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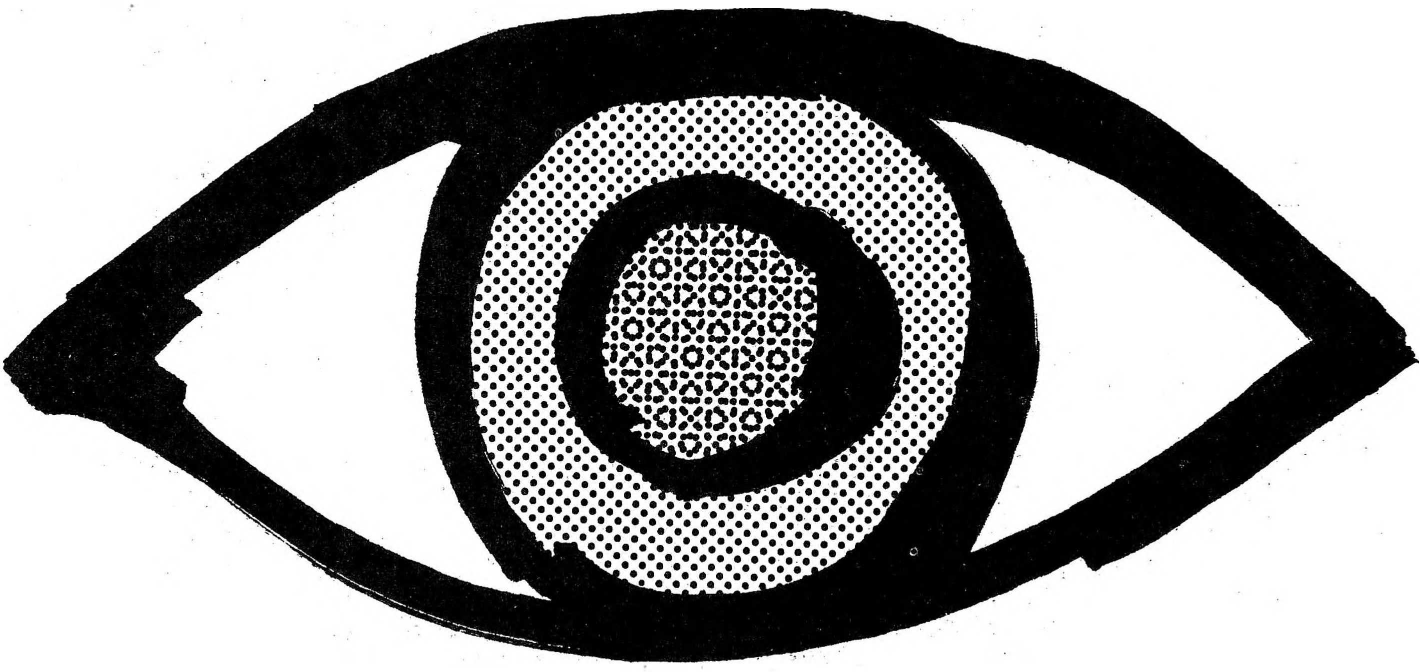

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Nuclear Magnetic Resonance Spectroscopy. Use of ^{13}C Spectra to Establish Configurations of Oximes[1]

Geoffrey E. Hawkes,[2] Klaus Herwig,[3] and John D. Roberts*

Contribution No. 4750 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91109

Received August 28, 1973

The use of ^{13}C nmr (cmr) spectra for the determination of configurations of oximes is described. The problems of quantitative analysis of syn–anti mixtures of oximes by cmr, because of differential T_1 and Overhauser effects, are considered. Chemical shifts for the cmr resonances of a number of aldehydes and ketones are reported.

The utility of ^{13}C nmr (cmr) spectra for structural studies is well established.[4] We report here its application to the determination of the configurations and composition of syn and anti isomers of aldoximes and ketoximes. While this investigation was being completed, the results of a similar study were published by Levy and Nelson.[5] We have reached similar conclusions on the basis of a much larger number of examples and have, in addition, considered cases complicated by conformational equilibration. The procedure seems to be of more general application than the elegant solvent-induced shift technique devised by Karabatsos and Taller.[6]

The assignments of the ^{13}C resonances of the oximes investigated in this work are shown in Tables I and II, which also include a substantial collection of new data on the ^{13}C shifts of several ketones and many aldehydes. Because the assignments of the resonances of the carbonyl compounds themselves are relevant to those of the oximes, we shall consider some of the problems involved with the carbonyl compounds.

^{13}C Shifts of Ketones. For many of the ketones in Table I, assignments have already been published.[7] In the case of cyclooctanone, we were not able to resolve the existing ambiguities[7b] of assignment. For methone (44), if one proceeds from menthane[8] with the substituent shifts deduced from various cyclohexane → cyclohexanone comparisons,[7b] one finds that the 3,4 carbons are expected to differ by only 0.5 ppm, whereas the observed difference is 5.7 ppm. Arguing from the respective effects of 4- or 6-methyl substitution on 2- or 3-methylcyclohexanone leads to the expectation that the C4 resonance of menthone should be upfield of the C3 resonance.[7b] However, the opposite conclusion can be derived either from translation of the 4-isopropyl substituent effect on methylcyclohexane to the appropriate carbons of 3-methylcyclohexanone or by consideration of 4-methyl substitution on 2-*tert*-butylcyclohexanone and 6-*tert*-butyl substitution on 3-methylcyclohexanone. That the C4 resonance is indeed the downfield one has been corroborated by the 50% larger lanthanide shift observed for the upfield resonance using $Eu(DPM)_3$.[9]

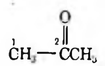
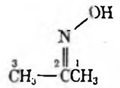
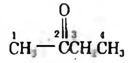
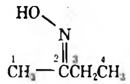
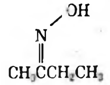
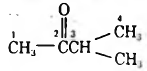
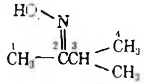
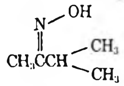
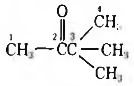
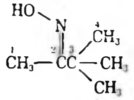
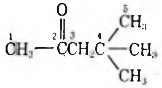
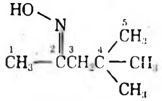
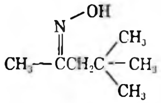
The ring methyl of menthane comes at 22.8 ppm[4] and compares favorably with that in menthone (22.3 ppm). This leaves the two methyl resonances of the isopropyl to be assigned with a shift difference of 2.5 ppm, which is reasonable for an isopropyl methyl adjacent to an asymmetric center.[10]

Isomenthone (47) is more complex. Because of a combination of "3-alkyl- and 2-alkyl-ketone" effects,[11] isomenthone is expected to have a high proportion of that conformation in which the isopropyl group is axial.[12] On the basis of the shifts of menthone, the resonances at 57.2 and 48.2 ppm for isomenthone seem reasonably ascribed to C2 and C6, respectively. The signal at 34.4 ppm was a doublet with single-frequency off-resonance decoupling (SFORD) and assigned to C5, while the signals at 26.8 and 27.0 ppm were too close together to be distinguished as CH_2 or CH by SFORD. Because both C3 and C4 of isomenthone would be expected to be shifted upfield by steric compression with the isopropyl axial (C4) in one conformation and the methyl axial in the other (C3), we have assigned the signals at 27.0 (or 26.8) and 29.6 to C3 and C4, respectively (which means upfield from the corresponding carbons of menthone by 1.5 and 4.5 ppm).

For nortricyclanone (50), the upfield signals at 18.9 and 16.9 ppm were assigned to C4, C5 and C3, respectively (2:1 ratio of intensities), and those at 37.3 and 31.3 ppm were allocated to C1 and C6, C7, respectively (1:2 ratio of intensities and SFORD multiplicities).

^{13}C Shifts of Ketoximes. All of the ketoximes we have investigated (**10**, **15**, **25**, and **57**) with α quaternary carbons appeared to be single isomers, which are most reasonably believed to have the oxime OH anti to the quaternary carbon. The oximes of symmetrical ketones (**2**, **20**, **27**, **29**, **31**, **33**, **35**, **37**, and **59**) also gave just one set of resonances. For the remaining ketoximes, where two isomers might be expected and were observed, the intensity ratios of signals due to the separate isomers are shown in Table

Table I. ^{13}C Chemical Shifts[a] for Ketones and Ketoximes

	No.	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
 $\overset{1}{C}H_3-\overset{O}{\overset{\parallel}{\overset{2}{C}}}CH_3$	1	30.7	206.2								
 $\overset{3}{C}H_3-\overset{N-OH}{\overset{\parallel}{\overset{2}{C}}}\overset{1}{C}H_3$	2	15.0	155.4	21.7							
 $\overset{1}{C}H_3-\overset{O}{\overset{\parallel}{\overset{2}{C}}}\overset{3}{C}H_2\overset{4}{C}H_3$	3	28.9	208.8	36.4	7.4						
 $\overset{1}{C}H_3-\overset{HO-N}{\overset{\parallel}{\overset{2}{C}}}\overset{3}{C}H_2\overset{4}{C}H_3$	4	13.0	159.1	28.9	10.7						
 $CH_3\overset{N-OH}{\overset{\parallel}{C}}CH_2CH_3$	5	18.9	159.5	21.7	9.6						
	6	27.1	212.1	41.3	17.8						
	7	10.8	162.2	34.3	19.5						
	8	15.1	162.7	25.7	18.7						
	9	24.5	213.9	44.3	26.4						
	10	10.0	164.1	37.3	27.5						
	11	32.3	208.5	55.8	30.9	29.6					
	12	16.4	157.0	49.2	31.6	29.9					
	13	22.7	157.0	42.0	32.2	30.7					

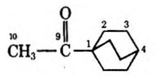
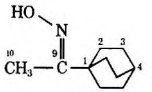
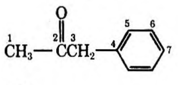
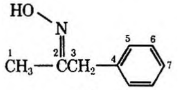
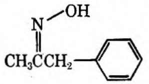
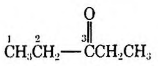
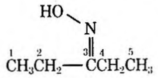
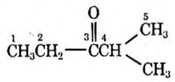
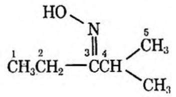
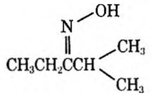
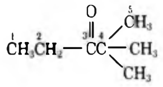
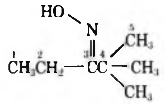
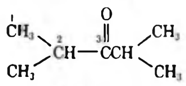
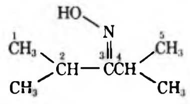
	**14**	44.5	27.5	25.5	24.1					214.2	25.5
	**15**	37.1	28.3	25.7	24.0					163.6	10.1
	**16**	29.0	206.0	50.7	134.3	129.3*	128.6*	126.9			
	**17**	13.4	157.6	42.0	136.9	129.1†	128.6†	126.4			
	**18**	19.5	156.9	34.9	136.7	129.1†	128.6†	126.4			
	**19**	8.0	35.6	212.1							
	**20**	10.1*	21.0	163.5	27.1	10.7*					
	**21**	7.9	33.5	215.2	40.7	18.4					
	**22**	10.7	20.0	166.4	33.6	20.0					
	**23**	10.8	23.3	165.8	26.5	19.0					
	**24**	8.2	29.6	216.3	44.0	26.5					
	**25**	11.1	19.0	168.1	37.6	27.6					
	**26**	18.6	38.9	218.4							
	**27**	18.9	27.7	168.6	30.8	21.3					

Table I *(Continued)*

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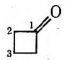
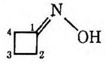
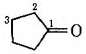
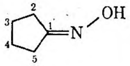
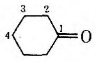
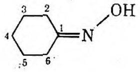
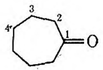
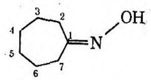
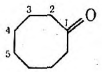
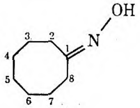
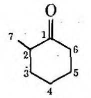
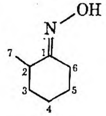
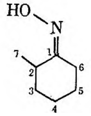
	**28**	208.9	47.8	9.9							
	**29**	159.7	30.7	14.6	31.6						
	**30**	219.6	37.9	22.7							
	**31**	167.1	27.1	25.1*	24.4*	30.6					
	**32**	209.7	41.5	26.6	24.6						
	**33**	160.4	25.7*	25.4*	24.4	26.7	31.9				
	**34**	215.0	43.9	24.4	30.6						
	**35**	164.3	30.49*	27.5‡	30.44*†	28.9†	24.7‡	33.9			
	**36**	218.0	42.0	27.4*	25.8*	24.9					
	**37**	163.7	27.3†	26.9†‡	26.8†‡	24.9‡	25.5‡	24.4‡	33.1		
	**38**	212.9	45.5	36.4	25.3	28.0	42.0	14.8			
	**39**	163.0	37.2	35.7	23.9	24.8	26.1	16.9			
	**40**	163.6	26.8*	26.7*†	20.5‡	28.4†‡	31.7	16.2			

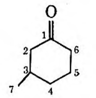
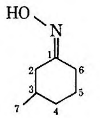
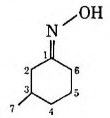
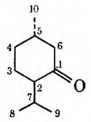
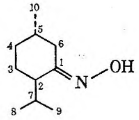
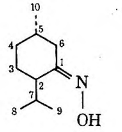
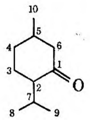
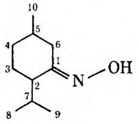
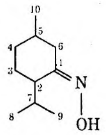
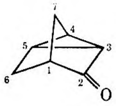
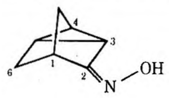
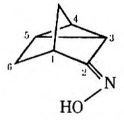
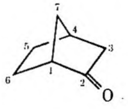
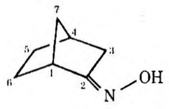
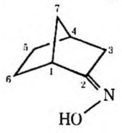
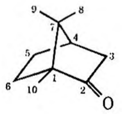
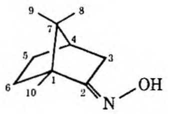
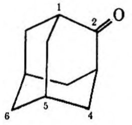
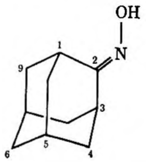
	**41**	211.6	50.0	34.2	33.4	25.3	41.1	22.1			
	**42**	160.4*	34.2†	32.5‡	32.3‖	24.5#	31.7	22.1**			
	**43**	160.5*	40.1	33.4‡	34.3†‖	23.9#	25.8	21.9**			
	**44**	212.0	56.1	28.4	34.1	35.6	51.0	26.0	21.3*	18.8*	22.3
	**45**	161.0	48.8	26.9	32.8†	32.4	31.9†	26.4	21.8‡#	19.1‡	21.4#
	**46**	161.2	40.0	22.0‖	26.7‖**	29.6	35.2	26.6**	20.4$^{****}_{***}$	18.1****	20.8***
	**47**	214.1	57.2	27.0*	29.6	34.4	48.2	26.8*	21.0†‡	19.9†	21.4‡
	**48**	163.0**	47.5	26.7****	28.3	34.5	29.7***	26.7	(21.2	20.6	22.5)#
	**49**	162.6**	39.3	27.3****	37.5	33.2	29.5***	29.7	(20.7	20.4	22.4)#
	**50**	37.3	213.8	16.9	18.9		31.3				

Table I (*Continued*)

	No.	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
	**51**	33.4	167.1	11.4	17.1		33.6				
	**52**	29.0	167.6	13.8	16.7		33.3				
	**53**	49.3	216.8	44.7	34.8	26.7	23.7	37.1			
	**54**	42.0	167.4	34.9	35.5	27.1	27.8	39.1			
	**55**	38.5*	166.3	37.2	35.6	26.0	27.4	38.3*			
	**56**	57.7	219.1	43.3	43.3	27.2	30.0	46.8	9.3	19.2	19.8
	**57**	51.7	169.5	33.1*	43.8	27.3	32.7*	48.2	11.1	18.5†	19.5†
	**58**	47.1	217.9		39.4	27.6	36.4				
	**59**	29.1	167.4	36.2	37.7*	27.9	36.6			39.0*	

[a] Shifts are in ppm downfield from TMS. Uncertainties of assignments are indicated by *, †, ‡, #, ||, **, ***, and **** according to the following system. For the ketones, the superscripts represent assignments which might reasonably be interchanged in a given horizontal row in the table. For the oximes, when the amounts of each isomer are comparable, then possible interchanges between assignments for a given isomer are shown for the same horizontal row of values and between isomer pairs in different horizontal rows.

III. The method of obtaining these ratios is described in the Experimental Section. The major isomer of the pairs **4-5**, **7-8**, **12-13**, **17-18**, **22-23**, **39-40**, **45-46**, and **54-55** is expected on the basis of steric hindrance to have the OH syn to the least substituted α-carbon. With this assumption, and with the aid of the SFORD spectra, the individual resonances can be assigned to particular carbons of all of these oximes, as has been done in Table I.

As has been noted by Levy and Nelson[5] on the basis of fewer examples, a consistent pattern of α-anti and α-syn carbon shift changes is observed when a ketone is converted to an oxime (eq 1). These changes are listed in Table IV with *upfield* shifts taken to be *negative*. It will be seen that the resonances of the carbonyl carbon and both α-carbons all shift upfield on oxime formation, with the effect for the α-syn carbon being greater than for the α-anti carbon, an effect noted earlier with cis-alkenes.[13] With the aid of this correlation, it is easy to assign the resonances of **2**, **20**, and **27** as in Table I. The corresponding substituent effects are shown in Table IV.

α-anti α-syn (1)

The carbon shift changes associated with conversion of a ketone to its oxime and the β-carbons are usually, but not always, small for acyclic ketones (see Table IV). There is a definite trend which speaks for more negative shifts at the syn than the anti β-carbons. This effect was used to assign the β resonances of **27**, which check out well with those of **7** and **8**.

Table I shows selections for α-carbon resonances of the cyclic ketoximes **29**, **31**, **35**, and **37**. The lowest field CH_2 signal was assigned to the anti α-carbon and the next lowest field CH_2 signal to the syn α-carbon. The latter assignments are hardly unambiguous for **31**, **35**, and **37** where two or more carbons come at about the same place. That the syn-anti α-carbon difference is steric in origin fits well with its very small magnitude for cyclobutanone oxime where the constraints on the ring carbons should substantially reduce the hindrance.

The procedures for cyclohexanone oxime and its 2- and 3-methyl derivatives, **33**, **39**, **40**, **42**, and **43**, were somewhat different. Except for the minor isomer of 2-methylcyclohexanone oxime (**40**) (Figure 1), which presented a special problem, a reasonably self-consistent set of assignments (with some uncertainties) was evolved from SFORD data, α syn-anti effects, and the assumption that the methyl substituent effects on the ^{13}C shifts of cyclohexanones[7b] carry over to the ketoximes (Table V). The signals at 24.4 and 26.7 ppm for cyclohexanone oxime were assigned to C4 and C5 on the basis of expected minimal changes at these carbons going from ketone to oxime. Special uncertainties came with **42** and **43** because these isomers were present in nearly equal amounts.

For the minor isomer of 2-methylcyclohexanone oxime (**40**), C2 is clearly at about 26.8 ppm from the SFORD spectrum, and C6 is the lowest field saturated-carbon resonance. None of the remaining oxime ring resonances, especially the one at 20.5 ppm, correlate with the ketone resonances. It seems possible that steric interference between the OH and 2-methyl results in a more or less complete conformational change which brings the methyl axial. If this is so, the 20.5-ppm resonance is likely to be C4, but we have no certain evidence for it.

The assignments for the major isomer of menthone oxime, **45**, were made to be consistent with those of menthone (**44**) and SFORD spectra.[14] For the minor isomer, **46**, C2 and C6 were assigned on the basis of the oxime substituent effects, although the C6 resonance is at a rather unusually high field. As with **40**, there seems to be a possibility that a conformational change takes place on oxime formation when a 2 substituent is syn to the oxime OH, because the ring CH_2 resonances do not correlate well with the ketone CH_2 resonances, especially with the oxime resonance at 22 ppm.

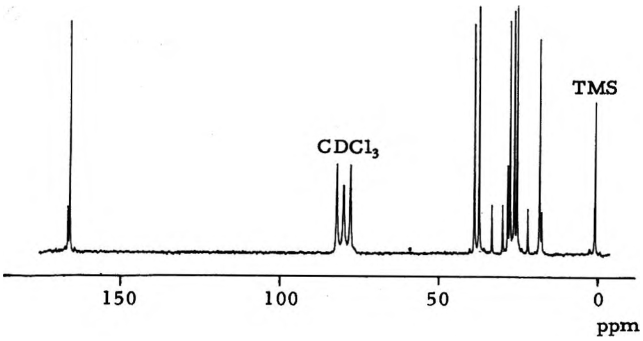


Figure 1. ^{13}C spectrum of 2-methylcyclohexanone oxime + Cr(acac)$_3$.

The isomenthone oxime isomers presented specially difficult problems because they were present in nearly equal amounts and because of the conformational uncertainties mentioned earlier with regard to menthone itself. Clearly, for the oxime with the OH syn to the isopropyl group (**49**), we expect that this group will be most favorably disposed in the axial position. That there are two upfield ring resonances in the mixture suggests that the isopropyl axial is particularly favored and the highest field resonance is of its C4 atoms. Except when confirmed by SFORD and in accord with the α syn-anti effects, these assignments are speculative.

The major isomer of nortricyclanone oxime has a cyclopropane carbon resonance at 11.4 ppm and two others at 17.1 ppm; the 33.4-ppm signal from its SFORD pattern is a CH resonance and must be C1. The syn and anti α-carbon shifts are thus −5.5 and −3.9 ppm, respectively, from the ketone. This isomer is assigned the configuration with cyclopropane syn to the OH group. The corresponding shifts for the minor isomer are −3.1 and −8.3 ppm which are, as expected for the OH group, syn to C1.

For norcamphor ketoxime, the major isomer should have the OH anti to C1, the more substituted carbon. For this isomer, the methine resonances at 42.0 and 35.5 ppm were assigned to C1 and C4, respectively. The C5, C6, and C7 signals were assigned to be consistent with those of the ketone, which leaves a resonance at 34.9 ppm for C3. These allocations give $\Delta_{\alpha\text{-syn}}$ and $\Delta_{\alpha\text{-anti}}$ of −9.8 and −7.3 ppm, respectively. The signals of the minor isomer were specified in the same way.

Camphor oxime (**57**) shows only one set of ^{13}C resonances which must be from the isomer with OH anti to C1. The assignment procedure here followed that for the major isomer of norcamphor oxime. For adamantanone oxime (**59**) only one isomer is possible. The larger of the methine signals at 27.9 ppm was ascribed to C5 and C7, while the other CH resonances at 29.1 and 36.2 ppm were assigned to C1 and C3, respectively, in accord with the expected syn-anti effect. The weaker CH_2 signal was easily ascribed to C6 but no clear decision between the other two larger signals was possible.

Table IV shows that conversion of $R_2C{=}O$ to $R_2C{=}NOH$ is accompanied by a very consistent mean change in the carbonyl resonance position of −50.0 ppm, with a standard deviation of 1.5 ppm. The only conspicu-

Table II
^{13}C Chemical Shifts[a] for Aldehydes and Aldoximes

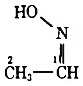
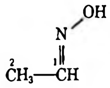
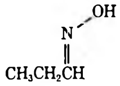
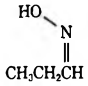
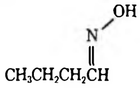
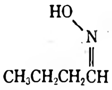
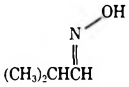
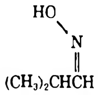
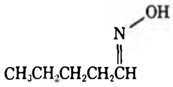
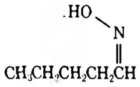
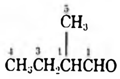
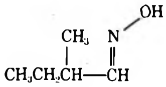
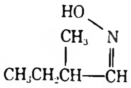
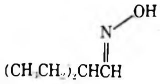
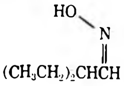
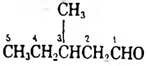
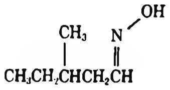
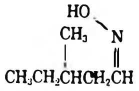
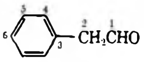
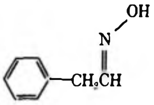
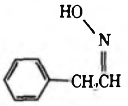
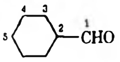
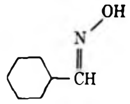
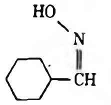
	No.	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
$\overset{2}{C}H_3\overset{1}{C}HO$	**60**	199.8	30.9								
 $\mathrm{\overset{2}{C}H_3{-}\overset{1}{C}H{=}N{-}OH}$	**61**	147.8	11.2								
 $\mathrm{\overset{2}{C}H_3{-}\overset{1}{C}H{=}N{-}OH}$	**62**	148.2	15.0								
$\overset{3}{C}H_3\overset{2}{C}H_2\overset{1}{C}HO$	**63**	202.8	37.3	6.0							
 $\mathrm{CH_3CH_2CH{=}N{-}OH}$	**64**	153.1	23.1	10.9							
 $\mathrm{CH_3CH_2CH{=}N{-}OH}$	**65**	153.7	18.6	10.4							
$\overset{4}{C}H_3\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}HO$	**66**	202.5	45.9	15.8	13.8						
 $\mathrm{CH_3CH_2CH_2CH{=}N{-}OH}$	**67**	152.1	31.5	20.1	13.6*						
 $\mathrm{CH_3CH_2CH_2CH{=}N{-}OH}$	**68**	152.6	27.0	19.5	13.9*						
$(\overset{3}{C}H_3)_2\overset{2}{C}H\overset{1}{C}HO$	**69**	204.7	41.2	15.5							
 $\mathrm{(CH_3)_2CHCH{=}N{-}OH}$	**70**	156.9	29.4	20.0							
 $\mathrm{(CH_3)_2CHCH{=}N{-}OH}$	**71**	157.8	24.5	19.7							
$\overset{5}{C}H_3\overset{4}{C}H_2\overset{3}{C}H_2\overset{2}{C}H_2\overset{1}{C}HO$	**72**	202.3	43.7	24.3	22.3	13.8					
 $\mathrm{CH_3CH_2CH_2CH_2CH{=}N{-}OH}$	**73**	152.3	29.2	28.8*	22.3	13.7					
 $\mathrm{CH_3CH_2CH_2CH_2CH{=}N{-}OH}$	**74**	152.8	24.9	28.4*	22.6	13.7					
 $\overset{4}{C}H_3\overset{3}{C}H_2\overset{2}{C}H(\overset{5}{C}H_3)\overset{1}{C}HO$	**75**	204.9	47.9	23.2	11.4	12.9					
 $\mathrm{CH_3CH_2CH(CH_3){-}CH{=}N{-}OH}$	**76**	156.4	36.1	27.7	11.4	17.7*					
 $\mathrm{CH_3CH_2CH(CH_3){-}CH{=}N{-}OH}$	**77**	157.0	31.2	27.7	11.4	17.1*					
$(\overset{4}{C}H_3\overset{3}{C}H_2)_2\overset{2}{C}H\overset{1}{C}HO$	**78**	205.0	55.0	21.5	11.4						
 $\mathrm{(CH_3CH_2)_2CHCH{=}N{-}OH}$	**79**	155.6	43.2	25.7	11.5						
 $\mathrm{(CH_3CH_2)_2CHCH{=}N{-}OH}$	**80**	156.4	38.3	25.4	11.6						
 $\overset{5}{C}H_3\overset{4}{C}H_2\overset{3}{C}H(\overset{6}{C}H_3)\overset{2}{C}H_2\overset{1}{C}HO$	**81**	202.4	50.9	29.8	29.8	11.4	19.6				

Table II
(*Continued*)

	No.	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10
	**82**	151.6	36.3	33.2	29.3	11.4	19.2				
	**83**	152.0	31.9	32.8	29.5	11.4	19.6				
	**84**	199.3	50.6	132.0	129.7*	129.1*	127.5				
	**85**	150.9	36.0	136.9	128.9	128.9	126.9				
	**86**	150.9	31.9	136.9	128.9	128.9	126.9				
	**87**	204.7	50.1	26.1	25.2	25.2					
	**88**	155.8	38.5	30.3	25.5*	25.6*					
	**89**	156.3	33.9	29.5	25.6*	25.9*					

[a] See footnote to Table I.

