediacy of the spirodiene **9**.[15] Phenyl migration in **9** via path a leads to stegane (**10**) whereas phenyl migration via path b gives rise to isostegane (**2**). Inspection of molecular models indicate path b is considerably more favored on the basis of configurational interactions than is path a.[16]

Acknowledgment. We would like to thank the National Institutes of Health and the Hoffmann-La Roche Corporation for support of this work. We also thank Professor A. S. Kende and Mr. L. S. Liebeskind for several helpful discussions during the course of this work.

References and Notes

(1) We suggest the name isostegane instead of deoxyisosteganone to denote both the lack of ketonic oxygen and the unnatural biphenyl twist. The name stegane is used instead of deoxysteganone.
(2) S. M. Kupchan, R. W. Britton, M. F. Ziegler, C J. Gilmore, R. J. Restivo, and R. F. Bryan, *J. Am. Chem. Soc.*, **95**, 1335 (1973).
(3) (a) L. R. Hughes and R. A. Raphael, *Tetrahedron Lett.*, 1543 (1976); (b) A. S. Kende and L. S. Liebeskind, *J. Am. Chem. Soc.*, **98**, 267 (1976); (c) F. E. Ziegler and J. A. Schwartz, *Tetrahedron Lett.*, 4643 (1975); (d) D. Becker, L. R. Hughes, and R. A. Raphael, *Chem. Commun.*, 430 (1974).
(4) We have been involved with this type of multi carbon–carbon bond forming reaction sequence using two electrophiles and one nucleophile for some time. See for example (a) J. L. Herrmann, M. H. Berger, and R. H. Schlessinger, *J. Am. Chem. Soc.*, **95**, 7923 (1973); (b) R. F. Romanet and R. H. Schlessinger, *ibid.*, **96**, 3701 (1974). A similar conjugate addition alkylation reaction has been reported in ref 3c.
(5) This compound was prepared in essentially quantitative yield from piperonal using standard reaction conditions.
(6) Prepared in 75% overall yield starting from butyrolactone using a modified procedure based on the reported by C. C. Price and J. M. Judge, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 255.
(7) Compound **5** (mp 73 °C) was prepared in 62% overall yield from gallic acid using standard reaction procedures.
(8) It is important to note that the alkylation segment of this reaction sequence occurs in good yield only if tetramethylethylenediamine is added, and, further, only if this reagent is added after the alkylating agent.
(9) All new compounds exhibited satisfactory spectral and physical data.
(10) Transformation **7** to **2** represents the second example of this type of cyclization successfully applied to the preparation of a cyclooctadiene system; the first example of this reaction type is described in ref 3b. It should be noted however, that the conversion of **7** into **2** is the only example of this cyclization reaction which leads directly to a tetracyclic cyclooctadiene system.
(11) This reaction may be carried out at significantly higher concentrations with a minimal loss in yield (5 to 10%). The remainder of the reaction mixture consists of phenolic substances which have not been fully characterized. A wide variety of other two-electron-transfer oxidants failed to bring about the conversion of **7** into **2**.
(12) Compound **8** (mp 173–174 °C) was prepared from **2** using pyridinium hydrobromide perbromide in chloroform: procedure of L. S. Liebeskind.
(13) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr.*, **A27**, 368 (1971).
(14) A similar phenomenon has been observed by Kende and coworkers. We thank Professor Kende for a preprint describing these results.
(15) Intermediates like **9** have been suggested for other nonphenolic coupling reactions. For examples see (a) S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *J. Am. Chem. Soc.*, **95**, 6861 (1973); (b) S. M. Kupchan, V. Kameswaran, J. T. Lynn, D. K. Williams, and A. J. Liepa, *ibid.*, **97**, 5622 (1975); and (c) S. M. Kupchan and C. Kim, *ibid.*, **97**, 5623 (1975).
(16) Molecular models strongly suggest that the configuration depicted in structure **9** represents an energy minimum for this species.

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Anhydrocholine

Summary: Choline, $(CH_3)_3N^+CH_2CH_2OH\ OH^-$, was found to exist in water-poor media mainly in the form of anhydrocholine, $(CH_3)N^+CH_2CH_2O^-$.

Sir: A characteristic feature of enzyme systems appears to be the existence of highly reactive regions on the enzyme surface. In these regions acidic or basic groups often function as if their pK's were much greater (or smaller) than they are in aqueous solution.[1] It is likewise possible that some small biomolecules might be particularly susceptible to such changes in acidity, either on an enzyme surface or in some other cellular environment, and that this variability might be a vital part of their function.

The effect of polar, water-poor mixed solvents on the binding of various substrates to an enzyme cavity model has been reported recently.[2] We wish to report a remarkable

Table I. Equilibrium Constants and Thermodynamic Parameters for the Reaction

$(CH_3)_3N^+CH_2CH_2OH + OH^- \rightarrow (CH_3)_3N^+CH_2CH_2O^- + H_2O$

Solvent[a]	T, K	K[b]	ΔH, kcal/mol	ΔS, cal/mol K
H_2O	291.15	13.9 ± 0.2	4.39 ± 0.22	20.3 ± 0.8
H_2O	322.90	29.3 ± 1.6		
0.60 aqueous ethanol	273.15	27.5 ± 1.0	2.58 ± 0.02	15.9 ± 0.1
0.60 aqueous ethanol	291.15	33.3 ± 1.3		
0.60 aqueous ethanol	322.90	55.9 ± 2.1		
0.85 aqueous ethanol	291.15	141.7 ± 6.7	−1.47 ± 0.08	4.79 ± 0.18
0.85 aqueous ethanol	322.90	110.4 ± 3.7		
0.60 aqueous DMSO	273.15	1766 ± 57	−2.35 ± 0.21	6.27 ± 0.87
0.60 aqueous DMSO	291.15	1397 ± 54		
0.60 aqueous DMSO	322.90	911.7 ± 84		

[a] Solvent composition indicated as mole fraction of organic solvent. [b] See ref 4.

change in the acidity of choline ion relative to water on going from water solvent to such a polar, water-poor medium.