Table III
Ketoxime Isomer Distributions Determined from the ^{13}C Spectra

Ketoximes[b]	Carbons[c]	% of major isomer[a]: With Cr(acac)$_3$[d]		Pulse delay[e]		Lit.[f]	$-\Delta G°$[g]
4, 5	C3	78	78	73	75		0.77
	C4	77		76		74	
	C1	71		68		72	
7, 8	C3	86	86	88	86	91	1.11
	C1	86		84		86	
12, 13	C3	83	82	81	82		0.93
	C1	80		82			
22, 23	C3	78	78	78	78		0.78
	C4	78		78			
17, 18	C3	74	72	71	71	74	0.58
	C1	70		70			
39, 40	C1	84	84	83	83		1.01
	C3 (**39**), C5 (**40**)	84		82			
42, 43			~50		~50		~0.00
45, 46	C2	82		74			0.93
48, 49			~50		~50		~0.00
51, 52	C2	79	79	79	80		0.81
	C3	79		80			
54, 55	C2	85	85	87			1.06
	C1 (**54**), C3 (**55**)	84					

[a] The uncertainties of the values determined from the ^{13}C spectra are probably of the order ±5%. [b] Presumed major isomer listed first. [c] The ^{13}C signals used for peak height measurements. [d] From ^{13}C spectra obtained with added Cr(acac)$_3$ to reduce differential NOE effect. [e] From ^{13}C spectra without Cr(acac)$_3$, but with a 12-sec pulse delay. [f] Literature values from ref 6, and K. D. Berlin and S. Rengaraju, *J. Org. Chem.*, **36**, 2912 (1971). [g] Free energies (kcal mol^{-1}) at 35°; these were determined from mean values.

ous deviations are of **37**, **51**, and **52** which are about 4 ppm from the mean.

There is only one exception (**49**, which, as discussed, may involve a major conformational change) to the generalization that $\Delta_{\alpha\text{-syn}} - \Delta_{\alpha\text{-anti}}$ is positive.

Values of Δ_β are also listed in Table IV. These are seen to be consistently positive for aliphatic ketones and of variable sign for alicyclic ketones.

^{13}C Shifts of Aldehydes. The spectral assignments in Table II for a number of aldehydes have been confirmed by SFORD spectra where possible and seem sufficiently unambiguous to preclude detailed discussion.

^{13}C Spectra of Aldoximes. The substituent shifts for the change $C_\beta C_\alpha CH{=}O \rightarrow C_\beta C_\alpha CH{=}NOH$ for aldehydes are sufficiently regular to be quite helpful in making assignments. Where both syn and anti isomers were present, these could often be identified by comparing the ^{13}C resonance intensities with the isomer ratios determined by Karabatsos and Taller from proton spectra.[6] Thus, the more intense methyl signal of acetaldoxime is at higher field, consistent with a larger upfield shift for the oxime OH syn than OH anti to the methyl group, and the finding that the syn isomer is the major one.[6] For the other aldoxime isomer mixtures, carbon shifts of the major components were consistent with the alkyl group being anti to the OH (see Table VI).

Brief comments seem desirable for a few specific substances. Thus, with valeraldoxime (**73**, and **74**), the closeness of the chemical shifts and the nearly equal isomer proportions allowed only the signal at 24.9 ppm to be surely assigned to the minor isomer. The other resonances were assigned by comparison with the shifts of propionaldoxime (**64** and **65**) and butyraldoxime (**67** and **68**). For

Table IV
^{13}C Substituent Shift Parameters for Conversion of Ketones to Ketoximes[a]

Oxime	$\Delta_{C=X}^{b}$	$\Delta_{\alpha\text{-syn}}^{b}$	$\Delta_{\alpha\text{-anti}}^{b}$	$\Delta_{\alpha\text{-syn}} - \Delta_{\alpha\text{-anti}}$	Δ_{β}^{b}
4	−49.7	−15.9	−7.5	−8.4	+3.3
5	−49.3	−14.7	−10.0	−4.7	+2.2
7	−49.9	−16.3	−7.0	−9.3	+1.7
8	−49.4	−15.6	−12.0	−3.6	+0.9
10	−49.8	−14.5	−7.0	−7.5	+1.1
12	−51.5	−15.9	−6.6	−9.3	+0.7
13	−51.5	−13.8	−9.6	−4.2	+1.3
15	−50.6	−14.4	−7.4	−7.0	+0.8
17	−48.4	−15.6	−8.7	−6.9	+2.6
18	−49.1	−15.8	−9.5	−6.3	+2.4
22	−48.8	−13.5	−7.1	−6.4	+1.8, +1.6
23	−49.4	−14.2	−10.2	−4.0	+1.9, +0.6
25	−48.2	−10.6	−6.4	−4.2	+2.9, +1.1
2	−50.8	−15.8	−9.0	−6.8	
20	−48.6	−14.6	−8.5	−6.1	+2.1, +2.7
27	−49.8	−11.2	−8.1	−3.1	+0.3, +2.7
29	−49.2	−17.1	−16.2	−0.9	+3.7
31	−52.5	−10.8	−7.3	−3.5	+2.4, +1.7
33	−49.3	−15.8 (−16.1)	−9.6	−6.2 (5)	−1.2, +0.1
35	−50.7	−13.4 (5)	−10.0	−3.4 (5)	+3.1, +0.3
37	−54.3	(−14.7)	−8.9	(−5.8)	?
39	−49.9	−15.9	−8.3	−7.6	−0.7, −3.2
40	−49.3	−18.7 (8)	−10.3	−8.4 (5)	−9.7, ? (−8.0)
42	−51.2 (1)	−15.8 (7)	−9.4	−6.4 (3)	−1.7, −0.8 (−0.8) (−1.4)
43	−51.1 (2)	−15.3	−9.9	−5.4	−0.8, −1.4 (−1.7) (−0.8)
45	−51.0	−19.1 (−18.2)	−7.3	−11.8 (−10.9)	−1.5, −3.2
46	−50.8	−16.1	−15.8	−0.3	−6.4, −6.0 (−1.7)
48	−51.1 (5)	−18.5 (7)	−9.7	−8.8 (−9.0)	−0.3 (1), +0.1 +0.3 (5)
49	−51.5 (1)	−17.9	−19.0 (−18.7)	+1.1 (+0.8)	+0.3 (1), −1.2 −0.3 (5)
51	−46.7	−5.5	−3.9	−1.6	−1.8, +2.3
52	−46.2	−8.3	−3.1	−5.2	−2.2, +3.0
54	−49.2	−9.8	−7.3	−2.5	+0.8, +3.9, +2.0
55	−50.5	−10.8 (−11.0)	−7.5	−3.3 (5)	+0.8, +3.7, +1.2 (4)
57	−49.6	−10.2 (6)	−6.0	−4.2 (6)	+0.5, +2.7, +1.4 (+3.1)
59	−50.5	−18.0	−10.9	−7.1	−1.7, −0.4

[a] In ppm, figures in parentheses represent uncertainties in assignment (see Table I). [b] These are ^{13}C shifts for ketoxime − ^{13}C shifts of ketone, and negative values indicate that the ketoxime signal is at higher field.

Table V
Methyl ^{13}C Chemical Shift Parameters[a] for Cyclohexanone and Cyclohexanone Oxime

Compound	C2	C3	C4	C5	C6
38	+5.0	+9.8	+0.7	+1.4	+0.5
39	+5.3	+9.0	−0.5	−0.6	+0.4
41	+8.5	+7.6	+8.8	−1.3	−0.4
42	+8.5	+7.1	+7.9	−2.2	−0.2
43	+8.2	+6.7	+9.9	−1.5	+0.1

[a] Shift differences between the methyl-substituted cyclohexanones (**38** and **41**) and cyclohexanone (**32**), and the methyl-substituted cyclohexanone oximes (**39, 42,** and **43**) and cyclohexanone oxime (**33**). Negative values indicate the signals for the methyl-substituted compounds and are at higher field.

Table VI
Aldoxime ^{13}C Substituent Parameters[a]

Aldoxime	$\Delta_{C=X}^{b}$	$\Delta_{\alpha\text{-syn}}^{b}$	$\Delta_{\alpha\text{-anti}}^{b}$	$\Delta_{\alpha\text{-syn}} - \Delta_{\alpha\text{-anti}}$	Δ_{β}^{b}
61	−52.0	−19.7		−3.8	
62	−51.6		−15.9		
64	−49.7		−14.2	−4.5	+4.9
65	−49.1	−18.7			+4.4
67	−50.4		−14.4	−4.5	+4.3
68	−49.9	−18.9			+3.7
70	−47.8		−11.8	−4.9	+4.5
71	−46.9	−16.7			+4.2
73	−50.0		−14.5	−4.3	+4.5 (1)
74	−49.5	−18.8			+4.1 (5)
76	−48.5		−11.8	−4.9	+4.5, +4.8
77	−47.9	−16.7			+4.5, +4.2
79	−49.4		−11.8	−4.9	+4.2
80	−48.6	−16.7			+3.9
82	−50.8		−14.6	−4.4	+3.4
83	−50.4	−19.0			+3.0
85	−48.4		−14.6	−4.1	+4.9
86	−48.4	−18.7			+4.9
88	−48.9		−11.6	−4.2	+4.2
89	−48.4	−16.2			+3.4

[a,b] See footnotes to Table IV.

phenylacetaldoxime (**85** and **86**), the ortho and meta carbons give a single unresolved signal. With cyclohexanecarboxaldoxime (**88** and **89**), the C2 and C6 resonances of the ring were assigned on the basis of a quite uniform downfield Δ_{β} effect for aldoximes (*cf.* Table VI). The remaining ring resonances were very close together.

The α-carbon substituent shifts for aldoximes, as mea-

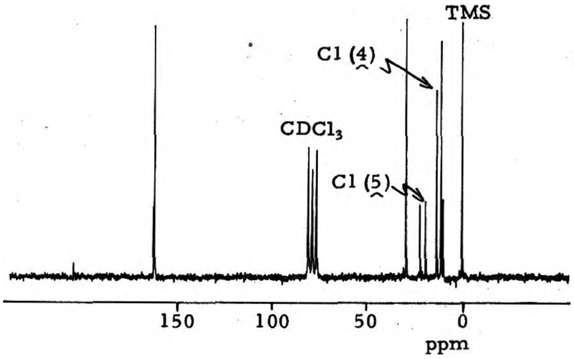


Figure 2. ^{13}C spectrum of butanone oxime + Cr(acac)$_3$.

sured by $\Delta_{\alpha\text{-syn}}$ and $\Delta_{\alpha\text{-anti}}$ (Table VI) fall into two ranges. If there is one substituent on the α-carbon, then $\Delta_{\alpha\text{-syn}} = -18.8$ ppm (std dev = 0.13) and $\Delta_{\alpha\text{-anti}} = -14.4$ ppm (std dev = 0.17), while with two substituents on the α-carbon $\Delta_{\alpha\text{-syn}} = -16.6$ ppm (standard deviation = 0.25) and $\Delta_{\alpha\text{-anti}} = -11.8$ ppm (std dev = 0.10). These differences seem regular enough to have diagnostic value.

Experimental Section

Oximes of cyclohexananone, camphor, and acetaldehyde were available commercially. The others were prepared from the carbonyl compound with a 20% excess of hydroxylamine hydrochloride in 15% aqueous sodium hydroxide solution at 60–70°. The oximes were distilled under reduced pressure or recrystallized before the spectra were taken. With menthone, this procedure gave four oxime isomers because of base-catalyzed interconversion of menthone and isomenthone. The oximes of these ketones were therefore synthesized using sodium acetate in methanol[15] in place of aqueous sodium hydroxide solution.

The ^{13}C spectra were obtained by the pulse-Fourier transform technique at 15.09 MHz, using the spectrometer described elsewhere.[16] The time for a 90° pulse was 10 μsec and the noise-modulated proton decoupling[17] covered a band width of 600 Hz. The single-frequency off-resonance decoupling (SFORD) technique has been described earlier.[17] The samples were run as approximately 1.5 M solution in CDCl$_3$ containing tetramethylsilane (TMS) as internal reference. The sample temperatures were about 35°.

For quantitative measurements, the following procedures were employed. First, from the full spectrum (5000 Hz, ~330 ppm) at least two completely resolved lines (one for each isomer) were singled out, usually in the saturated carbon region. Then, 55–60 mg of Cr(acac)$_3$ was dissolved in 2 ml of a 1.8–2.0 M solution of the oxime mixture and the spectrum repeated with a 3000-Hz spectral width, using the full 8K of available data storage of the computer to accumulate the free-induction decays. The flip angle was approximately 60° (7 μsec pulses) and the delay between pulses was 5–10 sec. The frequency-domain spectra then showed full peak widths at half-peak height of 3.5–4 Hz, compared to 1 Hz or less in the absence of Cr(acac)$_3$. There was 0.8 Hz/point in the resulting digitized spectra, which gave reasonably consistent peak height measurements. Further increase in the Cr(acac)$_3$ concentration resulted in loss of resolution without substantial improvement in the analyses. The chemical shifts were not substantially affected—there being less than 0.5 ppm change of the C=NOH resonance and 0.1 ppm of the other carbon signals.

Check determinations were made without Cr(acac)$_3$, using a 12-sec delay between 60° pulses. The way in which these were run did not eliminate the possibility of differential Overhauser effects from the proton decoupling. That this is important can be seen from results with acetone oxime where the ratios of the peak heights for the methyl carbons were 63:37 without Cr(acac)$_3$ and 52:48 with Cr(acac)$_3$. In some cases, as with methyl ethyl ketoxime (4 and 5), even with Cr(acac)$_3$, the peak intensities were still not in the expected ratios. With this substance, the syn α-methyl carbon of the dominant isomer shows a distinctly low intensity (Figure 2) compared to the other resonances.

Table VII
Aldoxime Isomer Distribution Obtained from ^{13}C Spectra

Aldoximes[a]	Percentage of major isomer	
	Pulse delays[b]	Lit.[c]
61, 62	64	61
64, 65	67	56
67, 68	56	54
73, 74	56	
70, 71	77	73
76, 77	68	70
79, 80	72	67
82, 83	51	
85, 86	49[d]	54
88, 89	71	70

[a] Presumed major isomer listed first. The uncertainties of the values obtained by the ^{13}C spectra are probably ±5%. [b] From ^{13}C spectra with 12-sec pulse delay. [c] Literature values from ref 1. [d] As reported in ref 1, the ratio changed with time: 17% after 1 hr, 34% after 3 hr, 44% after 10 hr, and 49% after 18 hr of the time the solution was prepared.

With the aldoximes, a new problem arose in that, with added Cr(acac)$_3$, there often appears to be substantial differential line broadening and changes in intensity of the minor isomer relative to the major isomer. This appears to be the result of differential complexing between isomers with the doping agent, and, for this reason, the isomer ratios reported in Table VII are only the result of determinations with 12-sec pulse delays. Hopefully, the use of ratios between analogously situated carbons in each isomer has diminished the contribution of differential Overhauser effects to these ratios. Where comparisons are possible, agreement with isomer ratios obtained by proton spectra[6] are reasonably satisfactory.

Registry No.—**1**, 67-64-1; **2**, 127-06-0; **3**, 78-93-3; **4**, 10341-63-6; **5**, 10341-59-0; **6**, 563-80-4; **7**, 10341-62-5; **8**, 10341-60-3; **9**, 75-97-8; **10**, 10341-64-7; **11**, 590-50-1; **12**, 49805-39-2; **13**, 49805-40-5; **14**, 24623-10-7; **15**, 49805-41-6; **16**, 103-79-7; **17**, 10048-64-3; **18**, 10048-65-4; **19**, 96-22-0; **20**, 188-11-0; **21**, 565-69-5; **22**, 49805-38-1; **23**, 49805-42-7; **24**, 564-04-5; **25**, 49775-30-6; **26**, 565-80-0; **27**, 1113-74-2; **28**, 1191-95-3; **29**, 2972-05-6; **30**, 120-92-3; **31**, 1192-28-5; **32**, 108-94-1; **33**, 100-64-1; **34**, 502-42-1; **35**, 2158-31-8; **36**, 502-49-8; **37**, 1074-51-7; **38**, 583-60-8; **39**, 32179-89-8; **40**, 49805-43-8; **41**, 591-24-2; **42**, 31661-10-6; **43**, 31661-09-3; **44**, 89-80-5; **45**, 49805-45-0; **46**, 49805-46-1; **47**, 491-07-6; **48**, 49775-31-7; **49**, 49805-47-2; **50**, 695-05-6; **51**, 49805-48-3; **52**, 49805-49-4; **53**, 497-38-1; **54**, 49805-50-7; **55**, 49805-51-8; **56**, 76-22-2; **57**, 37939-80-3; **58**, 700-58-3; **59**, 4500-12-3; **60**, 75-07-0; **61**, 5775-72-4; **62**, 5780-37-0; **63**, 123-38-6; **64**, 5775-80-4; **65**, 5780-46-1; **66**, 123-72-8; **67**, 5775-75-7; **68**, 5780-41-6; **69**, 78-84-2; **70**, 5775-73-5; **71**, 5780-39-2; **72**, 110-62-3; **73**, 5775-76-8; **74**, 5780-42-7; **75**, 96-17-3; **76**, 49805-55-2; **77**, 49805-56-3; **78**, 97-96-1; **79**, 49805-57-4; **80**, 49805-58-5; **81**, 15877-57-3; **82**, 49805-59-6; **83**, 49805-60-9; **84**, 122-78-1; **85**, 20268-21-7; **86**, 20259-49-8; **87**, 2043-61-0; 88, 30950-35-7; **89**, 30950-34-6.

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(1) Supported by the Public Health Service, Research Grant No. GM-11072 from the Division of General Medical Sciences, and by the National Science Foundation.

(2) NATO Postdoctoral Fellow, 1970–1972.

(3) Deutscher Akademischer Austauschdienst Postdoctoral Fellow; deceased Jan 1, 1973.

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Photochemical, Thermal, and Acid-Catalyzed Rearrangements of α,β-Epoxy Ketones. Synthesis of Spiro β-Diketones[1]

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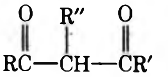
2-Cyclopentylidenecyclopentan-1-one oxide (**6**) and 2-cyclohexylidenecyclohexan-1-one oxide (**8**) have been isomerized thermally and photochemically *via* a 1,2-alkyl shift to spiro[4.5]decane-1,6-dione (**7**) and spiro-[5.6]dodecane-1,7-dione (**12**), respectively. Acid-catalyzed isomerization of **6** proceeds *via* a 1,2-acyl shift to yield spiro[4.5]decane-6,10-dione (**26**). Thermolysis of **8** also formed 1,2,3,4,6,7,8,9-octahydrodibenzofuran (**17**) in low yield. The mechanisms of these reactions are discussed. Photolysis and thermolysis of the epoxy ketones **6** and **8** in the presence of tri-*n*-butylstannane yielded the enones, 2-cyclopentylidenecyclopentan-1-one (**21**) and 2-cyclohexylidenecyclohexan-1-one (**22**), respectively.

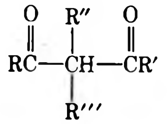
Recent work has indicated that isomerization of appropriately substituted α,β-epoxy ketones can serve as a useful preparative method for the synthesis of mono- (**1**) and disubstituted (**2**) β-dicarbonyl compounds.[2,3] This isomerization has been effected thermally,[4] photochemically,[5-14] and by using acidic catalysts.[2,3,15,16]

Owing to the number of isomerization products possible, it was of interest to learn the regiospecificity of the rearrangement for each of the various reaction conditions involved, and which was the preferred method to use synthetically.



$\overset{O}{\overset{\|}{RC}}-\overset{R''}{\overset{|}{C}H}-\overset{O}{\overset{\|}{C}}R'$

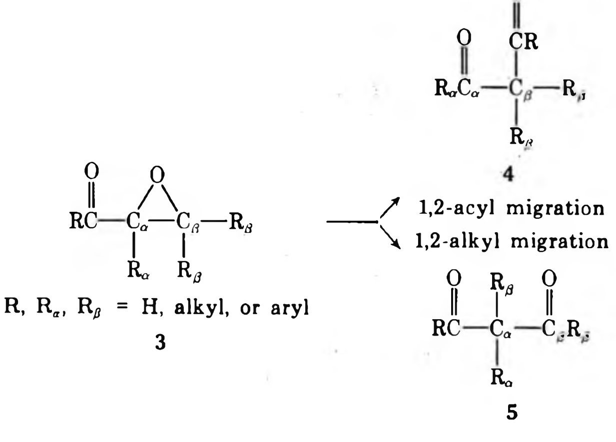
1



$\overset{O}{\overset{\|}{RC}}-\underset{\underset{R'''}{|}}{\overset{R''}{\overset{|}{C}H}}-\overset{O}{\overset{\|}{C}}R'$

2

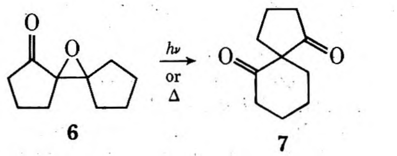
The isomerization of the α,β-epoxy ketones **3** can proceed *via* two major pathways. Isomerization *via* a 1,2-acyl migration yields the β-diketone **4**, whereas a 1,2-alkyl migration of R_β affords the different β-diketone **5**. A 1,2-alkyl migration of R_α affords an α-diketone. In this paper we report the results of the photochemical, thermal, and acid-catalyzed isomerizations of a series of spiro α,β-epoxy ketones *via* 1,2-acyl and 1,2-alkyl shifts to yield spiro β-diketones.



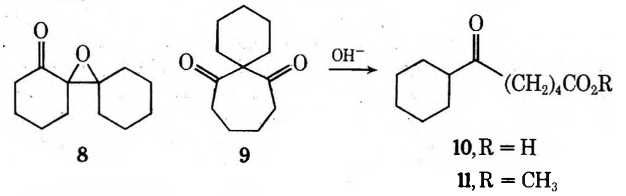
R, R_α, R_β = H, alkyl, or aryl

Results and Discussion

Recent studies[17-19] on the photolysis of the α,β-epoxy ketone **6** led to the convenient preparation of the spiro β-diketone **7**. However, the yield of **7** *via* this path was low (30%).[17,19] To improve the yield of this reaction, **6** was heated for 15 min at 225° and **7** was obtained as the only product in 89% yield.



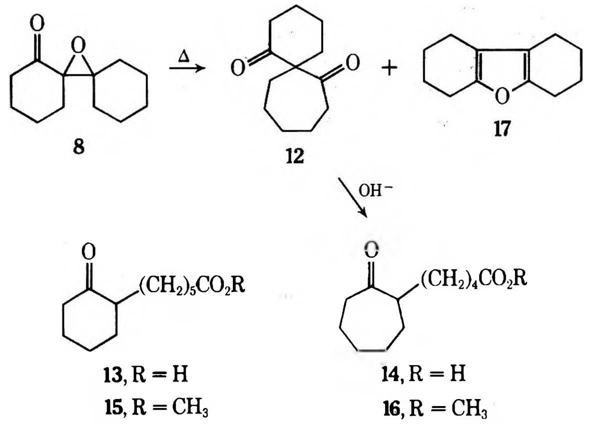
This result is in sharp contrast to the results of House and Wasson,[2] who reported that thermolysis of the six membered ring homolog of **6**, *i.e.*, **8**, afforded the spiro β-diketone **9**.



Reexamination of their structure proof for **9** showed that their structure was wrong. Alkaline hydrolysis of the proposed spiro β-diketone **9** afforded a keto acid to which the structure **10** was assigned.[2] The keto acid was characterized as its semicarbazone, mp 270–271°.[2] However, the literature melting point of the semicarbazone of **10** was 175°,[20] thereby indicating that **10** was not the correct structure for the hydrolysis product. Furthermore, authentic keto acid **10** was prepared according to the method of Reese[20] and shown to be different from the keto acid obtained as a hydrolysis product.

Since the keto acids had melting points near room temperature and were difficult to recrystallize, their methyl esters were prepared. Again the authentic methyl ester **11** showed different spectral properties from those of the ester obtained from the hydrolysis product. Therefore, what is the structure of the hydrolysis product and that of the β-diketone from which it is derived?

By analogy with the thermal isomerization of **6** to **7** and of pulegone oxide **23**,[4] thermolysis of **8** should proceed *via* a 1,2-alkyl shift to yield the spiro β-diketone **12**. Alkaline hydrolysis of **12** would then be expected to yield the keto acids **13** and **14**, which should be converted to the methyl esters **15** and **16**, respectively.

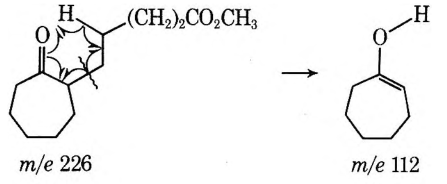


8 **12** **17**

13, R = H
15, R = CH_3

14, R = H
16, R = CH_3

Thermolysis of **8** yielded **12** (44%) together with 1,2,3,4,6,7,8,9-octahydrodibenzofuran (**17**) as a minor product (12%). The formation of **17** will be discussed later in this paper as part of the acid-catalyzed rearrangement products. Mass spectroscopy offered a very convenient method for distinguishing between the methyl esters **15** and **16**. McLafferty rearrangement of each of the keto esters should result in the transfer of a hydrogen and cleavage of the side chain attached to the cycloalkanone.[21] The mass spectrum of the keto ester hydrolysis product showed a base peak at *m/e* 112, due to the ion **18**. This indicates that the cycloheptanone **16** was the correct structure for the hydrolysis product. The structure of **16** was confirmed by synthesis from cycloheptanone and methyl 5-bromopentanoate.



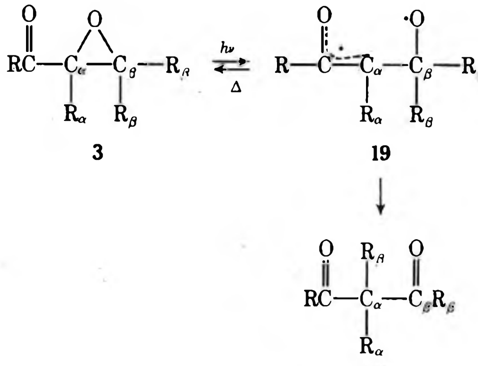
m/e 226
16

m/e 112
18

Therefore, it can be seen that thermolysis of the α,β-epoxy ketones **6** and **8** proceeds *via* 1,2-alkyl shifts to yield the spiro β-diketones **7** and **12**, respectively. These observations confirm the results of other α,β-epoxy ketone thermolyses which may also be explained by 1,2-alkyl shifts.[4]

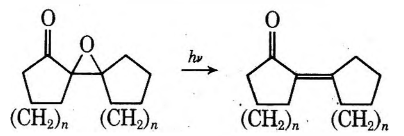
Since the photolysis of **6** proceeded *via* a 1,2-alkyl shift to yield **7**, the photolysis of the epoxy cyclohexanone **8** was also investigated. Irradiation of **8** in acetone gave the expected 1,2-alkyl shift product **12** in 14% yield as the only product. A literature survey on the photolysis of epoxy ketones to yield β-diketones showed that all photoisomerizations may be explained by 1,2-alkyl shifts (R sometimes equals H) of the β substituent.[5-14,17-19]

The most rational mechanism for the thermolysis and photolysis reaction is that they proceed *via* a reversible homolysis of the C_α-O bond. The carbonyl can then stabilize the radical charge at C_α as shown in the structure **19**. Concurrently or at a later stage R_β migrates to C_α, forming a carbonyl at C_α. However, recent quantum-yield data on the photolysis of optically active **6**[19] exclude one common diradical intermediate of type **19** for the three reaction paths involved (photoisomerization and photorearrangement to each isomer of the new product) in both the singlet and the triplet reactions. The quantum-yield data require that the rate of rearrangement is greater than the rate of rotation around the C_α-C_β bond in **19**, and that the rate difference is greater in singlet generated **19** than in the triplet analog.[19] Another possible explanation is that the C_α-C_β bond is cleaved followed by rotation which leads to racemization of **6**. In the formation of optically active **7** it is the R_β which is cis to the acyl group which migrates fastest in both the singlet and triplet reactions.



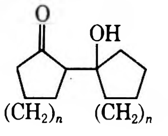
3 **19** **5**

In an effort to trap the intermediate oxy radical **19**, **6** and **8** were photolyzed in the presence of tri-*n*-butylstannane. However, none of the hydroxy ketone **20** was isolated; instead of starting enones **21** and **22** were obtained in very good yield. The above solutions were also heated at 50° for 2 hr and 30% of **21** and 20% of **22** were obtained.



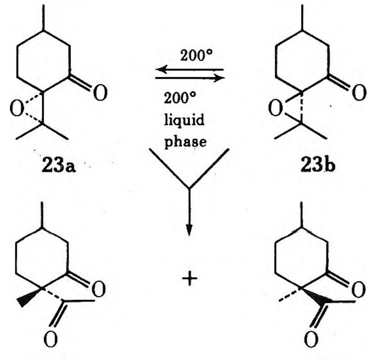
6, $n = 1$
8, $n = 2$

21, $n = 1$
22, $n = 2$

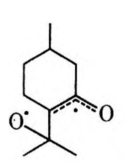


20

A similar stereospecificity has also been observed in the thermolyses of pulegone oxide.[4] The thermolysis of optically active pulegone oxide **23a** and **23b** in oxygen-containing solvents leads to the formation of **24a** and **24b** in relatively constant ratio. Here again the postulate of the thermolytic C_α-O epoxide cleavage to the intermediate **25**



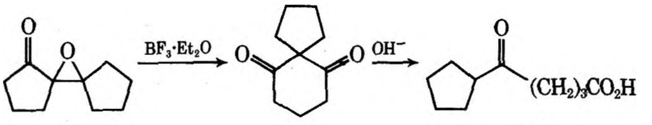
23a **23b** **24a** **24b**



25

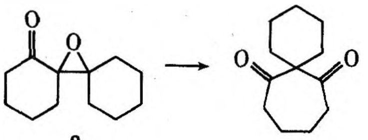
for the rearrangement requires that the rate of rearrangement is greater than the rate of rotation around the C_α–C_β bond in **25**. This result has been explained on the basis of a solvation complex.[4]

Since House and Wasson[2] had originally been interested in the acid-catalyzed rearrangement of **8**, we investigated the acid-catalyzed rearrangement of the previously uninvestigated epoxy ketone **6**. Treatment of **6** with boron trifluoride etherate afforded the spiro β-diketone **26**, which was different from that prepared by photolysis and thermolysis. Basic hydrolysis of the β-diketone **26** afforded the keto acid **27**. The spiro β-diketone **26** had previously been prepared by peroxytrifluoroacetic acid–boron trifluoride etherate oxidation of the enone **21**.[22]



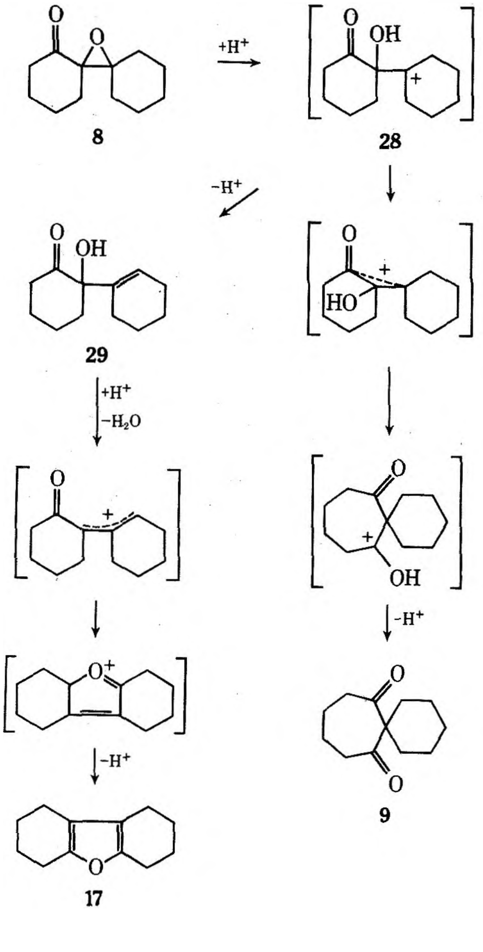
6 **26** **27**

More recently **8** has been isomerized to **9** in 93% yield using antimony pentachloride in liquid sulfur dioxide as the acidic catalyst.[16]

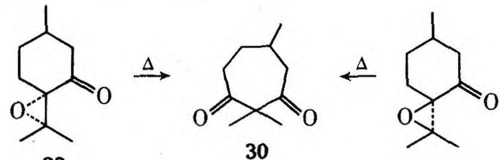


8 **9**

In both of the above cases the reaction can best be explained by a 1,2-acyl shift. Protonation of the epoxide **8** should cause the C_β–O bond to cleave, forming the hydroxy ketone **28**. If acyl migration now occurs, then the spiro β-diketone is formed. However, if a proton is lost from **28** to yield **29**, followed by loss of water, then 1,2,3,4,6,7,8,9-octahydrodibenzofuran (**17**) will be formed.[16] Thus it appears that the Lewis acid sites of the Pyrex glass surface in the thermolysis of **8** have resulted in the formation of a small amount of the dibenzofuran **17**. To confirm this hypothesis the glass surface was thoroughly washed with ammonia to remove these Lewis acid sites, and this resulted in a large decrease in the amount of **17** formed upon thermolysis.



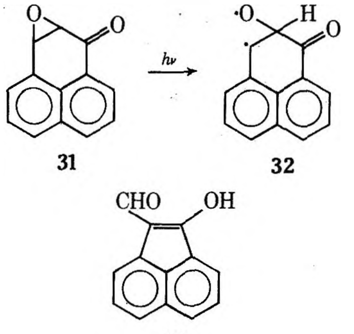
Similar 1,2-acyl shifts caused by Lewis acid sites in the Pyrex glass surface were also observed for the thermolysis of pulegone oxide **23** in the gas phase, resulting in the formation of the β-diketone **30**.[4]



23a **30** **23b**

Thus it appears that 1,2-alkyl migrations of R_α in α,β-epoxy ketones to yield β-diketones are best carried out thermally making sure all acidic catalysts have been removed. Acid-catalyzed rearrangements of α,β-epoxy ketones lead to a different β-diketone *via* a 1,2-acyl shift.

As with all generalizations, there is an exception. Recently, the photolysis of phenalenone oxide **31** to yield acenaphthen-1-one-2-carboxaldehyde (**33**) provided the first unambiguous example of a photochemical 1,2-acyl migration.[23] However this may be explained in that the C_β–O oxide bond in **31** would be expected to cleave first, leading to the stable intermediate biradical **32**.



31 **32** **33**

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer Infracord Model 137 spectrometer fitted with sodium chloride prisms. Ultraviolet spectra were determined in methanol with a Cary 14 recording spectrometer. Nmr spectra were obtained with Varian A-60A and XL100 spectrometers. The mass spectra were measured on an AE1 MS-9 mass spectrometer at an ionizing energy of 70 eV. Microanalyses were performed by Micro-Analysis Inc., Wilmington, Del. Vapor phase chromatography was done using an Aerograph, 90 P-3, on a 4 ft × 0.25 in. column which was packed with 20% Carbowax 20M on 60–80 mesh Chromosorb W AW-DMCS (column A) and on a 6 ft × 0.25 in. column which was packed with 15% SE-30 on 60–80 mesh Chromosorb W AW-DMCS (column B).

Photolysis of 2-Cyclopentylidenecyclopentan-1-one Oxide (6). A solution of **6** (132 mg) in acetone was photolyzed to yield **7** (40 mg) as previously reported.[17] Extensive attempts to isolate and characterize a by-product were unsuccessful.

Thermolysis of 2-Cyclopentylidenecyclopentan-1-one Oxide (6). **6** (42 mg) was sealed in a 7-mm test tube and heated for 15 min at 225°. After cooling, the product was isolated from the amber oil by preparative vpc on column A. A total of 37 mg (89%) of spiro[4.5]decane-1,6-dione (**7**) was obtained as a clear oil: bp 238–241° (lit.[17] bp 238–241°); ir ($CHCl_3$) 1732 (cyclopentanone C=O) and 1698 cm^{-1} (cyclohexanone C=O); mass spectrum (70 eV) *m/e* (rel intensity) 166 (38, M$^+$), 148 (14), 138 (35), 137 (20), 111 (100), 110 (90), 95 (34), 91 (27), 67 (52), 55 (74), 44 (95), 41 (67), identical with that of authentic **7**.

Thermolysis of 2-Cyclohexylidenecyclohexan-1-one Oxide (8). 8 (500 mg), synthesized according to the method of Reese,[20] was sealed in a 7-mm test tube and heated for 30 min at 250°. The residue was separated by preparative vpc on column A to yield 80 mg of reactant 8, 51 mg (12%) of 1,2,3,4,6,7,8,9-octahydrodibenzofuran (17)[16] as a clear oil, ir (CCl_4) 1600 and 1140 cm^{-1} (furan ring), nmr (CCl_4) δ 2.70–2.06 (m, 8 H) and 2.06–1.48 (m, 8 H), mass spectrum (70 eV) *m/e* (rel intensity) 176 (26, M^+), 148 (100), 120 (60), 105 (19), 92 (28), 91 (74), 79 (35), 77 (46), 65 (36), 51 (48), 41 (80), 39 (84), and 220 mg (44%) of spiro[5.6]dodecane-1,7-dione (12) as a colorless oil, bp 223–224° dec, ir (CCl_4) 1711 (cyclohexanone $C{=}O$) and 1696 cm^{-1} (cycloheptanone $C{=}O$), nmr ($CDCl_3$) δ 2.71–2.04 (m, 6 H) and 2.04–1.25 (m, 12 H), mass spectrum (70 eV) *m/e* (rel intensity) 194 (12, M^+), 176 (5), 166 (33), 148 (57), 125 (24), 124 (43), 123 (83), 119 (24), 111 (50), 109 (70), 98 (82), 97 (86), 95 (82), 91 (45), 81 (91), 79 (90), 67 (93), 55 (100), and 41 (98).

The diketone formed a monosemicarbazone which crystallized from ethanol as white plates, mp 223–224° (lit.[2] mp 224°).

To remove the Lewis acid sites, the 7-mm test tubes were immersed in concentrated ammonia for 3 days and oven dried before use. Using these base-washed tubes and following the method cited above, analysis of the reaction products by vpc on column B afforded 12 and 17 in the ratio 7.4:1, whereas without base washing the ratio was 3.8:1.

Hydrolysis of Spiro[5.6]dodecane-1,7-dione (12). A solution of 396 mg (2.04 mmol) of 12 and 2.0 ml (12 mmol) of 6 *N* aqueous sodium hydroxide in 14 ml of ethanol was refluxed for 30 min. After cooling, the reaction mixture was acidified with 10% aqueous hydrochloric acid and extracted three times with 30 ml of ether. The ether extracts were combined, washed with water until neutral, dried (Na_2SO_4), and evaporated *in vacuo*.

A total of 280 mg (65%) of 5-(2-cycloheptanone)pentanoic acid (14) was obtained as a clear oil. The product would not crystallize: ir (neat) 3100 (broad, OH of a carboxyl group) and 1700 cm^{-1} (broad, $C{=}O$ of a carboxyl group and a ketone); nmr ($CDCl_3$) δ 10.72 (s, 1 H, acid OH), 2.80–2.10 (m, 5 H), and 2.10–0.94 (m, 14 H).

The keto acid 14 was converted to its semicarbazone, which crystallized from ethanol as colorless needles: mp 158–160°; ir (KBr) 3460 (unassociated NH), 3250 and 3180 (associated NH superimposed upon a broad OH peak), 1708 ($C{=}O$ of a carboxyl group), and 1660 cm^{-1} ($C{=}O$ of an amide).

Anal. Calcd for $C_{13}H_{23}N_3O_3$: C, 58.09; H, 8.61; N, 15.60. Found: C, 58.18; H, 8.83; N, 15.37.

Preparation of Methyl 5-(2-cycloheptanone)pentanoate (16). To a solution of 250 mg (1.18 mmol) of 14 in 15 ml of dry ether was added slowly an ether solution of diazomethane until the solution remained yellow. Excess diazomethane was destroyed with 1 drop of 5% aqueous acetic acid. The reaction mixture was washed with water until neutral, dried (Na_2SO_4), and evaporated *in vacuo*. The product was isolated by preparative vpc on column A, which gave 150 mg (56%) of methyl 5-(2-cycloheptanone)pentanoate (15) as a clear oil: bp 275–276° dec; ir (CCl_4) 1740 (ester $C{=}O$) and 1702 cm^{-1} (cycloheptanone $C{=}O$); nmr (CCl_4) δ 3.56 (s, 3, CH_3O–); mass spectrum (70 eV) *m/e* (rel intensity) 226 (8, M^+), 195 (6), 177 (11), 166 (10), 159 (4), 149 (44), 137 (12), 123 (22), 112 (100), 98 (48), 97 (50), 87 (38), 84 (45), 74 (42), 67 (46), 55 (62), and 41 (58).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.04; H, 9.85.

Preparation of Methyl 6-Cyclohexyl-6-ketohexanoate (11). To a solution of 27 mg (0.13 mmol) of 6-cyclohexyl-6-ketohexanoic acid (10)[20] in 5 ml of dry ether was added slowly an ether solution of diazomethane until the solution remained yellow. The reaction was worked up as in the previous case. The product was isolated by preparative vpc on column A, which gave 20 mg (69%) of methyl 6-cyclohexyl-6-ketohexanoate (11) as a clear oil: bp 280–281°; ir (CCl_4) 1740 (ester $C{=}O$) and 1710 cm^{-1} (cyclohexanone $C{=}O$); nmr ($CDCl_3$) δ 3.64 (s, 3, CH_3O–); mass spectrum (70 eV) *m/e* (rel intensity) 226 (18, M^+), 195 (6), 185 (4), 177 (17), 170 (13), 166 (7), 158 (9), 153 (6), 149 (36), 143 (50), 139 (13), 115 (55), 111 (90), 101 (12), 97 (31), 87 (51), 83 (100), 81 (48), 73 (50), 67 (45), 59 (39), 55 (100), and 41 (53).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.09; H, 9.61.

Preparation of Methyl 5-(2-Cycloheptanone)pentanoate (16). To a suspension of 0.066 g (3.64 mmol) of sodium hydride in 10 ml of freshly distilled DMF was added slowly 0.25 g (2.23 mmol) of cycloheptanone and 0.44 g (2.25 mmol) of methyl 5-bromopentanoate. The yellow solution was stirred under nitrogen for 3 hr at 80°. After cooling, 25 ml of water was added, and the reaction mixture was concentrated. The residue was extracted with ether (3 × 50 ml). The ether extract was washed with brine until neutral, dried (Na_2SO_4), and evaporated *in vacuo*. The product was isolated by preparative vpc on column A, which gave 50 mg (10%) of methyl 5-(2-cycloheptanone)pentanoate (16) as a clear oil: bp 275–276° dec; ir (CCl_4), 1740 (ester $C{=}O$) and 1702 cm^{-1} (cycloheptanone $C{=}O$); nmr (CCl_4) δ 3.56 (s, 3, CH_3O–); mass spectrum (70 eV) *m/e* (rel intensity) 226 (8, M^+), 195 (6), 177 (11), 166 (10), 159 (4), 149 (45), 137 (12), 123 (22), 112 (100), 98 (48), 97 (50), 87 (38), 84 (45), 74 (42), 67 (47), 55 (62), 41 (58).

Photolysis of 2-Cyclohexylidenecyclohexan-1-one Oxide (8). A solution of 2.500 g (2.5 mmol) of 8 in 110 ml of acetone was stirred with a stream of nitrogen and irradiated with a 450-W Hanovia lamp through a Vycor filter. The reaction was stopped after 2 hr. The acetone solution was concentrated and preparative vpc on column B was used to collect 270 mg (54%) of reactant, 8, and 68 mg (14%) of spiro[5.6]dodecane-1,7-dione (12) (spectra identical with the spectra of the product obtained by thermolysis of the epoxide, 8).

Photolyses of 6 and 8 in Benzene with Tri-*n*-butylstannane. A solution of 10 mg of 6, 0.25 ml of benzene, and 85 mg of tri-*n*-butylstannane in a degassed 7-mm Pyrex test tube was irradiated with a 450-W Hanovia lamp for 2 hr. The vpc on column A indicated that over 95% of the reactant had been converted to 2-cyclopentylidenecyclopentan-1-one (21). The same procedure was used with compound 8, and, after 4-hr irradiation, over 90% of the reactant had been converted to 2-cyclohexylidenecyclohexan-1-one (22).

Duplicates of the above solutions were heated in a water bath at 50°. After 2 hr, 6 gave only 30% of 21, and, after 4 hr, 8 gave only 20% of 22.

Acidic Rearrangement of 2-Cyclopentylidenecyclopentan-1-one Oxide (6). A solution of 200 mg of 6 in 15 ml of benzene was treated with 0.2 ml of boron trifluoride etherate, and the resulting mixture was stirred at room temperature for 5 min. The reaction mixture was diluted with ether, washed with water, dried (Na_2SO_4), and concentrated under vacuum. The product was isolated by preparative vpc on column A. A total of 138 mg (69%) of spiro[4.5]decane-6,10-dione (26) was obtained as a clear oil: mp 10–11° (lit.[22] mp 11.5–12.5°); ir (CCl_4) 1725 and 1696 cm^{-1} (β-diketone); nmr (CCl_4) δ 2.57 (t, 4, methylene protons α to carbonyls) and 2.45–1.54 (m, 10); mass spectrum (70 eV) *m/e* (rel intensity) 166 (40, M^+), 138 (18), 137 (22), 125 (17), 111 (10), 110 (63), 109 (29), 97 (21), 96 (70), 95 (44), 79 (15), 77 (18), 70 (20), 68 (55), 67 (70), 66 (25), 55 (100), 43 (36), 42 (96), 41 (92), 40 (70), and 39 (94).

A solution of 97 mg (0.58 mmol) of 26 and 0.6 ml (3.6 mmol) of 6 *N* sodium hydroxide in 5 ml of ethanol was refluxed for 30 min. The product, after acidification with dilute aqueous hydrochloric acid, was extracted with ether. After removing the solvent the residue was converted directly to its semicarbazone, mp 180–181° (lit.[22] mp 180–182°).

Preparation of 6-Cyclohexyl-6-ketohexanoic Acid (10).[20] To a solution of 0.50 g (2.73 mmol) of 2-cyclohexylcyclohexan-1-one[20] in 0.6 ml of acetic acid was added slowly a solution of 0.9 g (11.1 mmol) of chromium trioxide, 1.25 ml of acetic acid, and 0.44 ml of water. This mixture turned dark green after a 5-min stirring over a steam bath. Then 1.75 ml of sulfuric acid in 25 ml of water was added, and the mixture was concentrated. The residue was extracted with ether (3 × 30 ml). The ether extract was washed with 50% sodium bicarbonate solution. The base wash was acidified with 10% hydrochloric acid and extracted with ether. The ether layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was crystallized with ether–petroleum ether (bp 30–60°) to give 0.26 g (45%) of 6-cyclohexyl-6-ketohexanoic acid as colorless needles: mp 54–55° (lit.[20] mp 58°); ir (KBr) 3200 (broad, OH of a carboxyl group) and 1700 cm^{-1} (broad, $C{=}O$ of a carboxyl group and a ketone).

The keto acid was converted to its semicarbazone, which crystallized from methanol as colorless needles: mp 174–176° (lit.[20] mp 175°); ir (KBr) 3460 (unassociated NH), 3240 (broad, OH of a carboxyl group), 1708 ($C{=}O$ of a carboxyl group), and 1660 cm^{-1} ($C{=}O$ of an amide).

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Registry No.—**6**, 36803-49-3; **7**, 36803-48-2; **8**, 26870,38-2; **10**, 20606-25-1; **10**, semicarbazone, 50803-78-6; **11**, 50803-79-7; **12**, 50803-80-0; **14**, 33371,95-8; **14** semicarbazone, 50803-81-1; **16**, 50803-82-2; **17**, 1010-77-1; **26**, 6684-66-8; cycloheptanone, 502-42-1; methyl 5-bromopentanoate, 5454-83-1; 2-cyclohexylcyclohexan-1-one, 90-42-6.

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Synthesis and Photorearrangement of 4,5-Epoxy-4,5-dihydropyrene

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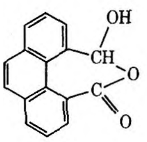
The title compound, 4,5-epoxy-4,5-dihydropyrene, which is important in cancer research was synthesized from pyrene *via* its ozonide and 4,5-phenanthrenedicarboxaldehyde. On ultraviolet irradiation, this epoxide rearranges to 2,3:3,4:4,5-tribenzoxepin, a new oxepin, 4-hydroxypyrene, pyrene, and other not yet identified products.

The importance of epoxides as intermediates in the metabolic detoxification of aromatic hydrocarbons has been established.[1] Aromatic epoxides can react to form a variety of products, including phenols and oxepins.[1,2] In recent years there has been considerable interest in synthesizing the K-region epoxides of carcinogenic hydrocarbons such as dibenz[*a,h*]anthracene,[3] benzo[*a*]pyrene, and 7,12-dimethylbenz[*a*]anthracene,[4] since these have been suggested as the possible carcinogenic metabolic intermediates in carcinogenesis by aromatic hydrocarbons.[5] Pyrene, a related noncarcinogenic hydrocarbon, is useful for comparative metabolic studies in laboratory animals and in *in vitro* cell culture studies.[6] Although important, the oxides of pyrene have not been successfully synthesized up to now. Boyland and Sims[6a] reported that in the oxidation of pyrene with perbenzoic acid an intermediate is formed which they believed to be 4,5-epoxy-4,5-dihydropyrene. This epoxide has also been detected as a microsomal metabolite of pyrene.[6c] The present paper describes the first reported synthesis of pure 4,5-epoxy-4,5-dihydropyrene (4). This epoxide is photochemically unstable and rearranges to form several products. It was of added importance, therefore, to study its photochemical rearrangement, as the intermediates formed therein may be of significance in the carcinogenic or detoxification processes of aromatic hydrocarbons.

Two general approaches have been used for the synthesis of K-region epoxides: (1) the conversion of dialdehydes[7] obtained by chemical oxidation of polycyclic aromatic hydrocarbons to the epoxide by the use of Mark's reagent, tris(dimethylamino)phosphine; (2) the cyclization of trans dihydrodiols with the dimethyl acetal of dimethylformamide.[4]



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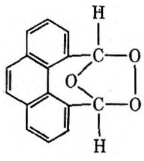

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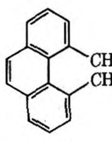

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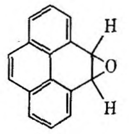

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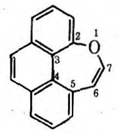

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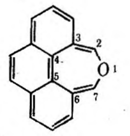


6

Previous attempts[8] to synthesize 4,5-phenanthrenedicarboxaldehyde by the catalytic hydrogenation of pyrene ozonide under various experimental conditions have resulted in the formation of 5-formyl-4-phenanthroic acid in the lactol form, I.[8] However, Sturrock and Duncan[9a] reported the formation of unstable, uncrystallizable, and impure dialdehyde in poor yield from the iodide reduction of pyrene monozonide. Criegee,[10] who prepared the dialdehyde by oxidation of *trans*-4,5-dihydroxy-4,5-dihydropyrene with lead tetraacetate, also reported similar findings. Both methods thus seemed unsuitable as preparative procedures.

In the present work, ozonization of a dilute solution of pyrene in anhydrous methylene chloride at -70° using 1 mol of ozone afforded mainly a colorless compound, mp 159-161°, in good yield. Based on its uv, ir, nmr, mass spectral, and C, H analysis, it was characterized as the monomeric monozonide of pyrene, 2.[9a,b] Catalytic hydrogenation of the ozonide 2 over Pd/C in ethyl acetate

Table I
Fluorescence Characteristics of Pyrene Epoxide and Photoproducts[a]

Compd	Conditions	Excitation maxima, mμ	Wave-length of analysis, mμ	Emission maxima, mμ	Wave-length of excitation, mμ
Pyrene epoxide	Ethanol, 2 μg/ml	*260*, 279 (sh), 298, 319	354	354, *379*, 396, 415 (sh)	262
	Cyclohexane, 2 μg/ml, deoxygenated	*260*, 278 (sh), 285 (sh), 298, 320	354	353, *373*, 392, 412 (sh)	262
	Cyclohexane–benzene (1:9), 2 μg/ml			(332) 355, *377*, 396, 418 (sh)	302
4-Hydroxypyrene	Ethanol, 0.08 μg/ml, deoxygenated	*239*, 270 (sh), 279, 342, 355 (sh), 377	380	*380*, 400, 420, 450 (sh)	262
4-Hydroxypyrene	Cyclohexane, 0.08 μg/ml, deoxygenated	*239*, 265 (sh), 275, 315 (sh), 328, 342, 347 (sh)	376	*376*, 396, 417, 440 (sh)	262
4-Methoxypyrene	Ethanol, deoxygenated	*239*, 268 (sh), 276, 315 (sh), 327, 339, 350 (sh)	375	*375*, 395, 417, 441	276
2,3:3,4:4,5-Tribenzoxepin	Ethanol, 2 μg/ml	*233*, 273, 290, 301	455	426, *455*, 488, 525, 570 (sh)	292
Pyrene	Ethanol, deoxygenated	*237*, 259, 269, 304, 317, 332	391	372, 382, *391*, 410 (sh), 437 (sh)	332

[a] 5-mμ slides were used both on the analyzer and exciter side; corrected excitation maxima in energy units and corrected emission maxima in quantum units; major peaks are italicized and shoulders are indicated in parentheses as sh.

yielded **1**, instead of the expected dialdehyde. Reduction of **2** with sodium iodide in glacial acetic acid yielded **1** and a crystalline solid in good yield. This solid was identified as 4,5-phenanthrenedicarboxaldehyde (**3**) by spectral and elemental analyses. In contrast to the earlier reports,[9a,10] compound **3** is stable and readily crystallized. The dialdehyde **3** was reduced to 4,5-bis(hydroxymethyl)-phenanthrene by lithium aluminum hydride. When refluxed with tris(dimethylamino)phosphine in dry benzene, the dialdehyde **3** was converted to 4,5-epoxy-4,5-dihydropyrene (**4**). The structure was confirmed by its uv, nmr, mass spectral, and combustion analysis.