The customary formulation of choline,[3] $(CH_3)_3N^+CH_2CH_2OH$ OH^-, is no doubt based on the fact that the choline ion, $(CH_3)_3N^+CH_2CH_2OH$, has a pK_a sufficiently close to that of water so that in dilute aqueous solution reaction 1

$$(CH_3)_3N^+CH_2CH_2OH + OH^- \rightleftarrows (CH_3)_3N^+CH_2CH_2O^- + H_2O \quad (1)$$

can be neglected. While following the rate of the base-catalyzed hydrolysis of acetylcholine conductometrically we observed that the conductance of solutions of choline were substantially lower than would be required by the customary formulation. Comparison of the conductance of a solution of choline with the conductances of separate solutions of NaOH, choline chloride, and NaCl yielded the equilibrium constants[4-6] listed in Table I.

Examination of the equilibrium constants shows a dramatic change in the relative acidities of choline ion and water on going to progressively less H-bonding media. This change is accompanied by an even larger shift in the enthalpy of reaction 1. This very large shift to an exothermic ΔH of reaction (by almost 7 kcal/mol) as one goes to the less aqueous medium is opposed by an accompanying decrease in entropy, thus damping the effect on the equilibrium constant. As this damping entropic effect might be absent in the highly ordered biological environments in which the choline ion functions, the factors favoring anhydrocholine,[7] $(CH_3)_3N^+CH_2CH_2O^-$, as a viable biomolecule[8] may be even more pronounced.

Acknowledgment. This work was supported in part by a grant from the City University of New York Faculty Research Award Program.

References and Notes

(1) E.g., lysozyme, where glutamic acid 35 appears to be protonated (i.e., a weak acid) in the enzyme, but then acts as a strong acid in the enzyme-substrate complex [D. C. Phillips, *Proc. Natl. Acad. Sci. U. S.*, **57**, 484 (1967)].
(2) B. Siegel and R. Breslow, *J. Am. Chem. Soc.*, **97**, 6869 (1975).
(3) For a recent review, see R. S. Harris, W. P. Griffith, J. F. Nyc, W. S. Hartcroft, and E. A. Porta in "The Vitamins", Vol. III, 2nd ed, W. H. Sebrell and R. S. Harris, Ed., Academic Press, New York, N.Y., 1971, pp 2–154.
(4)

$$K^{-1} = \left(\frac{L_{CholCl+NaOH} - L_{NaCl}}{L_{NaOH} + L_{CholCl} - L_{CholCl+NaOH}}\right) \times \left[C - \frac{C}{\left(\frac{L_{CholCl+NaOH} - L_{NaCl}}{L_{NaOH} + L_{CholCl} - L_{CholCl+NaOH}}\right) + 1}\right]$$

where L is the conductance of the indicated compound or compounds at concentration C. The equilibrium constant K was determined at at least three concentrations with C ranging from 10^{-4} to 10^{-2} M. These K values are defined using a value of unity for the concentration of H_2O in eq 1. Using the actual concentration of H_2O yields K values which are somewhat different and ΔH and ΔS values which are slightly different. It does not alter the picture represented by the values in Table I. In the two ethanolic media this calculation does not distinguish the relative contributions of OH^- and $C_2H_5O^-$ to the equilibrium, but rather measures the K of the equilibrium $(CH_3)_3N^+CH_2CH_2OH + SO^- \rightarrow (CH_3)_3N^+CH_2CH_2O^- + SOH$ (SOH = solvent).
(5) This yields the following values for the ionization of choline chloride in water $[(CH_3)_3N^+CH_2CH_2OH \rightarrow (CH_3)_3N^+CH_2CH_2O^- + H^+]$: pK_a (25 °C) = 12.8, ΔH° = 17.73 kcal/mol, ΔS° = 1.6 cal/mol deg. The only literature report on the acidity of choline chloride (based on the measurement of the pH of dilute solutions) gives a value of pK_a = 9 and is clearly in error [C. W. Lewis and W. C. M. Price, *Trans. Faraday Soc.*, **29**, 777 (1933)]. There is an interesting recent report on the anomalously low pH of aqueous KOH in concentrated solutions of choline salts, which can probably be accounted for by reaction 1 [J. Steigman and D. Sussman, *J. Am. Chem. Soc.*, **89**, 6400 (1967)].
(6) A far less convenient method of measuring equilibrium 1 is to observe the ^1H NMR spectrum of a mixture of choline chloride and sodium hydroxide. To check our results we did this in one case (water) and obtained substantially the same equilibrium constant as by the conductance method.
(7) Since the salt $(CH_3)_3N^+CH_2CH_2OH$ OH^- is called choline, the reasonable name for its dehydration product, $(CH_3)_3N^+CH_2CH_2O^-$, is *anhydrocholine*. Unfortunately, the use of the term choline for the cation, $(CH_3)_3N^+CH_2CH_2OH$, is also widespread. From this starting point one would arrive at the name *choline dipolar ion*, for $(CH_3)_3N^+CH_2CH_2O^-$. We prefer *anhydrocholine* as being shorter and more descriptive.
(8) Since anhydrocholine should be much more nucleophilic than the choline cation, it may, for example, be a good candidate for the reactive species at the active site of choline acetylase or choline kinase.
(9) Taken from the M.A. Thesis of Jeffrey Pessin, Brooklyn College of the City University of New York, 1975.

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