Upon attempting to obtain fluorescence spectra in a deoxygenated cyclohexane solution, the epxide **4** was found to be photochemically unstable. This observation led to photochemical decomposition studies of pyrene epoxide in various solvents. Pyrene epoxide in deoxygenated anhydrous methylene chloride was irradiated at 254 mμ. Changes in the uv absorption maxima and intensities were noted while monitoring the reaction. Silica gel tlc of the reaction mixture showed eight distinct spots. The major product isolated (36%) has the structure 2,3:3,4:4,5-tribenzoxepin (**5**) as determined by mass spectrum, C, H analysis, and nmr, which was definitive in deciding between **5** and its isomer 3,4:4,5:5,6-tribenzoxepin (**6**). 4-Hydroxypyrene and pyrene, although present in small amounts, were also identified as irradiation products.

Pyrene epoxide **4** is quite stable in methylene chloride and cyclohexane solutions in the dark at −10° and its decomposition to 4-hydroxypyrene is negligible over a period of several months, as shown by uv absorption and thin layer chromatography. A summary of the fluorescence characteristics of pyrene epoxide and its derivatives is given in Table I.

In order to determine the effects of solvents in the photodecomposition, dilute solutions of pyrene epoxide in absolute ethanol, cyclohexane, and 1:9 (v/v) cyclohexane–benzene were irradiated in a fluorescence cuvette using a xenon lamp as light source. Since even short exposure of pyrene epoxide to ultraviolet light resulted in a strong phenol emission, the photodecomposition was monitored with respect to phenol formation. Figure 1, a plot of irradiation time *vs.* phenol fluorescence intensity, shows that the phenol concentration is significantly greater in ethanol than in cyclohexane or cyclohexane–benzene. Extrapolation of plots of fluorescence intensity *vs.* 1/time to infinite time (not shown) yield the final fluorescence intensity due to 4-hydroxypyrene formed. Since the fluorescence intensity was determined for 4-hydroxypyrene solutions of known concentrations, per cent conversion of epoxide to the phenol can be calculated. Thus 48 and 19% of epoxide is converted to the phenol in ethanol and cyclohexane, respectively. Although a direct comparison cannot be made, it appears that ~10% conversion to the phenol takes place in cyclohexane–benzene. These data indicate that as the hydrogen-donating ability of the solvent decreases, epoxide is largely converted to products other than phenol. For example, in methylene chloride, a poor hydrogen donor, the tribenzoxepin **5** is the major product of the photodecomposition of pyrene epoxide.

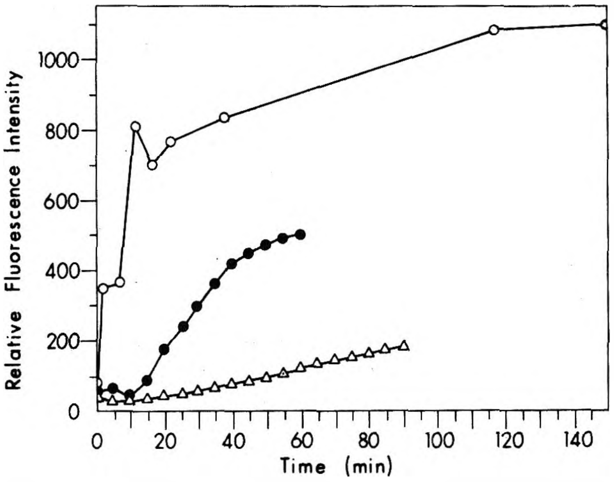
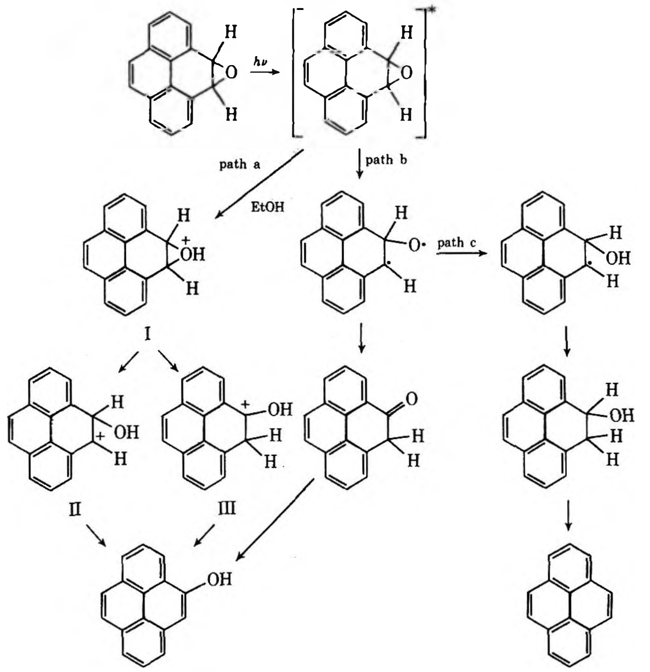


Figure 1. Photodecomposition of pyrene epoxide: ○, in absolute ethanol, λ_{ex} = 262, λ_{anal} = 380 mμ; ●, in cyclohexane, λ_{ex} = 262, λ_{anal} = 375 mμ; △, in 1:9 (v/v) cyclohexane–benzene, λ_{ex} = 302, λ_{anal} = 377 mμ.

Chart I



At present, a definitive mechanism for photolytic phenol formation cannot be postulated. The decomposition studies point to solvent participation by hydrogen-donating solvents. It is well known that molecules may become stronger bases (or acids) in the first excited singlet state.[11] Thus, in protolytic solvents such as ethanol, 4-hydroxypyrene may be formed according to path a in Chart I. This mechanism is similar to the ground-state mechanism postulated for acid-catalyzed cleavage of 1,3-cycloheptadiene oxide.[12] The protonated ground state intermediate (I) may undergo ring opening by C–O cleavage to form II or by an NIH shift[13] to form III. Both II and III can form the phenol by loss of a proton.

In nonprotolytic solvents such as cyclohexane and cyclohexane–benzene, the excited epoxide species may undergo homolytic C–O cleavage, yielding a stable benzylic biradical as shown in path b in Chart I. A 1,2-hydrogen shift, the equivalent of a free-radical type NIH shift, followed by tautomerization, would lead to 4-hydroxypyrene. A similar mechanism involving homolysis to a stable biradical followed by a 1,2-hydrogen shift has been postulated for the photodecomposition of epoxy olefins[14] and phenyloxirane.[15] Alternatively, the biradical might abstract hydrogen atoms from the solvent and form the reduced product pyrene after dehydration, as shown in path c, Chart I. The photolytic formation of benzene from benzene epoxide has been reported.[16] Since the experimental conditions for photolysis in cyclohexane and cyclohexane–benzene were not the same and since the nature of all major products is not known in these systems, it is at present not possible to explain why more phenol is formed during photolysis in cyclohexane than in cyclohexane–benzene.

The photochemical formation of 2,3:3,4:4,5-tribenzoxepin from pyrene epoxide may occur by a mechanism similar to that proposed for the formation of 2,3:4,5-dibenzoxepin from 9,10-dihydro-9,10-epoxyphenanthrene.[17] This mechanism involves a concerted rearrangement of the excited epoxide species followed by valence tautomerization to the oxepin.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 421 spectrophotometer as KBr pellets, and ultraviolet spectra with a Cary Model 14. Proton magnetic resonance spectra were recorded on the Varian Associates Model A-60A spectrometer in $CDCl_3$ using TMS as an internal standard. A custom-designed multipurpose luminescence spectrophotometer[18] was used to record the emission and excitation spectra. Corrected emission spectra were recorded in quantum units and corrected excitation spectra in energy units. The mass spectra reported below were obtained from the Morgan Schaffer Corp., Montreal, Canada. The sample was introduced through a direct inlet in most cases. The ozonizer used was a Welsbach Corp. Model T-408. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Thin layer chromatography (tlc) was carried out on precoated silica gel G plates (thickness 0.25 mm for analytical and 2.0 mm for preparative); spots were visualized with short- and long-wavelength uv hand lamps.

Pyrene Monozonide (2). Pyrene (2.02 g) dissolved in dry CH_2Cl_2 (400 ml) was cooled to −70° and treated with ozonized oxygen until 1 molar equiv had been added. It was immediately flushed with nitrogen to sweep out unreacted ozone. The brown residue obtained on evaporation of the pale yellow solution under reduced pressure at 35° was chromatographed on a silica gel column. A mixture of hexane-CH_2Cl_2 (6:4, v/v) eluted most of the unreacted pyrene (strong fluorescent band in uv) as the first fraction and then the monozonide, which crystallized from CH_2Cl_2–hexane mixture as colorless, shiny plates (1.3 g, 52.0%), mp 156–161° dec.[9] It exhibited the following spectral properties: uv max (EtOH) 212, 257, 263, 280, 292, 300, 338, and 355 nm (ϵ 34,700, 41,100, 44,300, 13,900, 12,500, 9300, 1300, 1400); ir[9a] 9.20, 9.50 (m-w), 10.5 (vs), 12.0 μ (m, twin peaks); nmr ($CDCl_3$) δ 6.70 (s, 2 H), 7.70 ppm (m, 8 H, aromatic); mass spectrum *m/e* 250 (parent ion); fluorescence excitation maxima (cyclohexane, deoxygenated, λ_{anal} 375 mμ) 255, 263, 290, 300, 338, 355 mμ; fluorescence emission maxima (λ_{ex} 255 mμ) 357, 375, 394, 413 mμ. *Anal.* Calcd for $C_{16}H_{10}O_3$: C, 76.79; H, 4.03. Found: C, 76.67; H, 4.12. Tlc in CH_2Cl_2-hexane (1:1, v/v) shows a single spot of R_f 0.7. It is sensitive to heat and light and does not form a precipitate with 2,4-dinitrophenylhydrazine. It releases iodine from sodium iodide solution in aqueous methanol and is stable at −10° for several months.

4,5-Phenanthrenedicarboxaldehyde (3). A mixture of the monozonide (1.0 g), sodium iodide (2.0 g), and acetic acid (45 ml) was allowed to stand at room temperature overnight and the liberated iodine was reduced with sodium thiosulfate solution. The mixture was extracted with CH_2Cl_2 and washed with sodium bicarbonate solution and water. The dried extract on concentration yielded colorless needles of 1, mp 272–276° dec (lit.[8c] mp 272–276°), which were filtered. The filtrate was concentrated and chromatographed on a silica gel column. Elution with CH_2Cl_2 gave first a colorless solid (0.2 g), mp 172–175° dec. The second fraction was the pale yellow dialdehyde (0.38 g). This was dissolved in dry ethyl acetate and filtered. The residue obtained on evaporation of the filtrate crystallized from CH_2Cl_2–hexane mixture as creamy-white needles (0.26 g, 28%), mp 169–171° (lit.[9,10] mp 169–171°). It had the following spectral characteristics: uv max (EtOH) 225, 251, 268 (sh), 296, 340 nm (sh) (ϵ 40,000, 26,900, 21,500, 22,700, 4800); ir 3.51, 3.62 (C–H stretch), 5.90, 5.92 μ (C=O stretch); nmr ($CDCl_3$) δ 7.91–8.23 (m, 8 H, aromatic), 10.13 ppm (s, 2 H, -CHO). *Anal.* Calcd for $C_{16}H_{10}O_2$: C, 82.04; H, 4.30. Found: C, 81.82; H, 4.39. Lithium aluminum hydride reduction of the dialdehyde afforded 4,5-bis(hydroxymethyl)phenanthrene which crystallized from CH_2Cl_2 as colorless needles, mp 159–161° (lit.[8b] mp 152–159°).

4,5-Epoxy-4,5-dihydropyrene (4). The dialdehyde (0.220 g) was dissolved in hot, dry benzene (10 ml) and tris(dimethylamino)phosphine (0.6 ml) was added to it. The mixture was heated to reflux under a nitrogen atmosphere. On addition of hexane and cooling, colorless crystals (0.145 g, 70.7%), mp 177–180° dec, were obtained. The product gives a single spot, R_f 0.34, on a silica gel plate using cyclohexane-dioxane (85:15, v/v) as solvent. However, some decomposition takes place when benzene is used as the eluent. The epoxide showed uv max (cyclohexane) 215, 256, 262, 270 (sh), 282, 288, 300 nm (ϵ 49,200, 48,600, 54,800, 30,800, 16,200, 16,100, 20,100) (*cf.* uv of the ozonide, 2); ir 8.1, 9.6, 12.1 μ; nmr ($CDCl_3$) δ 4.82 (s, 2 H), 7.88 (m, 8 H, aromatic); mass spectrum *m/e* 218 (parent ion). *Anal.* Calcd for $C_{16}H_{10}O$: C, 88.05; H, 4.62. Found: C, 87.68; H, 4.79. When refluxed in acetone with a few drops of HCl, it hydrolyzed to 4-hydroxypyrene. An authentic sample of the latter was prepared by acid-catalyzed dehydration of 4,5-dihydroxy-4,5-dihydropyrene,[19] mp 199–201° dec from

CH_2Cl_2-hexane mixture (lit.[20] mp 204-210° dec). The uv absorption spectrum of the phenol is identical with that reported in the literature.[6a] Its tlc in cyclohexane-dioxane (85:15, v/v) has R_f 0.13.

Irradiation of 4,5-Epoxy-4,5-dihydropyrene (4) in Methylene Chloride. Isolation of 2,3:3,4:4,5-Tribenzoxepin (5). The epoxide (0.110 g) dissolved in dry CH_2Cl_2 (200 ml) in a quartz vessel was irradiated at 254 nm using two mineral light uv lamps while N_2 was bubbled through the solution. The uv absorption of aliquots of the photolysis mixture showed an increase in the intensity of a new peak at 241 nm (4-hydroxypyrene) and later of another peak at 232 nm while the intensity of the epoxide peaks at 262 and 300 nm was decreasing. At the end of 15 hr, when all the epoxide has reacted, the solution was concentrated under reduced pressure and preparative tlc of the residue was carried out in the cyclohexane-dioxane (85:15, v/v) mixture.

The greenish fluorescent band of R_f 0.79 was identified to be pyrene by tlc, uv, fluorescence, and mass spectrum. In order to determine whether pyrene is indeed a photoproduct, the epoxide was chromatographed for contamination by pyrene. Although minute amounts of pyrene were detected by fluorescence emission spectroscopy, the amount of pyrene found after irradiation far exceeded that present as a contaminant of the starting epoxide.

The major band with R_f 0.71 on rechromatography and crystallization from hexane yielded colorless plates (0.04 g, 36.4%), mp 130-131°. It had the following spectral characteristics: uv max (EtOH) 232, 240 (sh), 276 (sh), 293, and 305 nm (ϵ 63,000, 48,200, 13,500, 14,400 and 13,000); ir 3.28, 6.00, 7.90, 8.10, 9.48, 9.50, 12.0, 12.8, 13.8, and 14.2 μ; nmr ($CDCl_3$) δ 5.90 and 6.53 (2 H, olefinic, J = 6.5 Hz), 7.42 ppm (m, 8 H, aromatic); mass spectrum m/e 218 (parent ion). *Anal.* Calcd for $C_{10}H_{16}O$: C, 88.05; H, 4.62. Found: C, 87.96; H, 4.75.

The band of R_f 0.26 was characterized as 4-hydroxypyrene by fluorescence excitation and emission spectra and uv and by converting it to 4-methoxypyrene by treating its methanolic solution with a solution of diazomethane in ether. This had identical tlc, fluorescence, and uv absorption characteristics with those of an authentic sample prepared similarly, mp and mmp 122-124° (lit.[19] mp 128-129°). However, 4-hydroxypyrene was present in small amounts in the irradiated mixture.

Effects of Solvents on the Photodecomposition of 4,5-Dihydro-4,5-epoxypyrene Pyrene epoxide was dissolved in three different solvents: (1) ethanol, (2) cyclohexane, and (3) 1:9 (v/v) cyclohexane-benzene. The concentration of pyrene epoxide in each solvent was 2 μg/ml. In order to preclude catalysis by impurities, the fluorescence cuvette was soaked in chromic acid for 15 min, rinsed thoroughly with distilled water, washed with nonfluorescent soap to destroy residual acid, and rinsed again with distilled water. The epoxide solution in the cuvette was deoxygenated by vigorously passing dry nitrogen through the sample for 12 min. The cuvette was stoppered with a glass stopper and sealed with parafilm to prevent oxygen from entering. Since the absorption maximum of pyrene epoxide is at 262 mμ, the samples in ethanol and cyclohexane were excited at this wavelength. In the cyclohexane-benzene system, 302 mμ was used as the excitation wavelength since benzene absorbed too strongly at 262 mμ. Fluorescence emission spectra were recorded every 5 min except for pyrene epoxide in ethanol, where photochemical decomposition proceeded extremely fast. In this case, fluorescence intensities were measured at the epoxide and phenol emission maxima at the beginning of the irradiation and spectra were recorded as the reaction slowed down; 5-mμ slits were used both on the analyzer and the exciter side.

Acknowledgment. This work was supported by Grant E-632 from the American Cancer Society and USPHS Grant ES-00260.

Registry No.—**1**, 50803-86-6; **2**, 16203-57-9; **3**, 16162-34-8; **4**, 37496-00-7; **5**, 50803-87-7; pyrene, 129-00-0; 4-hydroxypyrene, 31700-39-7; 4-methoxypyrene, 50803-88-8.

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Synthesis of 4,7-Dimethoxy-1,3,6-trimethylphenanthrene and 4,5-Dimethoxy-1,3,6,8-tetramethylphenanthrene by Photolysis of *trans*-5,5′-Dimethoxy-2,2′,4,4′-tetramethylstilbene[1]

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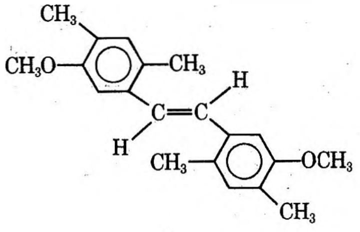
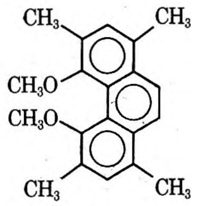
The synthesis of *trans*-5,5′-dimethoxy-2,2′,4,4′-tetramethylstilbene (1) starting from 2,5-dimethylfuran and dimethyl acetylenedicarboxylate is described. Photolysis of 1 in the presence of oxygen and iodine afforded 4,5-dimethoxy-1,3,6,8-tetramethylphenanthrene (2) in 4.5% yield and 4,7-dimethoxy-1,3,6-trimethylphenanthrene (3) in 15.5% yield, by loss of the elements of methane rather than hydrogen.

The main objective of this work was to synthesize *trans*-5,5′-dimethoxy-2,2′,4,4′-tetramethylstilbene (1) in the expectation that, on photolysis, 4,5-dimethoxy-1,3,6,8-tetramethylphenanthrene (2) would be obtained in good yield. As shown in Chart I, the synthesis of 1 was accomplished in excellent overall yield starting from the adduct between 2,5-dimethylfuran and dimethyl acetylenedicarboxylate,[3] 7, and proceeding through the known[3] compounds dimethyl 3-hydroxy-4,6-dimethylphthalate (8) and 3-hydroxy-4,6-dimethylphthalic acid (9). Unfortunately for our purposes, the photolysis of 1 yielded more 4,7-dimethoxy-1,3,6-trimethylphenanthrene (3, 15.5%) than 2 (4.3%), by loss of the elements of methane rather than hydrogen. Accordingly, a better synthesis of 2 is now being sought in our laboratories.



1



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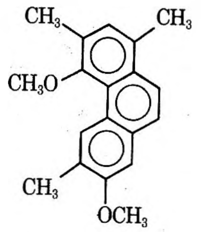
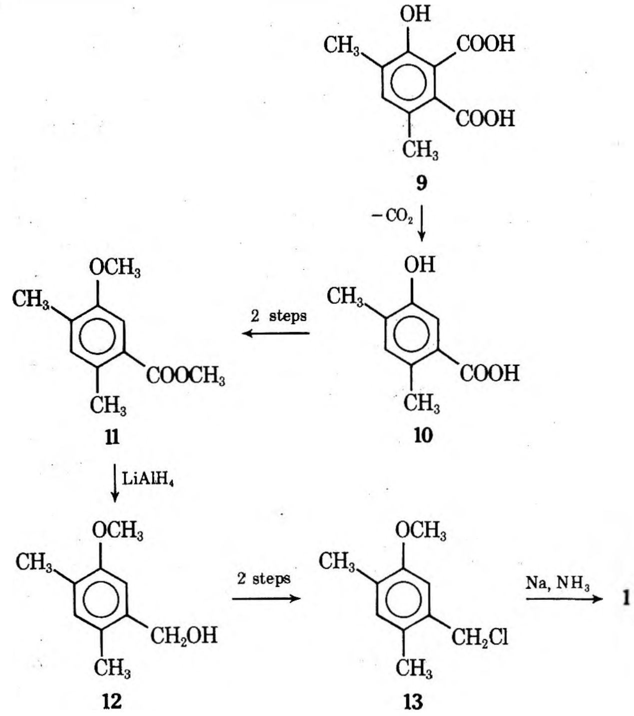


3

The successful photolyses of a variety of stilbenes in the presence of air or iodine to form phenanthrenes have been studied extensively,[4-6] although relatively few cases of phenanthrene formation have been studied with stilbenes which have a group (or groups) which end up in the 4 (or 5) position of phenanthrene. Only in the case of 5,5′-difluoro-2,2′-dimethylstilbene[7] (4) has the loss of methane been noted. In this case the yield of 4,5-difluoro-1,8-dimethylphenanthrene (5) was 49% (loss of H, H) and of 4,7-difluoro-1-methylphenanthrene (6) (loss of CH_3, H) was 13%. Possibly the reason why cyclization to 2 occurred to such a small extent in the case of 1 is that the two methoxy groups which would end up in the 4 and 5 positions of 2 are each buttressed by adjacent methyl groups and the resulting steric effect is responsible.

The synthesis of 1 is outlined in Chart I and the experimental details are described in the Experimental Section.

Chart I



The rearrangement of 7 to 8 on a small scale has been described and discussed.[3] On a much larger scale we have obtained 8 in 85% yield. After hydrolysis of 8 to 9, selective decarboxylation to 10 was readily effected by heating with copper in quinoline.[8] The conversion of 10 to 11 was best effected in 86% overall yield by esterification with methanol[9] followed by methylation of the sodium phenolate with methyl iodide in methanol–DMSO. The conversion of 12 to 13 was accomplished in excellent yield by treatment of the mesylate with sodium chloride by phase-transfer catalysis.[10] On treatment with sodium amide in liquid ammonia, 13 was converted into 1 in 76% yield.[11] Although many photochemical experiments were tried, the maximum yield of 2 was never greater than 4.3%.

Experimental Section[12]

Dimethyl 3-Hydroxy-4,6-dimethylphthalate (8). A total of 127 g (1.31 mol) of 2,5-dimethylfuran[13] and 187 g (1.32 mol) of freshly distilled dimethyl acetylenedicarboxylate,[14] bp 110° (29 mm), was sealed in seven Pyrex tubes which were held at 100° for 10 hr in an oven.[15] The contents of the tubes were combined and added with stirring to 400 ml of distilled trifluoroacetic acid, bp 72°, at 0°. Cooling was necessary to keep the temperature below 10°. After 72 hr at room temperature the trifluoroacetic acid was recovered by vacuum distillation and the residue yielded 257 g (85% overall)[16] of 8, bp 115° (0.4 mm), which had ir, nmr, and mass spectra as described.[3]

2,4-Dimethyl-5-hydroxybenzoic Acid (10). The above ester was hydrolyzed to 3-hydroxy-4,6-dimethylphthalic acid (9) as described[3] in 97% yield (crude). The crude acid was used for decarboxylation. In the best of several experiments, a stirred mixture of 38.5 g of **9**, 1 g of copper powder,[17] and 150 ml of distilled quinoline was heated from 200 to 230° during 3 hr, at which time 90% of the theoretical amount of CO_2 had been collected and no more was being evolved. After the usual work-up, crystallization of the residue from toluene-cyclohexane (1:3) yielded 27.6 g (90%) of **10**,[18] mp 187-188°, nmr δ 2.24 (s, 3, CH_3), 2.48 (s, 3, CH_3), 7.02 (s, 1, Ar), and 7.49 (s, 1, Ar).

Anal.[19] Calcd for $C_9H_{10}O_3$: C, 65.0; H, 6.1. Found: C, 65.2; H, 6.1.

Methyl 2,4-Dimethyl-5-methoxybenzoate (11). A mixture of 40 g of anhydrous $CaSO_4$ (40-80 mesh dried at 130° under reduced pressure), 72.5 g of **10**, 19 g of cation resin (AG 50W-X4, Biological and Radiation Laboratories, Richmond, Calif.), and 100 ml of absolute methanol was stirred and refluxed into a Soxhlet extractor containing 50 g of $CaSO_4$ for 15 hr. The cooled mixture was filtered and the solid was washed with 100 ml of methanol and 100 ml of ether. The solvents were removed on a rotary evaporator and the product was worked up as usual to yield 6 g (8%) of recovered **10** and 73.7 g (87%) of methyl 2,4-dimethyl-5-hydroxybenzoate, mp 88-89°, nmr methyl singlets (1 each) at δ 2.25, 2.49, and 3.87, ArH (1 each) at 6.98 and 7.43, after recrystallization from benzene-cyclohexane (1:3).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.7; H, 6.7. Found: C, 66.5; H, 6.7.

A solution of 146.7 g of the above ester in 500 ml of pure DMSO was added at 0° to a solution under nitrogen prepared by treating 29 g of sodium with 150 ml of methanol and 500 ml of DMSO. To the above solution was added 243 g of methyl iodide during 20 min while maintaining the temperature below 35°. After heating to 80° for 8 hr the NaI was collected by filtration and washed with benzene. After adding 2 l. of benzene and 1 l. of water to the filtrate, there was obtained 156.7 g (99%) of **11** as colorless needles suitable for reduction. A sample purified by vaporization to a cold finger melted at 36-37°, nmr methyl singlets (1 each) at δ 2.25, 2.49, 3.78, and 3.80, ArH (1 each) at 6.85 and 7.31.

In another similar experiment vacuum distillation of the crude product before crystallization afforded **11**, bp 72° (0.2 mm), in 91% yield.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3. Found: C, 68.2; H, 7.2.

2,4-Dimethyl-5-methoxybenzyl Alcohol (12). To the solution obtained by refluxing 1 l. of pure THF and 42 g of $LiAlH_4$ overnight was added dropwise a solution of 154.8 g of **11** in 300 ml of THF. The stirred mixture was held at reflux until tlc on silica gel showed that no **11** (R_f, $CHCl_3$, 0.92, C_6H_6, 0.68) remained (5 hr). After the usual work-up, crystallization from 1 l. of hexane yielded 122 g (92%) of **12**, mp 56-57°, nmr methyl singlets at δ 2.17, 2.20, and 3.78, CH_2OH (s, 4.58), ArH at 6.83 and 6.90. Distillation of the material in the residue afforded 7 g (6%) of **2**, bp 110-115° (0.5 mm).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.3; H, 8.5. Found: C, 72.5; H, 8.4.

2,4-Dimethyl-5-methoxybenzyl Chloride (13). To a stirred solution of 5.4 g of **12** and 4.5 g of triethylamine in 20 ml of benzene was added 7.0 g of methanesulfonyl chloride. After stirring at room temperature for 4 hr the precipitated salt was removed by filtration and washed with benzene. The combined filtrate and washings were washed twice with cold saturated brine. To the resulting benzene solution was added 0.2 g of Aliquat-336,[20] 30 ml of saturated KCl, and 20 g of powdered KCl. After stirring for 20 hr the benzene layer was worked up in the usual way to afford 5.5 g (93%) of crude **13** as a yellowish oil. Because of sensitivity to moisture and heating, attempts to obtain an analytically pure sample were not made. The nmr spectrum, methyl singlets (1 each) at δ 2.24 and 3.70, CH_2Cl (s, 4.49), ArH (1 each) at 6.72 and 6.89, was consistent with that to be expected from **13**. The mass spectrum showed a parent peak at *m/e* 184 (calcd 184) and P + 2, 186, 31.5% (lit.[21] 32.6%). Our experience showed that for best yields in the next reaction the chloride should be used as soon as isolated with no attempts at purification.

***trans*-5,5′-Dimethoxy-2,2′,4,4′-tetramethylstilbene (1).** In the best of several experiments, a solution of 15.9 g of **13** in 30 ml of dry ether was added rapidly to a stirred suspension at −78° of sodium amide prepared from 3.7 g of sodium and 300 ml of liquid NH_3 (distilled from Na). After the solution was maintained at −78° for 2.5 hr, 4 g of NH_4Cl was added and the ammonia was allowed to evaporate overnight. The usual work-up afforded a yellow residue which was chromatographed on a 15 × 0.75 in. column of Woelm grade A alumina using 3 l. of 1:1 benzene-cyclohexane to yield a colorless solid. On crystallization from 500 ml of 1:6 benzene-ethanol there was obtained 9.7 g (76%) of **1**: mp 168-169°; nmr CH_3 singlets at δ 2.23, 2.35, and 3.88, ArH and vinyl H, 6.98-7.14; uv (cyclohexane) 227 nm (ϵ 16,000), 292 (12,700), 330 (15,300); mass spectrum *m/e* 296 (calcd, 296).

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.0; H, 8.1. Found: C, 81.2; H, 8.0.

When the crude, but quite pure, bromide corresponding to **13**, prepared in over 90% yield by using a solution of sodium bromide instead of sodium chloride, was treated similarly with sodium amide, there was isolated by chromatography 11% of **1** and 22% of 5,5′-dimethoxy-2,2′,4,4′-tetramethyldibenzyl, mp 122-123°, nmr methyl singlets at δ 2.17, 2.21, and 2.81, methylene H at 3.75, and ArH at 6.02 and 6.59.

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.5; H, 8.8. Found: C, 80.5; H, 8.8.

4,5-Dimethoxy-1,3,6,8-tetramethylphenanthrene (2) and 4,7-Dimethoxy-1,3,6-trimethylphenanthrene (3). A solution of 3.4 g (0.0115 mol) of **1** and 1.60 g (0.0063 mol) of iodine in 2 l. of distilled cyclohexane was flushed with oxygen for 1 hr in a three-necked photolysis tube of quartz, equipped with an oxygen inlet, condenser, thermometer, and a 450-W Hanovia high-pressure mercury lamp. After the oxygen flow was discontinued, irradiation was conducted at 33-35° during which uv spectra were taken every 30 min. Irradiation was stopped after 4 hr when the ratio of phenanthrene absorbance at *ca.* 265 mμ and of stilbene absorbance at *ca.* 225 mμ was about three. The photolysis solution was washed with aqueous sodium bisulfite to remove iodine and worked up in the usual manner. The yellow residue was passed through a dry alumina column (10 × 0.5 in., Woelm alumina for dry-column chromatography, Waters Associates, Inc.) and eluted with cyclohexane until the lowest blue fluorescent band nearly reached the bottom of the column. After the top yellow and rainbow bands were removed by application of air pressure to the bottom of the column, the remainder was extracted with cyclohexane, ethanol, and ether. The solvent (about 1000 ml) was rotary evaporated. The residue was recrystallized from 10 ml of ethanol at room temperature for 2 days to give 0.20 g of solid and mother liquor. The solid was recrystallized twice from 5 ml of ethanol to give 0.15 g (4.3%) of **2**: mp 130-131°; ir 6.12, 6.23, 9.05, 9.81, and 9.99 μ; nmr CH_3 singlets at δ 2.47, 2.63, and 3.27, ArH (2 each) at 7.24, 7.67; uv λ_{max} (cyclohexane) 223 mμ (ϵ 13,200), 262 (33,600), 295 (13,200), and 335 (9400); exact mass 294.16190940 (calcd, 294.16240925).

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.6; H, 7.5. Found: C, 81.4; H, 7.6.

From the above mother liquor 0.8 g of crude **3** was obtained by further crystallization from ethanol. Recrystallization from 10 ml of ethanol yielded 0.5 g (15.5%) of **3**: mp 84-85°; ir 6.15, 6.36, 9.16, 9.78, and 10.05 μ; nmr CH_3 singlets at δ 2.47, 2.48, 2.62, 3.69, and 3.71, ArH singlets at 7.04 and 7.13, AB pattern at 7.49 and 7.69 (J = 9 Hz), and a singlet at 9.38 (the H at position 5 due to deshielding by the 4-OCH_3); uv λ_{max} (cyclohexane) 230 mμ (ϵ 16,300), 259 (55,400), 265 (64,900), 283 (14,400), 301 (11,100), and 313 (11,100); exact mass 280.14654235 (calcd, 280.14632020).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.4; H, 7.2. Found: C, 81.2; H, 7.2.

When Pyrex was used instead of quartz there was obtained a small amount of *cis*-5,5′-dimethoxy-2,2′,4,4′-tetramethylstilbene: mp 88-89°; nmr, two $ArCH_3$ singlets at δ 2.11 and 2.15, OCH_3 singlet at 3.40, three singlets, vinyl H, ArH at 6.49, 6.65, and 6.86; uv λ_{max} (cyclohexane) 226 mμ (ϵ 16,500), 230 (15,900), and a broad flat band at 250-305 (7100). When the irradiation was carried out in ethanol under similar conditions, no phenanthrene derivatives were formed.

Registry No.—*trans*-**1**, 50790-94-8; *cis*-**1**, 50790-95-9; **2**, 50790-66-4; **3**, 50790-67-5; **7**, 762-42-5; **8**, 22481-09-0; **10**, 50790-68-6; **11**, 32644-91-0; **12**, 32644-92-1; **13**, 50790-69-7; **13** bromide, 50790-70-0; 2,5-dimethylfuran, 625-86-5; methyl 2,4-dimethyl-5-hydroxybenzoate, 50790-71-1; methanesulfonyl chloride, 124-63-0; 5,5′-dimethoxy-2,2′,4,4′-tetramethyldibenzyl, 50790-72-2.

References and Notes

(1) This work was supported by Grant GP-12445 of the National Science Foundation.
(2) This research formed part of the M.S. Thesis presented by H. M. Chung to The Ohio State University in 1972.
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(12) All melting points and boiling points are uncorrected. Ir spectra were recorded using a Perkin-Elmer Infracord using NaCl disks or KBr pellets. Nmr spectra were recorded on a Varian A-60 instrument and are reported as δ units (TMS = .0) in $CDCl_3$. Uv spectra were run using a Cary 14 recording spectrophotometer. The phrase "worked up in the usual way" means that an ether-benzene solution of the products was washed with dilute acid and/or base, with saturated NaCl solution. The ether-benzene solution was then filtered through a cone of $MgSO_4$ and the solvent was removed on a rotary evaporator.

(13) Used as obtained from the Chemical Samples Co., Columbus, Ohio.

(14) Obtained from the Aldrich Chemical Co., Milwaukee, Wis.

(15) If desired the crude product may be purified by distillation to yield 7 bp 90° (0.3 mm), in 95% yield. However, the yield of 8 is the same if the crude product is used.

(16) In a similar experiment at 125° a very low yield of adduct 7 was obtained.

(17) Venus 44-F, obtained from the U. S. Bronze Powders, Inc., Flemington, N. J. In a similar experiment in which the copper was omitted, the yield was 81%. Hence studies in which copper is replaced by other solids may be of interest.

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Mechanistic Aspects of 2,3-Benzofulvene Formation from Sensitized Irradiation of 7-Azabenzonorbornadienes

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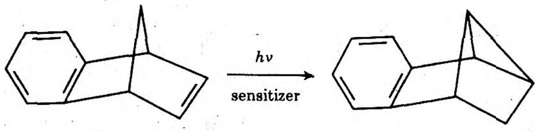
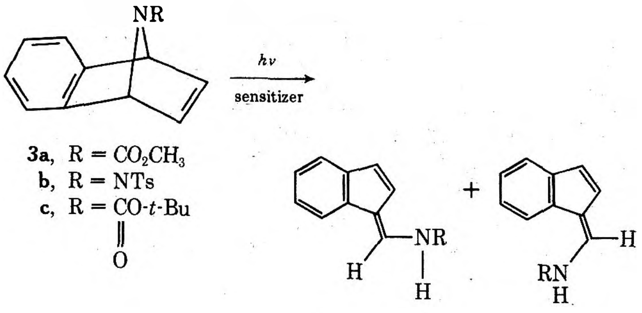
The singlet and triplet photochemistry of 7-*tert*-butoxycarbonyl-2,3-benzo-7-azabicyclo[2.2.1]hepta-2,5-diene (**3c**) has been studied. While direct excitation of **3c** at 300 nm affords *tert*-butyl 3-benzazepine-3-carboxylate (**6c**) with low efficiency (Φ = 0.05), acetone-sensitized irradiation yields 5-*tert*-butoxycarbonyl-5-azatetracyclo[5.4.0.0^{2,4}.0^{3,6}]undeca-1(7),8,10-triene (**7c**) in high synthetic yield (93%) and with high efficiency (Φ = 0.93). The structure assignment for **7c** is supported by spectroscopic data and its hydrogenation and acid-catalyzed rearrangement reactions. The general mechanism for 2,3-benzofulvene formation from triplet-sensitized rearrangement of 7-azabenzonorbornadienes is discussed.

The photochemical rearrangement of various benzonorbornadiene derivatives to tetracyclic products *via* the di-π-methane reaction is well characterized (*i.e.*, **1** → **2**).[2]



1 2

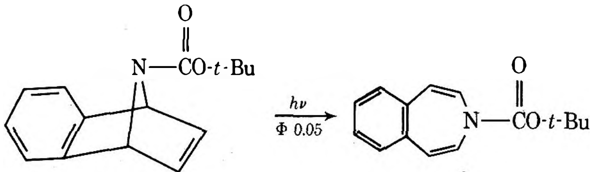
However, a photochemical study of the 7-aza derivative **3a** did not afford tetracyclic products analogous to **2**, but instead benzofulvene derivatives **4** and **5**.[3] We wish to report here the details of the direct and photosensitized rearrangement of **3c** and the establishment of one mechanistic pathway for the production of benzofulvene derivatives from sensitized irradiation of 7-azabenzonorbornadienes.



3a, R = CO_2CH_3
b, R = NTs
c, R = CO-*t*-Bu (C=O)

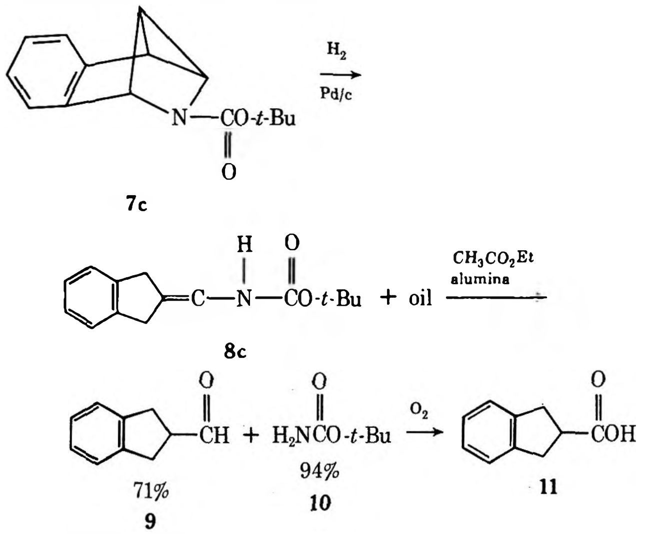
4 5

Irradiation of 7-*tert*-Butoxycarbonyl-7-azabenzonorbornadiene (3c). Direct irradiation of **3c** in cyclohexane at low conversion produces *tert*-butyl 3-benzazepine-3-carboxylate in low quantum efficiency. However, acetone-sensitized irradiation of **3c** results in rapid loss of **3c** and the formation of an acid and thermally labile product. While initial attempts at isolation of this material were complicated by product decomposition during irradiation and attempted purification, by using base-washed apparatus and maintaining the temperature below 30° a colorless liquid could be isolated in 94% yield after chromatography on activity IV basic alumina. This material, which was isomeric with **3c**, showed a carbonyl absorption (5.85 μ) in the ir and exhibited four distinct one-proton signals in the nmr in addition to the aromatic and *tert*-butyl absorptions:[1d] τ 5.17 (1 H, d), 6.14 (1 H, distorted t), 6.60 (1 H, m), 7.43 (1 H, m). The absence of olefinic absorption in the adduct suggests a tetracyclic structure, for which **7c** seemed most reasonable. This structural assignment is further supported by its hydrogenation and acid-catalyzed rearrangement studies reported below.



3c 6c

Several attempts at clean partial hydrogenation of **7c** were made. The most successful of these employed atmospheric hydrogenation in ethyl acetate using 5% Pd/C as catalyst. The uptake of 1–1.5 equiv of hydrogen followed by work-up yielded 20–30% of an impure crystalline material in addition to a yellow oil. The crystalline solid decomposed on attempted column chromatography on a variety of supports to *tert*-butyl carbamate and 2-formylindan; the latter compound underwent rapid air oxidation to 2-indancarboxylic acid. The structures of the *tert*-butyl carbamate and 2-indancarboxylic acid were rigorously established by comparison with synthesized authentic samples. Owing to the instability of this hydrogenation mixture, identification of the remaining products was not attempted. This sequence of reactions is outlined below.



7c

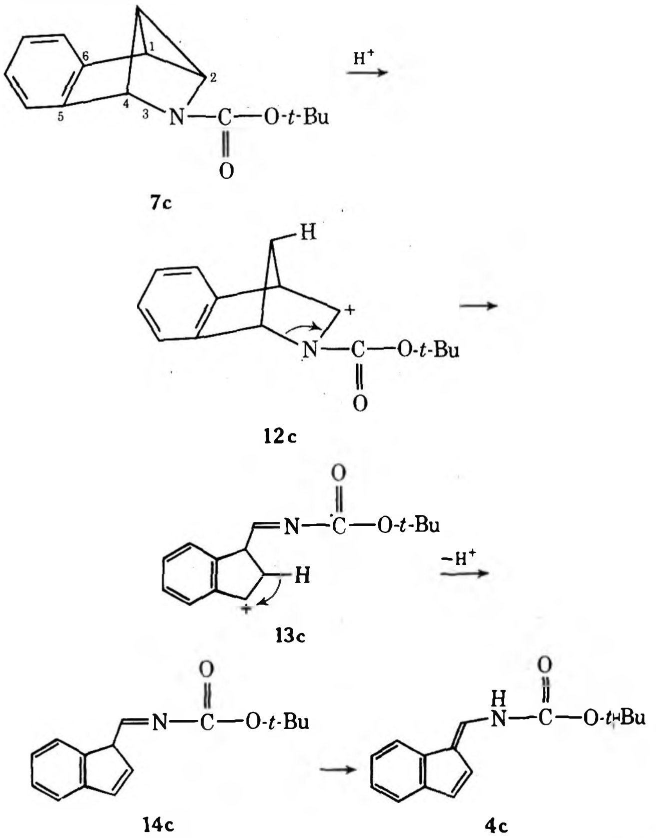
8c

9

10

11

In view of the acid sensitivity of the crude reaction mixture, the acid-catalyzed rearrangement of 7c was also studied. Treatment of 7c in ether with a trace of *p*-toluenesulfonic acid for 2 hr at room temperature afforded 4c in 93% yield. The structural assignment for this product is supported by the similarity of its spectrscopic properties with those reported for the analogous heterocyclic systems.[3] Furthermore, it was established that 4c was the major decomposition product in those irradiations in which precautions against temperature and fortuitous acid catalysis were not employed. The reaction course may be conveniently viewed as shown above.



7c

12c

13c

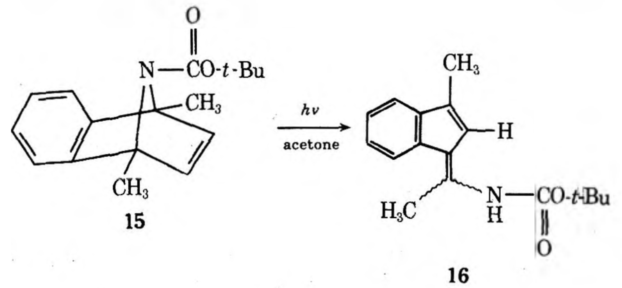
14c

4c

Having established that the acetone-sensitized photolysis of 3c proceeds in high yield to afford the product of di-π-methane rearrangement, it was of interest to measure the quantum efficiency of the 3c → 7c transformation for comparison with the parent hydrocarbon. Quantum-yield determinations at 3000 Å at ~20% conversion gave $\Phi = 0.93 \pm 0.1$. Thus, this nitrogen analog of the hydrocarbon rearranges with both high synthetic yield and high quantum efficiency.

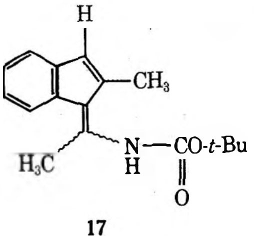
Photosensitized Rearrangements of Other 7-Azabenzonorbornadienes. The marked contrast between the results noted here and the previous work of Prinzbach for **3a** and **3b** prompted us to reexamine the photosensitized chemistry of **3a**. Irradiation of 0.1% acetone solutions of **3a** under conditions analogous to those employed for **3c** was followed by nmr examination of the crude irradiation mixtures. No signals in the nmr spectrum attributable to the tetracyclic azetidine structure were observed; instead, the spectrum closely resembled those described for the respective benzofulvenes, **4a** and **5a**.

Surmising that the steric hindrance afforded by the *tert*-butoxycarbonyl group could be a necessary prerequisite for isolation of the tetracyclic azetidine structure, the photosensitized irradiation of readily available **15** was examined. This molecule not only would have afforded a second example of the rearrangement but also would have simplified the nmr spectrum of the azetidine, perhaps allowing specific assignment of the one-proton signals noted in **7c**. However, here too no tetracyclic azetidine could be isolated. In this case 12 different runs were made and analyzed by nmr. The crude nmr spectra of these irradiations were complex and not reproducible from run to run, suggesting the presence of unstable intermediate(s). However, the only compound which could be isolated pure was a yellow, crystalline solid (53%). The ir of this material showed NH absorption at 2.95 μ and carbonyl absorption at 5.85 μ, while the uv spectrum exhibited maxima at 230 nm (ϵ 9530), 280 (19,000), and 324 (13,600), characteristic of the 6-amino-2,3-benzofulvene moiety. The nmr showed the aromatic and NH absorption as a broad multiplet at τ 2.34–2.97, one vinyl proton as a multiplet centered at τ 3.50, one methyl group as a singlet at τ 7.43, a second methyl group as a broadened singlet at τ 7.82, and the *tert*-butyl group as a singlet at τ 8.46. The uv spectrum establishes the material as a 6-amino-2,3-benzofulvene, while the absence of olefin absorption below τ 4 and the methyl resonance at τ 7.43 indicate that one methyl is bonded to the 6 position. Either **16** or **17** is in accord with

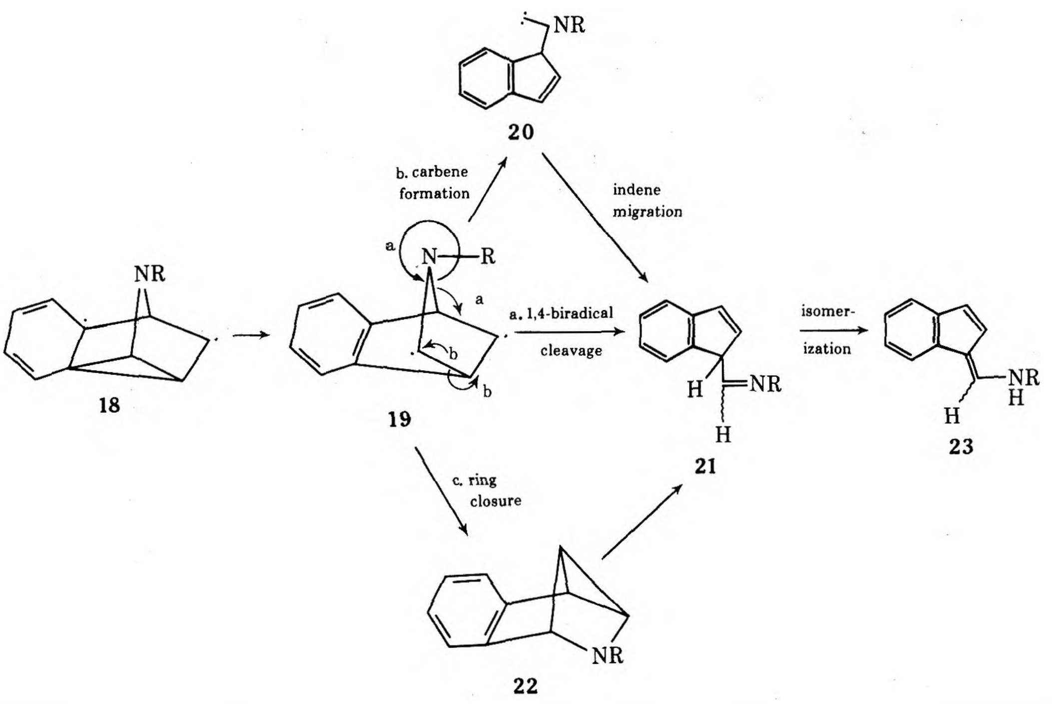


15

16



17



this spectroscopic data. As **16** is most readily accommodated in the general mechanistic scheme of this reaction, the product from **15** is tentatively assigned as **16**.

Discussion

These studies demonstrate that photosensitized rearrangement of **3c** produces the strained tetracyclic azetidine, **7c**, in high yield and quantum efficiency. A remaining question is the mechanism of benzofulvene formation in structurally similar systems. Three different routes for benzofulvene formation, each deriving from a structural rearrangement of the hypothetical di-π-methane intermediate **19**, can be considered. For each mechanism an uncharacterized intermediate, **21**, is present which produces the benzofulvene by tautomerization.

Path a involves 1,4-biradical cleavage to afford **21**, a process well precedented in 1,4-biradical systems. Path b involves cleavage to form carbene **20** followed by indene migration yielding **21** and has some analogy from the recent work of Ipaktschi on the photochemistry of dibenzonorbornadienes.[4] Path c involves di-π-methane rearrangement of **18** to **22**, which undergoes thermal or acid-catalyzed rearrangement to **23**. This work has rigorously defined path c as of major importance for the **3c** → **4c** conversion, since the intermediate tetracyclic azetidine can be isolated and subjected to further rearrangement to afford **4c**.

Our unsuccessful efforts to characterize tetracyclic azetidines under mild conditions from **3a** and **15** are puzzling. Since we deem it unlikely that **3a** and **15** are undergoing excited-state processes fundamentally different from that of **3c**, the failure to isolate tetracyclic rearrangement products must be due to their instability. Whether the instability of these strained isomers is due to structural effects in the molecules or due to trace impurities which catalyzed decomposition is at present unknown.

Experimental Section

Ir spectra were recorded with a Perkin-Elmer Infracord Model 137 spectrometer. Uv spectra were determined with a Cary 14 recording spectrometer. The mass spectra were measured with an AEI MS-9 mass spectrometer. Nmr spectra were measured at 60 MHz using TMS as internal standard. All elemental analyses were determined by Scandinavian Microanalytical Laboratory, Herlev, Denmark. All photolyses were carried out in an atmosphere of purified nitrogen.

7-*tert*-Butoxycarbonyl-2,3-benzo-7-azabicyclo[2.2.1]hepta-2,5-diene (3c). This material was prepared by the procedure of Carpino and Barr, mp 74–75° (lit. mp 72–73°).[5]

Direct Irradiation of 7-*tert*-Butoxycarbonyl-2,3-benzo-7-azabicyclo[2.2.1]hepta-2,5-diene (3c). The following is typical of several different irradiations performed (Table I). A stirred solution of 0.500 g (2.06 mmol) of **3c** in 70 ml of purified cyclohexane was irradiated for 90 min through quartz with a bank of 16 RPR-3000 Å lamps. After removal of the solvent from the yellow solution, the residue was chromatographed on silica gel (40 × 2.3 cm column slurry packed in 5% ether–hexane). Elution with 0.5 l. of 5% ether–hexane yielded 0.0257 g of a yellow, crystalline solid. Recrystallization of this material from methanol yielded *tert*-butyl 3-benzazepine-3-carboxylate (**6c**) as yellow needles: mp 95.5–97.0°; ir (KBr) 5.90 (s), 6.11 (w), 6.72 (w), 6.95 (w), 7.35 (m), 7.43 (s), 7.57 (s), 7.66 (m), 7.95 (s), 8.08 (m), 8.53 (m), 8.98 (m), 9.11 (w), 11.14 (s), 11.71 (w), 12.02 (w), 12.74 (s), 13.04 (m), and 13.30 μ (w); uv max (cyclohexane) 253 nm (ϵ 59,400) and 321 (1520); nmr (CCl_4) τ 3.29 (4 H, m), 3.94 (2 H, d, J = 10 Hz), 4.84, (2 H, d, J = 10 Hz), and 9.54 (s, 9 H).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.02; H, 7.01; N, 5.76. Found: C, 74.03; H, 7.25; N, 5.69.

Continued elution with 1.2 l. of 10% ether–hexane yielded 0.4616 g of recovered starting material as established by ir and nmr.

Triplet-Sensitized Irradiation of 7-*tert*-Butoxycarbonyl-2,3-benzo-7-azabicyclo[2.2.1]hepta-2,5-diene (3c). A solution of 0.500 g (2.06 mmol) of **3c** in 150 ml of dried, purified acetone was irradiated for 0.5 hr with Corex-filtered light from a Hanovia 450-W medium-pressure source. In order to avoid acid-catalyzed rearrangement of the photoproduct, the photolysis cell and all glassware subsequently used in work-up were washed with dilute ammonium hydroxide and dried at *ca.* 70° for several hours. Removal of the solvent *in vacuo* below 30° yielded a light yellow oil, which was chromatographed on activity IV Woelm basic alumina (2.3 × 38 cm column, slurry packed in 2% ether–hexane). Elution proceeded as follows: 0.3 l., 2% ether–hexane, small amount of uncharacterized material; 1.3 l., 2% ether–hexane, 0.4669 g (1.93 mmol, 94%) of **7c** as a clear oil homogeneous by tlc [ir (CCl_4) 3.32 (w), 5.85 (s), 6.85 (w), 7.23 (w), 7.37 (s), 7.55 (s), 7.76 (m), 8.02 (w), 8.18 (w), 8.56 (m), 8.70 (w), 8.84 (s), 9.12 (w), 11.10 (w), 11.26 (w), 11.55 μ (w); nmr (calcium carbonate treated CCl_4) τ 2.60 (1 H, m), 2.88 (3 H, m), 5.17 (1 H, d), 6.14 (1 H, distorted t), 6.60 (1 H, m), 7.43 (1 H, distorted t), and 8.79 (9 H, s); mass spectrum m/e (rel intensity) 243 (parent, 7), 39 (33), 41 (90), 44 (60), 55 (15), 56 (37), 57 (100), 56 (16), 114 (15), 115 (80), 116 (88), 117 (19), 140 (11), 141 (18), 143 (80), 144 (14), 170 (12), 187 (35); exact mass measurement, theoretical, 243.1259; observed, 243.1244].

Hydrogenation of 5-*tert*-Butoxycarbonyl-5-azatetracyclo$[5.4.0.0^{2,4}.0^{3,6}]$undeca-1(7),8,10-triene (7c). In a 250-ml standard taper base-washed erlenmeyer flask with stopcocked side

Table I
Direct Irradiation of 3c in Cyclohexane

Starting material, g	Irradiation time, min	Recovered 4, g	5, g	Yield,[a] %
0.50[b,c]	90	0.477	0.011	47
0.50[b,d]	90	0.462	0.026	67
0.50[b,d]	180		0.028	

[a] Yield based on recovered starting material. [b] Irradiation was in 70 ml of cyclohexane with RPR-3000 Å source. [c] Pyrex vessel. [d] Quartz vessel.

arm inlet was placed 50 mg of 5% Pd/C, a magnetic stirring bar, and 50 ml of reagent-grade ethyl acetate. After equilibration of the catalyst with hydrogen, a solution of 0.50 g of **7c** in 50 ml of ethyl acetate was injected *via* syringe and hydrogen uptake followed. After 50 min, 1.1–1.5 equiv of hydrogen had been allowed to react and the uptake of hydrogen ceased. Filtration of the reaction mixture through Celite, followed by removal of the ethyl acetate *in vacuo*, gave a clear oil which was triturated with a few drops of cold hexane and filtered to give 0.116 g (0.473 mmol, 23%) of white solid 2-(*tert*-butylcarbamoyl)methyleneindan (**8c**). Purification of this material by recrystallization was difficult since the melting point of recrystallized material changed with time. A triply recrystallized sample from ethyl acetate–hexane gave plates with a melting point as high as 143.5–144.5°. This purest material, when allowed to stand, decreased in melting point with time. The compound hydrolyzed on all column supports (silica gel; neutral alumina, activities II and III; basic alimina, activities II–IV; PDEAS) to *tert*-butyl carbamate and 2-formylindan (*vide infra*) and, therefore, could not be purified by chromatography. The ir spectra of crude and recrystallized solid were identical; the nmr spectra differed only in minor extra absorption in the aromatic and τ 6.9–7.3 regions. The triply recrystallized material, mp 143.5–144.5°, showed ir (KBr, Perkin-Elmer 457) 2.87 (s) and 3.01 (m) (NH split by Fermi resonance), 3.38 (w), 5.88 (s, carbonyl), 6.56 (s, amide II band), 6.87 (w), 6.93 (w), 7.19 (w), 7.32 (m), 7.43 (m), 7.77 (w), 7.90 (m), 7.85 (m), 8.04 (m), 8.50 (m), 8.55 (m), 8.78 (w), 9.13 (w), 9.37 (w), 9.57 (w), 9.72 (w), 9.91 (s), 10.12 (w), 11.37 (w), 13.35 (m), and 14.33 μ (w); uv max (95% ethyl alcohol) 261 nm (ϵ 852), 267 (1270), and 273 (1360); mass spectrum *m/e* (rel intensity) 245 (P, <0.5), 39 (28), 41 (59), 43 (22), 44 (13), 51 (11), 56 (29), 59 (88), 62 (27), 63 (13), 65 (11), 91 (23), 115 (82), 116 (100), 117 (68), 127 (12), 128 (28), 129 (15), 131 (17), 145 (36), 146 (77). The compound was sublimed at 80° (1.5 mm) and exact mass measured: calculated, 245.1416; found, 245.1413.

The residual oil (0.394 g) from the hydrogenation showed ir and nmr spectra similar to those of **8c**. However, numerous attempts at purification of this material proved futile.

Hydrolysis of 2-(*tert*-Butylcarbamoyl)methyleneindan (8c). A 12.7-mg (0.052 mm) sample of recystallized 2-(*tert*-butylcarbamoyl)methyleneindan was dissolved in 5 ml of ethyl acetate and stirred for 11 hr under nitrogen with a 0.50-g portion of Woelm alumina (neutral, activity III). An internal standard of 6.3 mg of acetophenone was added and the product mixture was analyzed quantitatively on a 15 ft × 0.125 in. column of 5% PDEAS on 60/80 mesh Chromosorb W at 90°. Results of this analysis showed the hydrolysis mixture to consist of 4.3 mg (0.037 mm, 71%) of *tert*-butyl carbamate and 7.3 mg (0.050 mmol, 96%) of 2-formylindan. Preparative gas-phase chromatography of the hydrolysis mixture on a 10 ft × 0.25 in. column of PDEAS on 60/80 Chromosorb W at 99° gave the highly volatile *tert*-butyl carbamate (38%), identical in melting point, vpc retention time, and ir with the authentic sample, and 59% of 2-formylindan: ir (neat) 3.27 (w), 3.40 (m), 3.49 (m), 3.66 (m, O=CH), 5.85 (s, C=O), 6.23 (w), 6.78 (m), 6.89 (m), 6.99 (m), 7.24 (w), 7.60 (w), 7.70 (w), 8.01 (w), 8.58 (w), 9.28 (w), 9.49 (w), 9.80 (w), 10.67 (w), 11.25 (w), 12.27 (w), 12.88 (w), and 13.40 μ (s). The 2-indanyl aldehyde rapidly air oxidized to crystalline 2-indancarboxylic acid, identical in melting point and ir with the authentic sample.

1-*tert*-Butoxycarbonylaminomethyleneindene (4c). A sample of **7c**, prepared from 0.500 g (2.06 mmol) of **3c** in the manner described above, was dissolved in 5 ml of anhydrous ether. After the addition of 2–3 mg of *p*-toluenesulfonic acid, the vessel was stoppered and the solution was stirred in the dark at ambient temperature for 2 hr. At this time the ether was evaporated and the yellow reaction residue was immediately impregnated on activity IV Woelm basic alumina (2.3 × 34 cm column, slurry packed in 2% ether–hexane). Elution proceeded as follows: 500 ml, small amount of unidentified oil; 125 ml, 30 mg of unidentified yellow solid; 125 ml, nil; 750 ml, 0.466 g (1.92 mm, 93%) of yellow solid 1-*tert*-butoxycarbonylaminomethyleneindene (**4c**) [mp (methanol, pale yellow needles) 152–153.5°; ir (KBr) 2.88 (w, NH), 3.21–3.37 (w), 5.76 (m, C=O), 6.07 (m), 6.73 (m), 6.98 (m), 7.24 (w), 7.36 (w), 7.81 (m), 8.17 (m), 8.76 (s), 9.04 (w), 9.30 (w), 9.48 (w), 10.06 (m), 10.90 (w), 11.07 (w), 11.53 (m), 11.68 (m), 12.74 (m), 13.05 (m), 13.19 (m), 13.52 (w), 13.78 (m), and 14.37 μ (w); uv max (CH_3CN) 233 nm (ϵ 5160), 272 (25,800), 279 (30,000), and 333 (20,500); nmr ($CDCl_3$) τ 2.17–2.53 (3 H, m), 2.57–2.94 (3 H, m), 3.13 (1 H, AB, J = 5.5 Hz), 3.27 (1 H, J = 5.5 Hz), and 8.48 (9 H, s); mass spectrum *m/e* (rel intensity) 243 (P, 29), 244 (P + 1, 4), 50 (3), 51 (2), 53 (1), 55 (12), 56 (21), 57 (100, B), 58 (4), 59 (42), 60 (1), 61 (1), 62 (4), 63 (6), 64 (2), 65 (1), 70 (4), 71 (2), 74 (2), 75 (2), 86 (2), 87 (3), 88 (4), 89 (2), 113 (5), 114 (32), 115 (29), 116 (28), 117 (1), 140 (9), 141 (12), 142 (3), 143 (53), 144 (5), 169 (74), 170 (9), 187 (68), and 188 (7)].

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.27; H, 7.22; N, 5.61.

Triplet-Sensitized Irradiation of 7-Methoxycarbonyl-2,3-benzo-7-azabicyclo[2.2.1]hepta-2,5-diene (3a). The same procedure was employed as for the triplet-sensitized irradiation of **3c** except that 250-mg (1.25 mmol) samples of **3a** were irradiated in 150 ml of purified acetone in base-washed glassware from −10° to ambient temperatures. After removal of solvent *in vacuo* at approximately 0°, an ambient-temperature nmr of the photoproduct was taken in calcium carbonate treated carbon tetrachloride. In no case were the characteristic proton absorptions [τ 5.17 (1 H, d), 6.14 (1 H, distorted t), 6.60 (1 H, m), and 7.43 (1 H, distorted t)] of a polycyclic azetidine observed. Instead, complex nmr spectra with absorptions occurring in the regions reported for benzofulvenes were obtained.[3]

***tert*-Butyl 2,5-Dimethylpyrrole-1-carboxylate.** A procedure analogous to that used for the preparation of *tert*-butyl pyrrole-1-carboxylate[5] was employed with the following quantities of material: 23.8 g (0.25 mol) of 2,5-dimethylpyrrole, 7.8 g (0.201 mol) of potassium, and 28.8 g (0.201 mol) of *tert*-butyl azidoformate. After work-up, ether and tetrahydrofuran were removed by atmospheric distillation below 80° and 2,5-dimethylpyrrole was removed by short-path distillation between 66 and 82° (15 mm). The remaining dark liquid was chromatographed on 600 g of silica gel (5.8 × 50 cm colum, slurry packed in 1% ether–hexane). Elution proceeded as follows: 0.5 l., 1% ether–hexane, nil; 0.5 l., 1% ether–hexane, 0.630 mg of unidentified dark oil; 1.5 l., 1% ether–hexane, nil; and 4.5 l., 3% ether–hexane, 8.96 g (0.046 mol, 23%) of slightly yellow liquid *tert*-butyl 2,5-dimethylpyrrole-1-carboxylate (pure by nmr). Clear liquid *tert*-butyl 2,5-dimethylpyrrole-1-carboxylate can be obtained by distillation at 106–108° (15 mm) or 38–40° (1 mm): ir (NaCl plates) 3.37 (m), 5.76 (s, carbonyl), 7.25 (m), 7.37 (s), 7.56 (s), 7.68 (s), 8.04 (m), 8.57 (m), 8.97 (s), 11.77 (m), and 12.81 μ (m); nmr (CCl_4) τ 4.37 (2, H, s), 7.68 (6 H, s), and 8.47 (9 H, s).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.33; H, 8.72; N, 6.90.

7-*tert*-Butoxycarbonyl-2,3-benzo-1,4-dimethyl-7-azabicyclo[2.2.1]hepta-2,5-diene (15). An analogous procedure was employed as for the preparation of **3c** using the following reagents: 8.61 g (44.2 mmol) of *tert*-butyl 2,5-dimethylpyrrole-1-carboxylate, 9.7 g (55.4 mmol) of *o*-fluorobromobenzene, and 1.5 g (62.5 mmol) of magnesium. After work-up and removal of tetrahydrofuran by atmospheric distillation, the remaining brownish liquid was distilled through a short-path apparatus, bp 88–90° (0.05 mm). This nearly pure (by nmr) orange distillate was impregnated on Woelm activity IV basic alumina (2.3 × 38 cm column, slurry packed in 2% ether–hexane) and eluted with 2% ether–hexane. Slightly orange 7-*tert*-butoxycarbonyl-2,3-benzo-1,4-dimethyl-7-azabicyclo[2.2.1]hepta-2,5-diene (**15**, 3.3 g, 12.2 mmol, 28%) was recovered: ir (NaCl plates) 5.86 (s, carbonyl), 6.91 (m), 7.28 (m), 7.35 (m), 7.59 (s), 7.92 (m), 8.03 (m), 8.59 (s), 9.40 (m), 12.86 (m), 13.40 (s), and 14.46 μ (m); nmr (CCl_4) τ 2.95 (4 H, symmetrical m), 3.42 (2 H, s), 7.94 (6 H, s), and 8.67 (9 H, s). Molecular distillation, bp 90° (0.05 mm), gave **15** as a colorless oil.

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.40; H, 7.81; N, 5.37.

This compound turns orange on standing but still appears to be pure by nmr.

Triplet-Sensitized Irradiation of 7-*tert*-Butoxycarbonyl-2,3-benzo-1,4-dimethyl-7-azabicyclo[2.2.1]hepta-2,5-diene (15). The same procedure was employed as for the triplet-sensitized irradiation of **3c** except that 125–250-mg (0.55–1.10 mmol) samples of **15**

were irradiated in 150 ml of purified acetone in base-washed glassware from −10° to ambient temperatures. After removal of solvent *in vacuo* at approximately 0°, an ambient-temperature nmr of the photoproduct was taken in calcium carbonate treated carbon tetrachloride. Results were not reproducible but in no case were the characteristic proton absorptions [τ 5.17 (1 H, d), 6.14 (1 H, distorted t), 6.60 (1 H, m), and 7.43 (1 H, distorted t)] of a polycyclic azetidine **7c** observed. Some of the nmr spectra resembled those of fulvenes. One of the 250-mg (1.10 mmol) runs was chromatographed on Woelm activity IV basic alumina (2.3 × 33 cm column, slurry packed in 2% ether–hexane). Elution proceeded as follows: 1.0 l., 2% ether–hexane, small amount of unidentified yellow oil; 1.5 l., 5% ether–hexane, 0.134 g (0.59 mmol, 53%) of 1-*tert*-butoxycarbonylamino-1,4-dimethylmethyleneindene (**16**) [yellow plates, mp 97.5–98.5° (pentane–ether); ir (KBr) 2.95 (m, NH), 5.85 (s), 6.13 (s), 6.64 (s), 6.92 (m), 7.00 (m), 7.37 (m), 7.61 (m), 7.67 (m), 7.97 (m), 8.10 (s), 8.65 (s), 11.53 (m), 13.32 (s), and 13.56 μ (m); uv max (CH_3CN) 230 nm (ϵ 9530), 280 (19,100), and 324 (13,600); nmr (CCl_4) τ 2.34–2.97 (5 H, m), 3.50 (1 H, m), 7.43 (3 H, s), 7.82 (3 H, broad s), and 8.46 (9 H, s); mass spectrum *m/e* (rel intensity) 271 (18, P), 272 (4, P + 1), 51 (5), 55 (5), 56 (9), 57 (100, B), 59 (32), 77 (5), 115 (6), 127 (13), 128 (39), 129 (14), 130 (13), 153 (7), 154 (8), 155 (6), 156 (6), 170 (17), 171 (62), 172 (8), 182 (6), 197 (65), 198 (13), 215 (48), and 216 (6)].

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75,25; H, 7.80; N, 5.16. Found: C, 75.04; H, 7.76; N, 5.01.

Quantum Yield Measurements. These determinations were made in the previously described[6] two-compartment cell on magnetically stirred solutions under a nitrogen atmosphere using light from a Bausch and Lomb high-intensity grating monochrometer. The light intensity was measured immediately prior to and immediately following irradiation, and if these values differed by more than 10% the run was discarded.

Direct Irradiation of 3c. A solution of 0.50 g of carbamate in 65 ml of purified cyclohexane was irradiated at 300 nm and the analysis for formation of **5c** was made by uv analysis at 321 nm. The data below summarize the quantum yields measured at the indicated per cent conversion: Φ = 0.048 (0.26%), Φ = 0.065 (0.34%), Φ = 0.060 (0.60%), Φ = 0.057 (0.61%), Φ = 0.043 (0.85%), and Φ = 0.045 (0.91%).

Sensitized Irradiation of 3c. A solution of 0.243 g of **3c** in 65 ml of purified acetone was irradiated at 300 nm and 20.5 mg of benzalazine was added to the irradiated solution. After removal of solvent *in vacuo*, the residue was dissolved in sodium carbonate washed carbon tetrachloride for nmr analysis. The nmr spectra taken immediately after irradiation allowed calculation of the amount of **7c** formed by comparing the area of the benzalazine singlet (τ 1.48, 2 H) with the one-proton signals of the photoproduct at τ 5.17, 6.14, and 6.60. The results for two determinations were Φ = 0.95 and Φ = 0.91 at 16–17% conversion.

Registry No.—**3a**, 28035-70-3; **3c**, 5176-28-3; **4c**, 50585-27-8; **5c**, 50585-28-9; **6c**, 34813-08-6; **7c**, 34813-09-7; **8c**, 34813-10-0; **15**, 50585-34-7; **16**, 50585-35-8; 2-formylindan, 37414-44-1; *tert*-butyl 2,5-dimethylpyrrole-1-carboxylate, 50585-36-9; 2,5-dimethylpyrrole, 625-84-3; *tert*-butyl azidoformate, 1070-19-5; o-fluorobromobenzene, 1072-85-1.

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Stereochemical Course of Bromocyclizations of γ,δ-Unsaturated Alcohols. II.[1] Approaches to Various Oxaazabicyclooctane and -nonane Systems

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γ,δ-Unsaturated alcohols, *N*-methyl-2-hydroxymethyl-2-phenyl-4-pentenoic acid amide (**2**), 2-hydroxymethyl-2-phenyl-4-penten-1-ol (**6**), 3-hydroxymethyl-3-phenyl-5-hexen-1-ol (**10**), 3,3-diphenyl-1-methylamino-5-hexen-2-ol (**14d**), 1-chloro-3,3-diphenyl-5-hexen-2-ol (**14c**), and 3,3-diphenyl-1-methylamino-2-methyl-5-hexen-2-ol (**19**) were bromocyclized to the corresponding tetrahydrofurfuryl bromides (**3**, **7** and **8**, **11** and **12**, **15a**, **15c**, and **20** and **21**). The stereochemistry in each case was determined unambiguously by further intramolecular cyclization or lack of it to the corresponding oxaazabicyclooctanes (**4**, **5**, **16**, and **22**) and oxaazabicyclononane (**13**).

We have previously described the synthesis of several substituted tetrahydrofurfurylamines by bromocyclizations of corresponding γ,δ-unsaturated alcohols, followed by substitution of bromine with alkylamines.[1] The interesting pharmacological properties of some of these compounds coupled with simplicity of the synthetic approach have stimulated our additional investigation in this field with the aim to extend the synthesis to various bicyclic systems.

Results

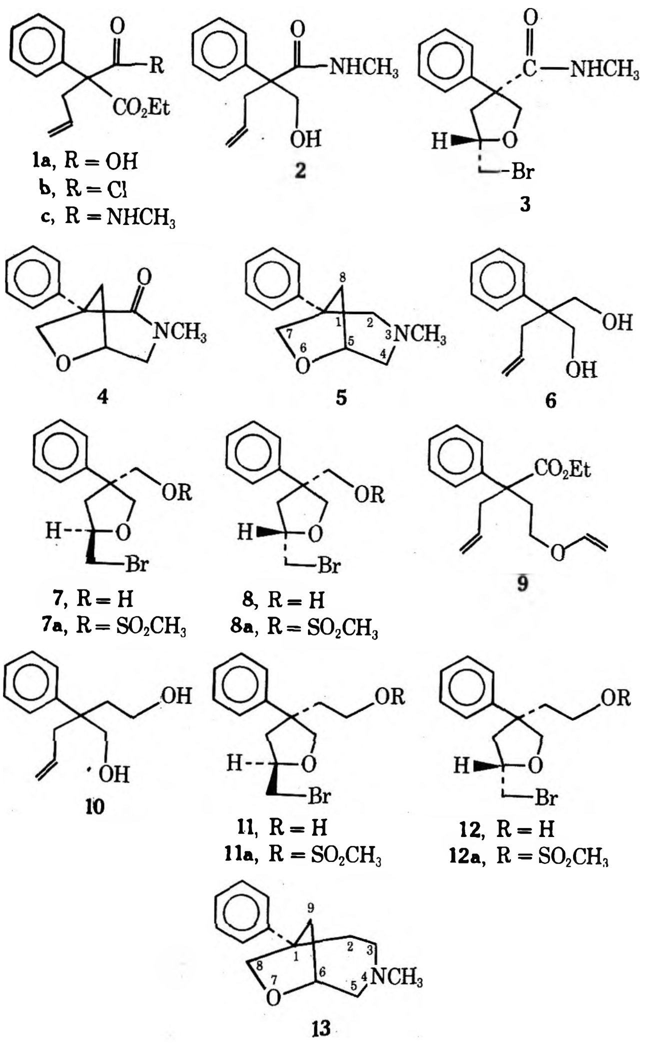
The original attempt to synthesize 3-methyl-1-phenyl-6-oxa-3-azabicyclo[3.2.1]octane (**5**) was made *via* diethyl (allyl phenyl) malonate **1** (Chart I, R = OEt) which was selectively hydrolized to the monoacid **1a**. Sequential treatment of **1a** with thionyl chloride, methylamine, and $LiAlH_4$ afforded the amido alcohol **2** *via* acid chloride **1b** and amide **1c**, respectively.

Bromocyclization of **2** afforded stereoselectively *cis*-3-*N*-methylcarboxamido-3-phenyltetrahydrofurfuryl bromide (**3**).[2] Treatment of **3** with sodium hydride in DMF afforded 3-methyl-1-phenyl-6-oxa-3-azabicyclo[3.2.1]octan-2-one (**4**). The attempted reduction of **4** to **5** with $LiAlH_4$ was not successful, resulting in either unchanged starting material or the product of ring fission.

Another approach utilizing diol **6** was more fruitful. The bromocyclization of **6** was known to give a mixture[1] of two isomers which we have now separated by column chromatography. The ratio of cis isomer **8** to trans isomer **7** was found to be very close to 1:2. The stereochemistry was assigned on a basis of successful conversion of **8** *via* mesylate **8a** to the desired **5** upon treatment with methylamine.

In a similar approach, 4-methyl-1-phenyl-7-oxa-4-azabicyclo[4.2.1]nonane (**13**) was prepared (Chart I). Successive alkylation of ethyl phenylacetate by treatment with sodium hydride and chloroethyl vinyl ether, followed by sodi-

Chart I

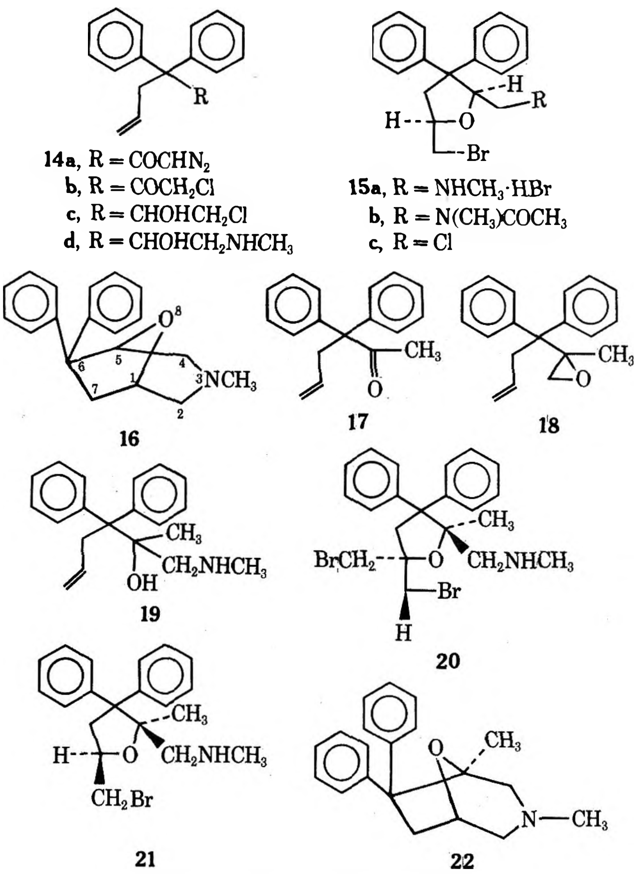


um hydride and allyl bromide, afforded ethyl 2-(2-vinyloxyethyl)-2-phenyl-4-pentenoate (**9**). Reduction of **9** with $LiAlH_4$ to the diol **10** and bromocyclization of **10** afforded a 1:1 mixture of trans and cis bromo alcohols **11** and **12**. The mixture was separated by column chromatography and **12** was converted *via* mesylate **12a** to the bicyclic base **13** upon treatment with methylamine.

The starting material for 3-methyl-6,6-diphenyl-8-oxa-3-azabicyclo[3.2.1]octane (**16**) was 2,2-diphenyl-4-pentenoic acid chloride (**14**) (Chart II, R = COCl), which was treated with diazomethane to give diazo ketone **14a**. Treatment of **14a** with hydrogen chloride afforded chloro ketone **14b**, which was reduced with $LiAlH_4$ to the chlorohydrin **14c**. Treatment of **14c** with methylamine gave amino alcohol **14d**, which upon bromination afforded exclusively cis product **15a**. The alternative 2-bromomethyl-4,4-diphenyl-5-hydroxypiperidine structure for the bromocyclization product was eliminated from consideration since treatment of the free base of **15a** with acetic anhydride–pyridine gave the amide **15b** (ir 1640 cm^{-1}) rather than an ester. Heating of the free base of **15a** in DMSO at 45–50° for 20 hr afforded **16**, thus proving conclusively the cis stereochemistry of **15a**. The same result was obtained when chlorohydrin **14c** was bromocyclized and the product (**15c**) subsequently treated with methylamine.

Amino alcohol **19** was prepared in two steps from allyl diphenylacetone (**17**). Treatment of **17** with Corey's[3] reagent afforded epoxide **18**, which was opened with methylamine to give **19**. Bromocyclization of **19** afforded a 1:1 mixture of **20** and **21**. Chromatography of the mixture on an alumina column effected cyclization of **21** to 6,6-diphenyl-5-methyl-8-oxa-3-azabicyclo[3.2.1]octane (**22**), while **20** was isolated unchanged.

Chart II



Discussion

It was originally postulated that addition–cyclization reactions involved intermolecular addition of an electrophile to the double bond, followed by internal nucleophilic displacement.[4]

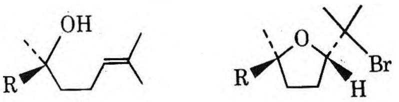
Linstead and May[5] were first to point out that simultaneous addition and ring closure is more likely. Subsequently, this class of reactions was treated as intermolecular concerted processes involving a more or less delocalized cationic transition state[6,7] as shown below.

X = O, S, N
Y = Br, I, Hg^+

The stereochemistry of this class of reactions was first studied by Tanaka, *et al.*[8] They found that bromocyclization in the damarene type triterpene series (Chart III) was stereospecific and trans. Demole and Enggest[6] have attributed the stereospecific conversion of **23** to **24** to the steric interaction of the triterpene polycycle R and isopropenyl group so that the less hindered trans isomer is formed.

Similarly, the exclusive cis cyclization of alcohols **14c** and **14d** can be interpreted in terms of steric interactions between the phenyl group and bromonium ion in B (Chart IV, **14c**, R = CH_2Cl; **14d**, R = CH_2NHCH_3) in the transition state, thus favoring cyclization through the bromonium ion A. The alternative configuration C is considered to be less stable owing to steric interactions between phenyl groups and R, and consequently it is not expected to contribute appreciably to the product formation. The comparable steric effects of the methyl and methylami-

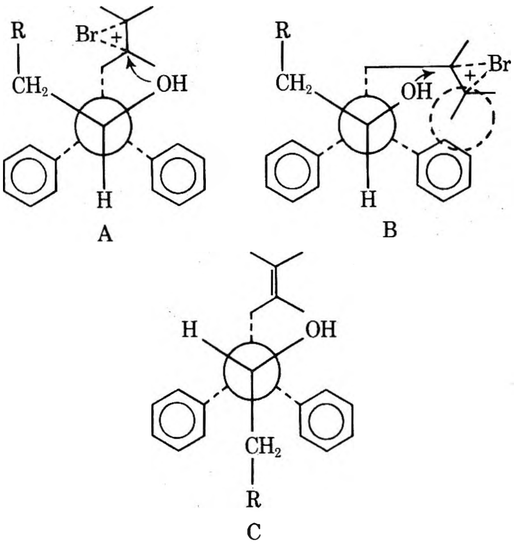
Chart III



23 24

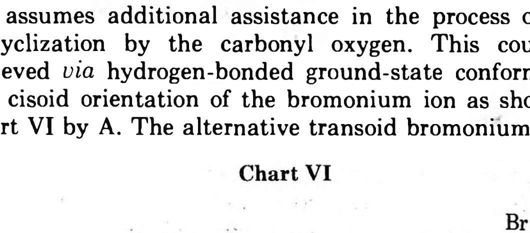
nomethyl groups in alcohol **19** results in nonstereospecific bromocyclization and thus a 1:1 mixture of isomers is obtained.

Chart IV



The stereochemical course of bromocyclization of alcohols **6** and **10** can be viewed as being governed by the relative steric effects of the phenyl group and substituent R (Chart V). When R is CH_2OH as in alcohol **6**, the transition state A is two times favored over transition state B and the 2:1 ratio of trans isomer **7** to cis isomer **8** is obtained. With the increase of the size of R as in **10** (R = CH_2CH_2OH) the steric effects of the phenyl group and R become comparable and the mixture of products converges to a 1:1 ratio.

Chart V



The exclusive cis cyclization of alcohol **2** is less clearly understood. A possible explanation could be arrived at if one assumes additional assistance in the process of bromocyclization by the carbonyl oxygen. This could be achieved *via* hydrogen-bonded ground-state conformation and cisoid orientation of the bromonium ion as shown in Chart VI by A. The alternative transoid bromonium ion B does not have the same degree of orbital overlap with the two oxygens concerned.[9]

Chart VI

The bromocyclizations of appropriately substituted γ,δ-unsaturated alcohols followed by further intramolecular cyclization herein described represents a useful and convenient synthetic approach to various bicyclic systems.

Experimental Section

All melting and boiling points are uncorrected. Infrared spectra were recorded with a Unicam Sp-200G grating ir spectrometer; nmr spectra were taken on a Varian A-60A spectrometer. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill.

Monoethyl (Allyl Phenyl) Malonate (1a). The selective hydrolysis of diethyl (allyl phenyl) malonate[1] was accomplished *via* a modified procedure of Kissinger and Ungnade.[11] To an ice-cold solution of diethyl (allyl phenyl) malonate (27.63 g, 0.1 mol) in 70 ml of absolute ethanol was added a solution of potassium hydroxide (10 g, 0.25 mol) in 200 ml of 75% ethanol. The mixture was stirred for 1 hr at 0° and left for 5 days at 5°. It was then partitioned between ice-cold water and petroleum ether (bp 30–60°). The water layer was acidified with cold dilute hydrochloric acid and extracted with ether to afford, after drying and concentration, 21.6 g (87%) of monoester **1a** as an oil: ir (neat) 1725 cm^{-1}; nmr ($CDCl_3$) δ 1.15 (3 H, t), 3.1 (2 H, d), 4.15 (2 H, q), 4.9–6.5 (3 H, m), 7.1–7.4 (5 H, m).

***N*-Methyl-2-carbethoxy-2-phenyl-4-pentenoic Acid Amide (1c).** The crude monoester **1a** (21.6 g, 87 mmol) was treated with thionyl chloride (25 ml) and a few drops of pyridine at 100° for 4 hr. The excess of thionyl chloride was removed *in vacuo*. The residual oil was dissolved in petroleum ether and the solution was washed successively with ice-cold portions of water (50 ml), 5% sodium bicarbonate (50 ml), and brine (50 ml). Then it was dried (Na_2SO_4) and concentrated *in vacuo*, and the residual oil was distilled to afford acid chloride **1b** (16.35 g, 70.5%): bp 123–125° (0.05 mm); ir (neat) 1745, 1795 cm^{-1}; nmr (CCl_4) δ 1.26 (3 H, t), 3.13 (2 H, d), 4.23 (2 H, q), 4.82–6.2 (3 H, m), 7.1–7.6 (5 H, m). The acid chloride was dissolved in anhydrous ether (200 ml) and treated with a solution of methylamine (*ca.* 125 mmol) in THF (250 ml) at 0°. The methylamine hydrochloride was removed by filtration over an alumina cake, and the filtrate was concentrated *in vacuo* to afford **1c** as an oil (12.26 g, 78%): bp 120–125° (0.02 mm); ir (neat) 1665, 1720, 3330 cm^{-1}; nmr (CCl_4) δ 1.17 (3 H, t), 2.63, 2.72 (3 H, NCH_3), 2.93, 3.17, 3.40 (2 H, td, J = 6.5 Hz, $CH_2CH{=}CH_2$), 4.16 (2 H, q) 4.8–6.1 (3 H, m), 7.0–7.4 (5 H, m).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.93; H, 7.64; N, 5.48.

***N*-Methyl-2-hydroxymethyl-2-phenyl-4-pentenoic Acid Amide (2).** To a stirred solution of $LiAlH_4$ (1.52 g, 38 mmol) in dry ether (60 ml) was added a solution of amide **1c** (10 g, 38 mmol) in dry ether (60 ml) over a period of 30 min. Then the mixture was treated with 1 *N* NaOH (75 ml); the precipitate was removed by filtration. The filtrate was concentrated *in vacuo* to yield alcohol **2** (5.2 g, 60%) as a white solid: mp 120–121° (benzene–petroleum ether); ir ($CHCl_3$) 1645, 3440 cm^{-1}; nmr ($CDCl_3$) δ 2.78, 2.85, 2.93 (5 H, NCH_3 and $CH_2CH{=}CH_2$), 3.73–4.20 (2 H, AB q, J = 12 Hz), 5.0–6.2 (3 H, m), 7.34 (5 H, s).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 70.89; H, 7.82; N, 6.47.

5-Bromomethyl-3-phenyl-3-tetrahydrofuroic Acid *N*-Methylamide (3). To a solution of alcohol **2** (4.38 g, 20 mmol) in chloroform (50 ml) was added dropwise a 1 *M* solution of bromine in carbon tetrachloride (20 ml). After addition the mixture was washed with a 5% solution of sodium bicarbonate, dried (Na_2SO_4), and concentrated *in vacuo* to yield **3** (5.2 g, 87%) as a white solid: mp 79–81° (ether–petroleum ether); ir (Nujol) 1700, 3320 cm^{-1}; nmr ($CDCl_3$) δ 2.05–2.75 (2 H, m, C_4 H_2), 3.16 (3 H, s, NCH_3), 3.67 (2 H, d, J = 5 Hz, CH_2Br), 3.74–4.16 (2 H, AB q, J = 12 Hz, C_2H_2), 4.2–4.65 (1 H, m), 7.45 (5 H, s).

Anal. Calcd for $C_{13}H_{16}BrNO_2$: C, 52.36; H, 5.49; N, 4.69. Found: C, 52.24; H, 5.51; N, 4.63.

3-Methyl-1-phenyl-6-oxa-3-azabicyclo[3.2.1]octan-2-one (4). A solution of bromo amide **3** (3.0 g, 10 mmol) in DMSO (20 ml) was added to a suspension of sodium hydride (440 mg of 55%, 10 mmol, washed with petroleum ether) in DMSO (5 ml), and the reaction mixture was stirred for 30 min. Then it was partitioned between water and benzene, and the organic layer was washed with water, dried, and concentrated to afford **4** (1.95 g, 90%): mp 125–127° (benzene–petroleum ether); ir ($CHCl_3$) 1710 cm^{-1}; nmr ($CDCl_3$) δ 2.16–2.95 (2 H, m, C_8 H_2), 3.13 (3 H, s, NCH_3), 2.63

and 2.80 (2 H, dd, J = 12 Hz, C_7 H_2), 3.96, 4.18, and 4.35 (2 H, td, J = 2.5 Hz, C_4 H_2), 4.76 (1 H, q, $J_1 = J_2$ = 2.5 Hz, C_5 H).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.49. Found: C, 71.80; H, 7.00; N, 6.50.

***cis*- and *trans*-4-Hydroxymethyl-4-phenyltetrahydrofurfuryl Bromides (8 and 7).** A mixture of isomers (8 g), prepared according to the procedure previously given,[1] was separated by column chromatography (silica gel, 1200 g). Elution of the column with a mixture of benzene–ether (1:1) afforded cis isomer **8** (2.5 g, 31.3%): bp 126–130° (0.02 mm); nmr ($CDCl_3$) δ 1.88–2.65 (2 H, m, C_3 H_2), 3.45 (2 H, d, J = 6 Hz, CH_2Br), 3.6 (2 H, s, $-CH_2OH$), 3.87–4.34 (2 H, AB q, J = 9 Hz, C_5 H_2), 4.21 (1 H, m), 7.1–7.5 (5 H, m). Further elution of the column afforded trans isomer **7** (4.2 g, 52.6%): bp 126–130° (0.02 mm); nmr ($CDCl_3$) δ 1.85, 2.05, 2.51, 2.72 (2 H, ABX qd, J = 13 Hz, C_3 H_2), 3.3 (2 H, d, J = 6 Hz, outer peak split into doublets, J = 1.5 Hz, CH_2Br), 3.62 (2 H, s, CH_2OH), 3.85–4.15 (2 H, AB q, J = 8 Hz, C_5 H_2), 4.1–4.7 (1 H, m), 7.0–7.5 (5 H, m).

***cis*-4-Methanesulfonyloxymethyl-4-phenyltetrahydrofurfuryl Bromide (8a).** The cis alcohol **8** (1.355 g, 5 mmol) in benzene (20 ml) was treated with methanesulfonyl chloride (0.81 g, 7 mmol) and triethylamine (0.71 g, 7 mmol) for 4 hr at room temperature. Then the mixture was washed with water, dried, and concentrated to afford ester **8a** (1.74 g, 100%) as an oil: nmr ($CDCl_3$) δ 2.0, 2.15, 2.42, 2.56 (2 H, ABX qd, J = 13 Hz, C_3 H_2), 2.65 (3 H, s, SO_2CH_3), 3.52 (2 H, d, J = 6 Hz, CH_2Br), 3.96–4.40 (2 H, AB q, J = 9 Hz, C_5 H_2), 4.05–4.5 (1 H, m), 4.35 (2 H, s, $CH_2OSO_2CH_3$), 7.0–7.5 (5 H, m).

Anal. Calcd for $C_{13}H_{17}BrO_4S$: C, 44.72; H, 4.90. Found: C, 44.93; H, 4.93.

***trans*-4-Methanesulfonyloxymethyl-4-phenyltetrahydrofurfuryl Bromide (7a).** The trans ester **7a** was obtained in quantitative yield from **7**, as described for **8a**.

Anal. Calcd for $C_{13}H_{17}BrO_4S$: C, 44.72; H, 4.90. Found: C, 44.91; H, 5.14.

3-Methyl-1-phenyl-6-oxa-3-azabicyclo[3.2.1]octane (5). A solution of cis mesylate **8a** (500 mg, 1.4 mmol) in DMSO (5 ml) was saturated with methylamine gas and heated in a pressure bomb for 2 hr at 100°. After cooling, the mixture was partitioned between water and benzene. The organic layer was washed with water, dried, and concentrated *in vacuo* to afford bicyclic base **5** (250 mg, 86%) as an oil: nmr ($CDCl_3$) δ 1.6–2.1 (2 H, AB q, C_8 H_2), 2.4 (3 H, s, NCH_3), 2.5–3.0 (4 H, m, C_4 H_2 and C_2 H_2), 3.8–4.3 (2 H, AB q, C_7 H_2), 4.3–4.6 (1 H, m, C_5 H), 7.1–7.5 (5 H, m). The hydrochloride salt of **5** was crystallized from methanol–ether, mp 270–272°.

Anal. Calcd for $C_{13}H_{17}NO \cdot HCl$: C, 65.13; H, 7.10; N, 5.84. Found: C, 64.87; H, 7.09; N, 5.85.

2-Phenyl-2-(2-vinyloxyethyl)-4-pentenoic Acid Ethyl Ester (9). The ethyl phenylacetate (49.26 g, 0.3 mol) was added dropwise to a cooled (ice water) and stirred suspension of sodium hydride (13.64 g of 55%, 0.3 mol, freed from carrier with petroleum ether) in DMF (500 ml) followed by 2-chloroethyl vinyl ether (31.96 g, 0.3 mol). After standing at room temperature for 16 hr the mixture was added to a stirred suspension of sodium hydride (13.64 g. 0.3 mol). Then to it was added allyl bromide (36.3 g, 0.3 mol), and the mixture was left at room temperature for 6 hr. Then it was partitioned between water and benzene. The organic layer was washed with water, dried, and concentrated *in vacuo*. The residual oil was distilled and the fraction boiling at 92–95° (0.02 mm) was collected to afford ester **9** (56.3 g, 68.5%): ir (neat) 1730 cm^{-1}; nmr ($CDCl_3$) δ 1.17 (3 H, t, CH_3CH_2O), 2.4 (2 H, t, J = 6 Hz, CH_2CH_2O-), 2.84 (2 H, d, J = 6 Hz, $CH_2CH{=}CH_2$), 3.63 (2 H, dt, J_1 = 6, J_2 = 2 Hz, CH_2CH_2O-), 4.9–6.0 (3 H, $CH_2CH{=}CH_2$), 6.38 (1 H, symmetrical q, J = 7 Hz, $OCH{=}CH_2$), 7.3 (5 H, s).

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.73; H, 8.17.

3-Hydroxymethyl-3-phenyl-5-hexen-1-ol (10). The ester **9** (27.5 g, 0.1 mol) in dry ether (50 ml) was added dropwise to a solution of $LiAlH_4$ (2.3 g, 60 mmol) in ether (150 ml). The mixture was heated to reflux for 45 min, the excess of hydride was decomposed in NaOH (11.5 ml), the mixture was filtered, and filtrate was concentrated *in vacuo*. The residual oil was dissolved in methanol (100 ml) and 6 *N* hydrochloric acid (20 ml) and the mixture was heated at 30–35° for 15 min. It was then diluted with water (50 ml), heated at 35–40° for another 15 min, and concentrated *in vacuo* to *ca.* 50 ml. After cooling, a solid was removed by filtration to yield diol **10** (14.4 g, 70%), mp 76–79°. A sample recrystallized from benzene melted at 82–83°: ir (Nujol) 3240 cm^{-1}; nmr ($CDCl_3$) δ 1.8–2.2 (2 H, m, CH_2CH_2OH), 2.46 (2 H, d, J = 6 Hz, $CH_2CH{=}CH_2$), 3.4–3.7 (2 H, m, CH_2CH_2OH), 3.52–3.88 (2 H, AB q, J = 12 Hz, CH_2OH), 4.8–6.0 (3 H, m, $-CH{=}CH_2$), 7.4 (5 H, s).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.89; H, 8.80. Found: C, 76.20; H, 8.89.

4-(2-Hydroxyethyl)-4-phenyltetrahydrofurfuryl Bromides (11 and 12). To a stirred and cooled (ice water) solution of diol **10** (7.23 g, 35 mmol) and pyridine (2.8 g, 35 mmol) in dichloromethane (30 ml) was added dropwise a solution of bromine in carbon tetrachloride (35 ml, 1 *M*). The mixture was then washed with water, dried, and concentrated *in vacuo*. The residual oil was distilled and the fraction boiling at 115–117° (0.02 mm) was collected to afford mixture of **11** and **12** (9.4 g, 94%), ir (neat) 3420 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}BrO_2$: C, 54.73; H, 6.01. Found: C, 54.78; H, 6.12.

The mixture was separated by column chromatography (1.2 kg of silica gel, dry packed). Elution with ether afforded cis isomer **12** (3.1 g): nmr ($CDCl_3$) δ 1.89, 2.02, 2.50, 2.61 (2 H, ABX qd, J = 13 Hz, C_3 H_2), 1.9–2.2 (2 H, m, CH_2CH_2OH), 3.20–3.50 (4 H, m, CH_2Br and CH_2CH_2OH), 3.8–4.3 (1 H, m), 3.90–4.37 (2 H, AB q, J = 9 Hz, C_5 H_2), 7.3 (5 H, s).

Further elution of the column afforded an unresolved mixture (0.6 g) followed by trans isomer **11** (3.2 g): nmr ($CDCl_3$) δ 1.98–2.75 (4 H, m, C_3 H_2 and CH_2CH_2OH, 3.25–3.55 (4 H, m, CH_2Br and $-CH_2OH$), 3.9–4.25 (2 H, Ab q, J = 8 Hz, C_5 H_2), 4.2–4.65 (1 H, m), 7.1–7.3 (5 H, m).

***cis*-4-(2-Methanesulfonylethyl)-4-phenyltetrahydrofurfuryl Bromide (12a).** The alcohol **12** (2.0 g, 7 mmol) in dry benzene (15 ml) was treated with triethylamine (1.0 g, 10 mmol) and methanesulfonyl chloride (1.016 g, 10 mmol) at room temperature for 4 hr. The mixture was then washed with water, dried, and concentrated to afford **12a** as an oil (2.5 g, 98%): nmr ($CDCl_3$) δ 1.83–2.80 (4 H, m), 2.83 (3 H, s), 3.5–4.45 (7 H, m), 7.45 (5 H, s).

Anal. Calcd for $C_{14}H_{19}BrO_4S$: C, 46.26; H, 5.27. Found: C, 46.29; H, 5.50.

***trans*-4-(2-Methanesulfonylethyl)-4-phenyltetrahydrofurfuryl Bromide (11a).** In a similar procedure, the trans ester **11a** was obtained in quantitative yield from **11**.

Anal. Calcd for $C_{14}H_{19}BrO_4S$: C, 46.26; H, 5.27. Found: C, 46.25; H, 5.49.

4-Methyl-1-phenyl-7-oxa-4-azabicyclo[4.2.1]nonane (13). A solution of mesylate **12a** (0.50 g, 1.38 mmol) and methylamine (*ca.* 1.0 g) in DMSO (5 ml) was heated in a pressure bomb on a steam bath for 1 hr. After cooling, the mixture was partitioned between water and ether. The ether layer was extracted with dilute hydrochloric acid and the acidic extract was basified with ammonium hydroxide. The free base was extracted with benzene, dried, and concentrated to afford **13** (252 mg, 84%): mp 75–77° (petroleum ether); nmr ($CDCl_3$) δ 1.7–2.4 (4 H, m, C_2 H_2 and C_9 H_2), 2.4 (3 H, s, NCH_3), 2.54–3.07 (4 H, m, C_3 H_2 and C_5 H_2), 3.85–4.28 (2 H, AB q, J = 7 Hz, outer doublet split, J = 1.5 Hz, C_8 H_2), 4.42–4.67 (1 H, m, C_6 H), 7.1–7.5 (5 H, m).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.65; H, 8.97; N, 6.41.

1-Diazo-3,3-diphenyl-5-hexen-2-one (14a). A mixture of the 2,2-diphenyl-4-pentenoic acid (20 g, 79.3 mmol) and thionyl chloride (30 ml) was heated to reflux for 1 hr. The excess of thionyl chloride was then distilled *in vacuo*, and the traces were removed azeotropically with benzene. The residual oil was distilled and the fraction boiling at 112–115° (0.02 mm) was collected to yield acid chloride (16 g, 73.5%) as colorless oil, ir (neat) 1780 cm^{-1}. It was dissolved in ether (50 ml) and added to an excess of diazomethane solution in ether (800 ml), prepared from EXR-101 (28 g). The mixture was fitted with an efficient condenser and left at room temperature for 24 hr. The ether was then removed *in vacuo* to afford diazo ketone **14a** (17 g) as a yellow oil: ir (neat) 1635, 2120 cm^{-1}; nmr δ 5.05 (1 H, $COCHN_2$).

Anal. Calcd for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.18; H, 5.94; N, 9.65.

1-Chloro-3,3-diphenyl-5-hexen-2-one (14b). The solution of diazo ketone **14a** (17 g, 61.5 mmol) in ether (150 ml) was saturated with hydrogen chloride gas and left at room temperature for 1 hr. The ether was then removed *in vacuo* and the residue was crystallized from petroleum ether (bp 35–60°) to afford slightly yellow chloro ketone **14b** (13.6 g, 78%): mp 53–55°; ir (Nujol) 1625 cm^{-1}; nmr (CCl_4) δ 3.06 (2 H, d, J = 7, Hz), 3.94 (2 H, s) 4.75–5.90 (3 H, m), 7.3 (10 H, s).

Anal. Calcd for $C_{18}H_{17}ClO$: C, 75.91; H, 6.00. Found: C, 76.12; H, 6.11.

1-Chloro-3,3-diphenyl-5-hexen-2-ol (14c). To a solution of chloro ketone **15b** (30 g) in ether (300 ml) was added in few portions $LiAlH_4$ (3 g) and the mixture was heated to reflux for 30 min. After cooling and decomposition of excess hydride with water, the mixture was treated with 1 *N* hydrochloric acid (400 ml) and ether (300 ml). The ether layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residual oil was distilled to afford chlorohydrin **14c** (25.1 g, 83%), bp 120–125° (0.02). The analytical sample was purified by chromatography (silica gel, eluent petroleum ether and benzene), to remove small amount of corresponding epoxide: ir (neat) 3560 cm^{-1}; nmr (CCl_4) δ 2.52–3.45 (3 H, m), 3.75 (1 H, dd, J_1 = 10, J_2 = 1.5 Hz), 4.45–4.50 (1 H, m), 4.75–5.6 (3 H, m), 7.2 (2 H, d, J = 2 Hz).

Anal. Calcd for $C_{18}H_{19}ClO$: C, 75.38; H, 6.68. Found: C, 75.41; H, 6.47.

3,3-Diphenyl-1-methylamino-5-hexen-2-ol (14d). A cold solution of chlorohydrin **14c** (4.1 g, 14.3 mmol) in DMSO (8 ml) was saturated with methylamine gas and the mixture was heated for 20 hr in a pressure bomb at 48–52°. Then it was partitioned between water and benzene. The organic layer was washed with water and extracted with dilute hydrochloric acid. The acid extract was basified with ammonium hydroxide and the free base was again extracted with benzene. The extract was dried and concentrated *in vacuo*, and the residue was crystallized from benzene–petroleum ether to afford **14d** (2.7 g, 67%): mp 74–75°; nmr (CCl_4) δ 1.9–3.3 (5 H, m), 2.3 (3 H, s), 4.5 (1 H, dd, J_1 = 9, J_2 = 3 Hz), 4.85–5.7 (3 H, m), 7.4 (10 H, s).

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.08; H, 8.64; N, 4.77.

***N*-Methyl-5-bromomethyl-3,3-diphenyltetrahydrofurfurylamine Hydrobromide (15a).** To the stirred solution of amino alcohol **14d** (5.63 g, 20 mmol) in dichloromethane (50 ml) was added a 1 *M* solution of bromine in carbon tetrachloride (20 ml) over a period of 10 min. The mixture was then treated with dry ether (160 ml) and cooled for 2 hr. Then the solid was removed by filtration to afford **15a** (6.9 g, 78%): mp 173–175°; ir (Nujol) 2420, 2710 cm^{-1}; nmr (free base, $CDCl_3$) δ 2.2–3.4 (4 H, m), 2.73 (3 H, s, NCH_3), 3.8 (2 H, d, J = 5 Hz, CH_2Br), 4.0–4.50 (1 H, m, C_5 H), 5.57 (1 H, t, J = 7 Hz, C_2 H), 7.33 (10 H, s).

Anal. Calcd for $C_{19}H_{22}BrNO \cdot HBr$: C, 51.72; H, 5.25; N, 3.18. Found: C, 51.97; H, 5.24; N, 3.13.

***N*-Acetyl-*N*-methyl-5-bromomethyl-3,3-diphenyltetrahydrofurfuryl Amine (15b).** The free base of **15a** (4.5 mmol, obtained by treatment of 2.0 g of hydrobromide salt in dichloromethane with aqueous ammonia) was treated with acetic anhydride (500 mg) and triethylamine at room temperature to yield **15b** (1.65 g, 93%): mp 130° (dichloromethane–petroleum ether); ir (Nujol) 1645 cm^{-1}; nmr ($CDCl_3$) δ 2.1 (3 H, s) 2.4–3.4 (5 H, m), 3.1 (3 H, s), 3.65 (2 H, d, J = 6 Hz), 3.95–4.35 (1 H, m), 5.0–5.3 (1 H, m), 7.2–7.5 (10 H, m).

Anal. Calcd for $C_{21}H_{24}BrNO_2$: C, 62.69; H, 6.01; N, 3.48. Found: C, 62.19; H, 6.01; N, 3.63.

3-Methyl-6,6-diphenyl-8-oxa-3-azabicyclo[3.2.1]octane (16). The salt **15a** (3.08 g, 7.0 mmol) in dichloromethane (20 ml) was shaken with ammonium hydroxide, dried, and concentrated *in vacuo*. The residue was dissolved in DMSO (20 ml) and heated for 20 hr at 45–50°. The mixture was then partitioned between dilute ammonium hydroxide and benzene, and the organic layer was washed with water, dried, and concentrated *in vacuo*. The residual oil was purified by chromatography (alumina, eluent dichloromethane) to afford crystalline **16** (1.44 g, 74%): mp 93–94° (from petroleum ether); nmr ($CDCl)_3$ δ 1.93 (3 H, s), 2.1–2.7 (5 H, m), 3.15 (1 H, d, J = 12 Hz), 4.45 (1 H, d, J = 7 Hz), 4.75 (1 H, t, $J_1 = J_2$ = 2 Hz), 7.1–7.3 (10 H, m).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.94; H, 7.63; N, 5.04.

Alternatively, **16** was obtained in 65% overall yield when chlorohydrin **14c** was treated with 1 equiv of bromine in carbon tetrachloride and the product **15c** (an oil), without purification, was treated with methylamine in DMSO at 50–55° for 24 hr.

1,2-Epoxy-3,3-diphenyl-2-methyl-5-hexene (18). Sodium hydride (5.585 g of a 55% suspension, 0.128 mol) was washed free of the carrier with petroleum ether and covered with dry DMSO (20 ml). To this was added with stirring a solution of trimethylsulfonium iodide (24.684 g, 0.121 mol) in dry DMSO (150 ml) followed by 25.0 g (0.1 mol) of ketone **17** in DMSO (60 ml). The inner temperature throughout addition was maintained at 22–25° by cooling with an ice-water bath. The mixture was stirred for 22 hr at room temperature and then it was partitioned between water and ether–petroleum ether (1:1). The organic layer was washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to afford crude **18** (25.7 g, 97%): bp 105° (0.05 mm); nmr ($CDCl_3$) δ 1.23 (3 H, s), 2.75–3.0 (2 H, m), 4.7–5.9 (3 H, m), 7.1–7.3 (10 H, m).

Anal. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.99; H, 7.78.

3,3-Diphenyl-1-methylamino-2-methyl-5-hexen-2-ol (19). A solution of crude epoxide **18** (12.0 g, 45.5 mmol) in DMSO (15 ml) was saturated with methylamine gas at 0° and heated for 6 days at 48–52° in a pressure bomb. The reaction mixture was then partitioned between water and ether, and the basic fraction was isolated by acid–base treatment to afford **19** (4.25 g, 20.6%) as an oil: nmr ($CDCl_3$) δ 1.2 (3 H, s), 2.24–2.95 (2 H, AB q, J = 12 Hz), 2.35 (3 H, s), 3.18 (2 H, d, J = 7 Hz), 4.75–5.9 (3 H, m), 7.0–7.4 (10 H, m). The oxalate salt was crystallized from methanol, mp 194–196°.

Anal. Calcd for $C_{20}H_{25}NO \cdot C_2H_2O_4$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.90; H, 7.14; N, 3.61.

3,5-Dimethyl-6,6-diphenyl-8-oxa-3-azobicyclo[3.2.1]octane (22) and *trans*-5-Bromomethyl-3,3-diphenyl-2-methyl-*N*-methyltetrahydrofurfurylamine (20). The amino alcohol **19** (4.13 g, 14 mmol) in carbon tetrachloride (50 ml) was stirred and treated with 1 *M* bromine in carbon tetrachloride (14 ml). The solid precipitate (5.0 g of a mixture of **20** and **21**) was filtered off and treated with ammonium hydroxide and ether. Drying and evaporation of the ether afforded an oil (3.7 g) which was chromatographed on basic alumina. Elution with chloroform afforded bicyclic base **22** (1.45 g, 37%) as an oil: nmr ($CDCl_3$) δ 1.07 (3 H, s), 1.91 (3 H, s), 2.1–3.25 (6 H, m), 4.5 (1 H, dd, J_1 = 7, J_2 = 1.5 Hz), 7.05 (5 H, s), 7.3 (5 H, s). The hydrochloride salt was crystallized from methanol–ether, mp 234–236°.

Anal. Calcd for $C_{20}H_{23}NO \cdot HCl$: C, 69.05; H, 7.53; N, 4.02. Found: C, 68.74; H, 7.15; N, 4.01.

Further elution of alumina with 20% methanolic chloroform afforded trans amino bromide **20** (1.75 g, 34%) as an oil, which was relatively stable, and upon repeated chromatography did not yield any more of **22**: nmr ($CDCl_3$) δ 1.27 (3 H, s), 2.38 (3 H, s), 2.65–3.8 (6 H, m), 4.2–4.7 (1 H, m), 7.1–7.3 (10 H). The hydrochloride salt was recrystallized from MeOH–ether, mp 218–222°.

Anal. Calcd for $C_{20}H_{24}BrNO \cdot HCl$: C, 58.48; H, 6.13; N, 3.41. Found: C, 58.52; H, 6.38; N, 3.18.

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Registry No.—**1a**, 50790-06-2; **1b**, 50790-07-3; **1c**, 50790-08-4; **2**, 50790-09-5; **3**, 50789-91-8; **4**, 50790-10-8; **5**, 50790-11-9; **5** hydrochloride, 50790-12-0; **7**, 50789-92-9; **7a**, 50789-93-0; **8**, 50789-94-1; **8a**, 50789-95-2; **9**, 50790-13-1; **10**, 50790-14-2; **11**, 50789-99-6; **11a**, 50789-96-3; **12**, 50789-97-4; **12a**, 50789-98-5; **13**, 50790-15-3; **14a**, 50790-16-4; **14b**, 50790-17-5; **14c**, 50790-18-6; **14d**, 50790-19-7; **15a**, 50790-00-6; **15a** free base, 50790-01-7; **15b**, 50790-02-8; **16**, 50790-20-0; **17**, 41921-51-1; **18**, 50790-21-1; **19**, 50790-22-2; **19** oxalate, 50790-23-3; **20**, 50790-03-9; **20** hydrochloride, 50790-04-0; **21**, 50790-05-1; **22**, 50790-24-4; **22** hydrochloride, 50790-25-5; diethyl (allyl phenyl) malonate, 50790-26-6; methanesulfonyl chloride, 124-63-0; ethyl phenylacetate, 101-97-3; 2-chloroethyl vinyl ether, 110-75-8; allyl bromide, 106-95-6; 2,2-diphenyl-4-pentenoic acid, 6966-03-6; 2,2-diphenyl-4-pentenoic acid chloride, 50790-27-7.

References and Notes

(1) Paper I: I. Monkovic, Y. G. Perron, R. Martel, W. J. Simpson, and J. A. Gylys, *J. Med. Chem.*, **16**, 403 (1973).

(2) The stereochemistry of tetrahydrofurfuryl bromides throughout this paper is defined with respect to the functionalized substituents such as $-CH_2Br$ and $-C(=O)NHCH_3$.

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(9) A referee brought up the question concerning the lack of participation of nitrogen and carbonyl oxygen in alcohols (**14d** and **2**, respectively. Perhaps the hydrogen bonding in both instances significantly contributes to the nucleophilicity of the hydroxylic oxygen. Thus an indirect participation of nitrogen in **14d** and carbonyl oxygen in **2**, acting as proton acceptors, may be postulated. However, in the case of **14d** the known preference[6,10] for formation of five-membered rings to six-membered ones should also be a significant factor.

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Site Selectivity in Attack by Carbenes on Substituted Benzenes. 5-Diazomethyl-1,4-diphenyl-1,2,3-triazole[1]

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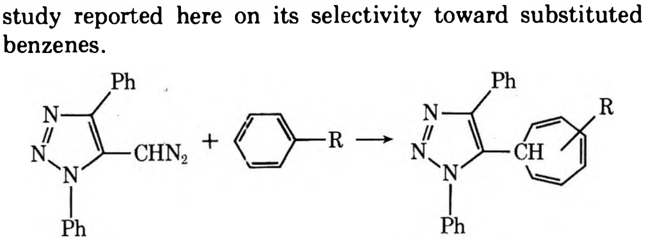
5-Diazomethyl-1,4-diphenyl-1,2,3-triazole (I) reacts with monosubstituted benzenes at 40–50° to give 72–90% yields of mixtures of 7-(1,4-diphenyltriazol-5-yl)tropilidenes in which the predominant isomer has the substituent in the 3 position (CH_3 or F) or the 2 position (CH_3O). The relative reactivities of monosubstituted benzenes toward the carbene from I were determined by competition experiments; they could be correlated by a Hammett equation in σ_p with $\sigma = -1.0$, corresponding to an electrophilic species with a selectivity more closely resembling that of carboethoxynitrene than carboethoxycarbene. 5-(α-Diazobenzyl)-1,4-diphenyltriazole thermolyzed more slowly than the diazomethyl analog, but still showed first-order kinetics with a rate constant independent of solvent in the absence of a proton source. It did not form addition or insertion products, but gave a mixture consisting principally of the symmetrical tetrasubstituted ethylene, the corresponding ethane, and 5-benzoyl-1,4-diphenyltriazole. These products, the result of dimerization, abstraction of hydrogen, and reaction with O_2, imply the intermediacy of a carbene in the triplet state.

The importance of the method of generation of a carbene on its chemical behavior has become evident in recent years. Among examples that may be cited, ethyl diazoacetate when photolyzed in cyclohexene gives addition product (7-carboethoxynorcarane) and insertion products in a ratio of 26:21, but when the reaction is brought about by thermolysis with a copper catalyst, addition of the carbene is the only result observed.[2] The factors that have been proposed[3-6] to account for such differences are spin multiplicity, state of electronic or vibrational excitation, solvation, and coordination or other bonding to metals. Some significant studies of uncatalyzed thermolysis of diazo compounds have been made,[7] but, in view of the importance of obtaining unambiguous evidence about the behavior of carbenes, it is desirable to obtain a wider selection of observations made on carbenes generated without the aid of catalysts or similar reactants, and without high input of energy (thermal or photochemical). We have reported[8] on a carbene source that might meet these requirements: 5-diazomethyl-1,4-diphenyl-1,2,3-triazole (I). It gives products of typical carbene reactions on thermolysis only slightly above room temperature (40–50°), in the dark and in the absence of any catalyst. In certain reactions, it showed a higher selectivity than sources of methylene or carboethoxycarbene, a feature believed to be in part due to electronic stabilization of the carbene. Because its reactions included ring expansion of benzene to tropilidene cleanly and in good yield, we undertook the study reported here on its selectivity toward substituted benzenes.



I

Results and Discussion

The diazo compound I was originally prepared[8] by the Bamford–Stevens process, utilizing decomposition of the lithium derivative of 1,4-diphenyltriazole-5-carboxaldehyde *p*-toluenesulfonylhydrazone. Because this reaction was only erratically reproducible and was cumbersome in operation, we have developed a route involving oxidation of the unsubstituted hydrazone with phenyliodoso acetate, which proved superior to all conventional reagents, such as manganese dioxide or mercuric oxide, for oxidizing hydrazones, and consistently gave yields of 80% or better.

The crystalline diazo compound was dissolved in a large excess of a substituted benzene and the mixture was heated at 45–55°. A mixture of isomeric tropilidenes was obtained, from which only one component could generally be isolated by crystallization. For quantitative assay, the mixed isomers were freed from aldazine and other contaminants by column chromatography and were examined by nmr. Success of this assay depends on the sensitivity of the chemical shifts of the tropilidene protons to the substituent and of the substituent to its position, such that not all substrates that would be desirable allow the products to be assayed satisfactorily. Attempts with chromatographic or other types of spectrographic assay offered no improvement.

The products obtained from toluene illustrate the method, which is based on comparison with the known shifts[9] of the protons of tropilidene (1-H, δ 5.28 ppm; 2-H, 6.12 ppm; 3-H, 6.55 ppm; 7-H, 2.20 ppm). In the diphenyltriazolyltropilidenes, the 7 hydrogen is shifted to about 3.1 ppm by the adjacent triazolyl substituent; the five olefinic protons fall in the regions 5.82–6.42 (allylic vinyl) and 4.95–5.32 ppm (simple vinyl), and the methyl groups of the positional isomers fall at 1.97, 1.84, and 1.76 ppm. The methyl signals were assigned to the 3-, 2-, and 1-methyl isomers, respectively, according to the relative shifts of the corresponding ring protons. This assignment was confirmed by comparison with the spectrum of the one isomer that could be isolated by fractional crystallization; in the vinyl region, the relative areas of the signals at 6.14 (allylic vinyl) and 5.15 ppm (simple vinyl) were 4:1 and the methyl group must therefore occupy a 1 position (vinyl). The remaining simple vinyl proton (6-H) was coupled with 7-H (J = 3.0 Hz) and with 5-H (J = 4.6 Hz), as required.

Of the substituted benzenes used as substrates, isopropoxybenzene gave a 92% yield of isomeric tropilidenes whose nmr signals could not be accurately resolved; nitrobenzene reacted so incompletely (*ca.* 10%) as to preclude meaningful assay of the isomer ratio; and aniline and dimethylaniline followed a different reaction path, apparently starting with attack on nitrogen, and could not be made to contribute to this study. The other results are summarized in Table I.

The relative reactivities of differently substituted benzenes toward 1,4-diphenyltriazol-5-ylcarbene were deter-

Table I
Isomeric x-Substituted 7-(1,4-Diphenyltriazol-5-yl)tropilidenes from Monosubstituted Benzenes C_6H_5-G.

Substrate	Yield,[a] %	Isomer distribution[b] 3-G	2-G	1-G
$CH_3C_6H_5$	90	50.0	27.3	22.7
$CH_3OC_6H_5$	94	34.8	38.3	26.4
FC_6H_5	72	50.0	23.5	26.5

[a] Isolated, purified product mixture. [b] Per cent composition of purified product mixture.

mined from competition experiments, in which equimolar amounts of pairs of substrates were allowed to react with 1 molar equiv of I in sealed tubes, and the change in relative amounts of the substrates was monitored by vpc at intervals. Under these conditions, the rates relative to benzene can be calculated from the relation

$$\frac{k_{(C_6H_5G)}}{k_{(C_6H_6)}} = \log \frac{[C_6H_5G]_t}{[C_6H_5G]_{t_0}} \Big/ \log \frac{[C_6H_6]_t}{[C_6H_6]_{t_0}}$$

The reliability of this treatment depends on freedom from extraneous losses of substrate; product assays had already shown that side reactions were minimal, and attack on the solvent (*sym*-tetrachloroethane) was negligible. Figure 1 shows plots of the relative rates as a function of the extent of reaction. The points determine straight lines from the origin; their slopes give the rates relative to benzene. The numerical results are collected in Table II, and are compared with similar data that have been reported[10] for carboethoxycarbene and carboethoxynitrene.

Although it is of uncertain justification[10] to apply Hammett substituent constants derived from electrophilic substitution reactions to ring-expansion reactions, it is practical and interesting, and previous studies in this area[10] have used them. In Figure 2, the relative rates are plotted against σ_p; the best least-squares fit is log $k = 0.16 - 0.8\ \sigma_p$ with a probable error of 0.06 (the scatter of points is much larger with σ_m, probable error 0.25). However, trifluoromethylbenzene reacted about twice as fast as would be expected, but there were attendant analytical complications; if it is omitted from the calculations, the expression becomes $0.11 - 1.0\ \sigma_p$. Either way, the value for the Hammett regression factor qualitatively confirms that we are dealing with an electrophilic carbene; comparison with the values −0.38 reported[10] for carboethoxycarbene and −1.32 for carboethoxynitrene is especially interesting, for it demonstrates that the triazolylcarbene more closely resembles nitrenes, with their greater selectivity, than other carbenes. This fact supports the view that the triazolylcarbene is significantly stabilized by interaction with the heterocyclic ring; the possibility that the selectivity may also be influenced by the conditions used to generate the carbene is an aspect that we plan to investigate.

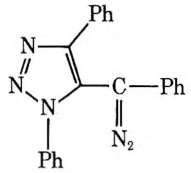
A somewhat parallel study has been made[11] of carbenoid attack on alkylbenzenes, using the very different system ethylidene iodide plus diethylzinc or diethylcadmium, which produces 7-methyltropilidenes presumably through a species related to methylcarbene. A qualitatively similar isomer ratio for toluene—22% 1-methyl, 32% 2-methyl, 46% 3-methyl—and a reactivity relative to benzene of 2.5 were found. Although the attacking species may be far from a free carbene in this system, it evidently has similar electronic demands to our triazolylcarbene. Another study,[12] in which iodoform and diethylzinc were used to convert alkylbenzenes to ethylalkyltropilidenes, reached rather different results. The major isomer obtained from toluene was the 1-methyltropilidene; however, the investigators believed that the product ratios were not determined by the initial carbenoid attack, but by a subsequent step in which a tropylium iodide reacted with ethylzinc iodide. The mobility of the iodide moiety would erase any directing effect operating in the initial attack.

Table II
Relative Rates of Attack on Substituted Benzene Substrates

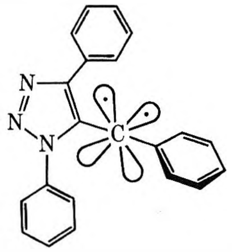
	k(Ph-G)/k(Ph-H) Diphenyl-triazolylcarbene	Carboethoxy-carbene	Carbo-ethoxy-nitrene
i-$PrOC_6H_5$	2.03 ± 0.34[a]		
$CH_3OC_6H_5$		1.15	2.88
$EtOC_6H_5$	2.44 ± 0.53		
$CH_3C_6H_5$	2.08 ± 0.21	1.06	2.06
C_6H_6	1.00	1.00	1.00
FC_6H_5		0.80	0.62
ClC_6H_5		0.84	0.77
$O_2NC_6H_5$	0.22 ± 0.03		
$F_3CC_6H_5$	0.81 ± 0.05	0.55	0.22

[a] These deviation figures were determined graphically from plots of log ($[RC_6H_5]/[RC_6H_5]$) *vs.* log ($[C_6H_5]/[C_6H_6]$) by comparing the slopes from each point to the origin with the computed least mean squares slope.

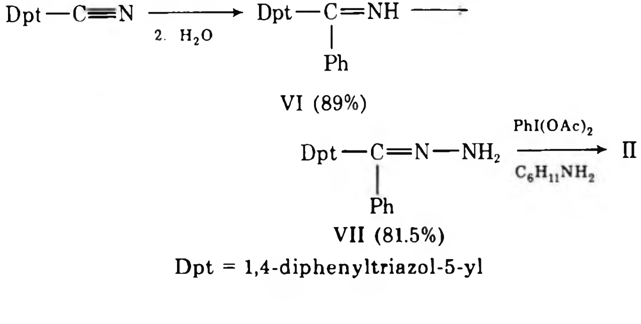
We also wished to examine the α-phenyl analog of I, 5-α-diazobenzyl-1,4-diphenyltriazole (II), which would give a carbene sterically substantially more hindered, and in which the triplet state could be expected to have increased stabilization. In the carbene from II, crowding should favor orientation of the α-phenyl group orthogonal to the triazole ring; this orientation would allow maximum overlap of the π-electron systems of the α-phenyl group and the triazole ring, respectively, with the two orthogonal p orbitals that accommodate the two unpaired electrons of the triplet state of the carbene. Furthermore, a linear orientation of the substituents in the sp-hybridized triplet carbene would entail less crowding than the *ca.* 120° angle about the sp^2, singlet carbene.



II



Diazo compound II was prepared from 5-chloro-1,4-diphenyltriazole by successive conversion to the nitrile, the phenyl ketimine, and the hydrazone (of 4-benzoyl-1,4-diphenyltriazole). Conversion of the chloride to the cyanide by reaction with sodium cyanide, a published procedure,[13] was found to be very sensitive to moisture in the solvent.



Dpt = 1,4-diphenyltriazol-5-yl

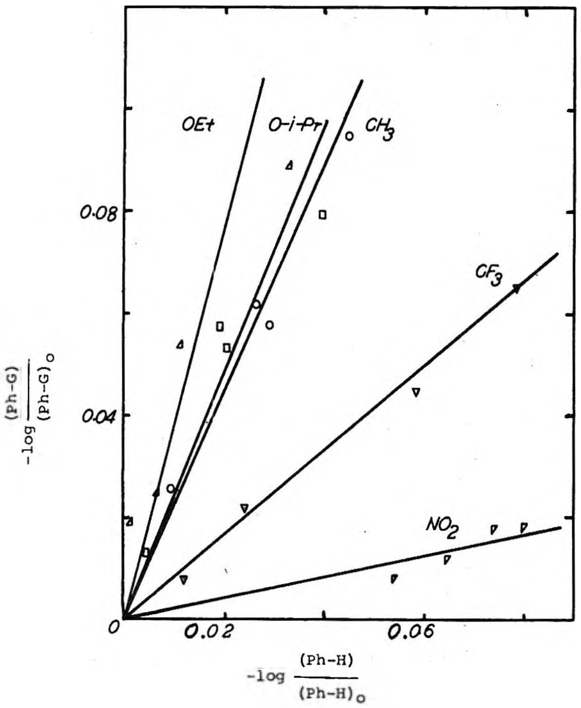


Figure 1. Relative rates from decomposition of 5-diazomethyl-1,4-diphenyl-1,2,3-triazole in aromatic substrates (Ph-G): △, G = OEt; □, G = O-*i*-Pr; ○, G = CH$_3$; ▽, G = CF$_3$; ▼, G = NO$_2$.

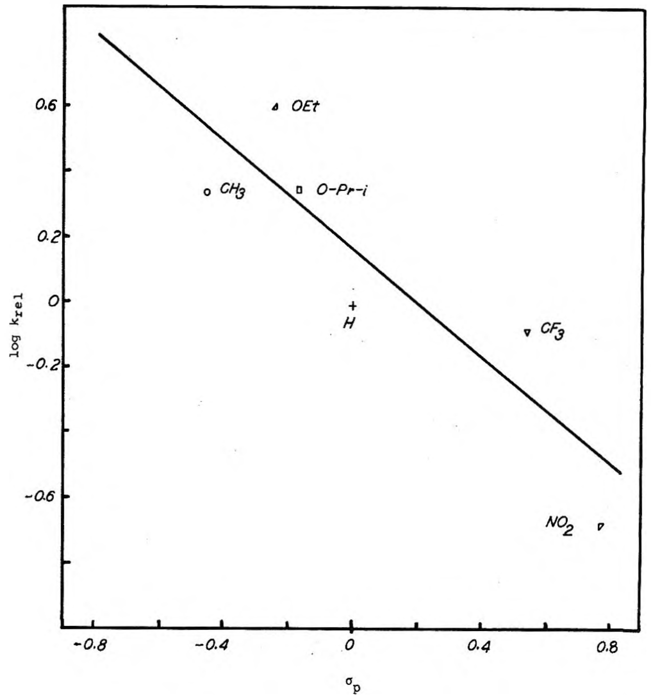


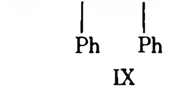
Figure 2. Plot of Hammett substituent constants, σ_p, against relative rates of reaction of aromatic substrates with 1,4-diphenyl-1,2,3-triazol-5-ylcarbene.

When dimethyl sulfoxide that was not strictly anhydrous was used, the yield of nitrile dropped sharply, and a mixture of the 5-carboxamide and 1,4-diphenyltriazole took its place. The latter was found to arise by decarboxylation of 1,4-diphenyltriazole-5-carboxylic acid, which came from hydrolysis of the amide. Other routes to II were tried without success; in particular, 5-benzyl-1,4-diphenyltriazole resisted free-radical bromination and could not be converted to the 5-(α,α-dibromobenzyl) derivative, and 5-benzoyl-1,4-diphenyltriazole resisted all attempts to convert it to its hydrazone.

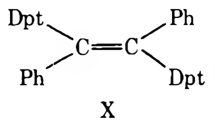
Conversion of the ketimine VI to the hydrazone was slow, and was accompanied by formation of the primary amine, 5-(α-aminobenzyl)-1,4-diphenyltriazole (VIII), which was also prepared from VI by reduction with sodium borohydride. The amount of VIII was much greater in runs on a small scale; it is presumed to arise by reduction of VI by diimide formed by action of air on hydrazine (reduction of 5-benzoyl-1,4-diphenyltriazole to the carbinol upon prolonged refluxing with hydrazine has also been observed.)[14]

The kinetics of thermolysis of II were determined spectrophotometrically in anisole and in nitrobenzene; they were accurately first order, and the constants did not differ significantly between the two solvents (9.9 and 8.8 × 10^{-3} min^{-1}, respectively, at 70°). This is considerably slower than thermolysis of I (at 50°, k = 8.9 × 10^{-3} min^{-1}).[8] In dioxane containing traces of moisture, however, the rate was roughly 20 times as fast as in anisole or nitrobenzene and the principal product, the carbinol Dpt-CHOH-Ph, was different. These observations are consistent with the interpretation that decomposition in aprotic solvents produces a carbene, but proton sources, such as water, may catalyze a noncarbenoid reaction that may become dominant. This contrasts with the behavior observed by Bethell, Whittaker, and Callister[15] for diphenyldiazomethane, the rate of thermolysis of which in acetonitrile was not markedly accelerated by water, even though the reaction path was diverted to formation of carbinol.

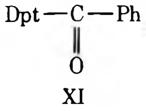
The products of thermolysis in the solvents used in the kinetic experiments and in three other aromatic solvents were examined by thin layer and column chromatography, fractional crystallization, and nmr and ir. The mixtures were complex, and that from benzene showed at least eight components by tlc; some of them were dark colored, uncrystallizable materials. Only three could be obtained crystalline for identification: the symmetrically tetrasubstituted ethane IX, the corresponding ethylene X, and 5-benzoyl-1,4-diphenyltriazole (XI). These same three products were formed in each of the other aromatic solvents, as shown in Table III. The other portions of the reaction mixtures were carefully scrutinized by nmr for evidence that any compound had been formed by attack on the aromatic solvents, but none could be obtained; if addition or insertion products were indeed formed, their amounts must have been less than *ca.* 5%. The yields of IX, X, and XI were determined from the amounts isolated pure augmented by semiquantitative estimates of the amounts in the mother liquors, reckoned from the relative sizes of their tlc spots.


$$\underset{\text{Ph}}{\text{Dpt—}\underset{|}{\text{CH}}}\text{—}\underset{\text{Ph}}{\underset{|}{\text{CH}}\text{—Dpt}}$$

IX



X


$$\text{Dpt—}\underset{\text{O}}{\overset{}{\underset{\|}{\text{C}}}}\text{—Ph}$$

XI

These products, the result of abstraction of hydrogen, dimerization, and reaction with oxygen, are those typical of triplet carbenes;[16] products attributable to singlet carbenes were evidently not formed in significant quantities. Presumably the steric effect mentioned above operated to accelerate spin inversion so as to forestall competing reactions by the singlet carbene which, according to conservation of spin, must have been the initial species. The large amount of ketone XI formed in nitrobenzene might be considered anomalous, but we believe it is not; the solvents were swept with nitrogen before use, but the amount of residual dissolved oxygen was not checked, and must have been variable.

Table III
Composition[a] of Products of Thermolysis of 5-Diazobenzyl-1,4-diphenyltriazole (II)

Solvent	IX, %	X, %	XI, %
Benzene	42.4	5.5	6.7
Toluene	38.0	12.3	12.5
Anisole	55.2	5.5	4.7
Isopropoxybenzene	46.2	3.0	10.9
Nitrobenzene	39.3	0	25.6

[a] Estimated error between 0 and ±2.1.

The complete absence of the ketazine from the thermolysis products was surprising, for ketazines are generally formed from diazoalkanes and their high melting points and low solubility make the isolation of even small amounts easy. We could not check the possibility that the ketazine was converted to the symmetrical ethylene X by reaction with diazo compound, because the precursors, such as the ketone and hydrazone, were so unreactive that the ketazine could not be prepared by any means. However, the proclivity of hindered diazo compounds to form ethylenes by dimerization of carbenes, rather than forming azines, has been reported by Zimmerman and Paskovich.[17] If formation of azine depends on reaction of singlet carbene with diazoalkane, as appears to be the case,[15] rapid spin inversion to the triplet would suppress it, as would steric hindrance. By contrast, thermolysis of I gives aldazine in 8–14% yields.

The effect of changing from phenylcarbene to diphenylcarbene, previously reported[16,18] on the basis of photolysis and thermolysis of the diazo compounds, and inferred to result from reaction of the carbenes respectively in the singlet and triplet states, is thus confirmed in this parallel instance.

Experimental Section[19]

1,4-Diphenyl-1,2,3-triazole-5-carboxaldehyde Hydrazone. This preparation utilized the finding by Barton, O'Brien, and Sternhall[20] that formation of azine during conversion of aldehydes to hydrazones is greatly reduced in the presence of triethylamine. To a hot solution of 5 g (0.02 mol) of 1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde[14] in 350 ml of absolute ethanol were added 14 ml of triethylamine and 28 ml of 95%+ hydrazine, in that order. The solution was allowed to reflux for 1 hr, and was then concentrated under reduced pressure to *ca.* 100 ml; about 800 ml of ether was added; and the solution was poured into 800 ml of water and extracted. The ethereal layer was washed with five 250-ml portions of water and was then dried ($CaCl_2$); removing the ether under aspirator vacuum left a colorless, viscous oil, which according to tlc was at least 80% hydrazone (ir spectrum identical with that of authentic material[14]). The oil could he crystallized from aqueous ethanol, but losses due to formation of azine were large. Therefore, the oil was oxidized to I immediately.

5-Diazomethyl-1,4-diphenyl-1,2,3-triazole (I). The oily hydrazone from 5 g (0.01 mol) of aldehyde was dissolved in 40 ml of methylene chloride and 5.1 ml (3.965 g, 0.04 mol) of cyclohexylamine, and the solution was cooled to −10°. A solution of 6.44 g (0.02 mol) of (diacetoxyiodo)benzene (phenyliodoso acetate)[21] in 85 ml of methylene chloride was added with stirring at a rate such that the temperature was maintained at −5 ± 2°. The mixture was stirred for an additional 1 hr at about 0°, and was then cooled to −25° and filtered. The filtrate was extracted with four 100-ml portions of ice-water, and was then dried ($CaCl_2$). The solvent was removed *in vacuo* without external warming, leaving a dark brown oil; trituration with 70 ml of ether precipitated 2.65 g of bright orange solid, mp 101° (ir spectrum and tlc behavior identical with those of I).[14] The overall yield from aldehyde was 49%.

1,4-Diphenyl-1,2,3-triazole-5-carboxamide (III). Using the procedure of Friedman and Shechter,[13] but with dimethyl sulfoxide from a partly used bottle, and thus presumably moist, there was obtained 2.28 g (58%) of a white solid, mp 210–215°, from 4.00 g (0.0157 mol) of 5-chloro-1,4-diphenyl-1,2,3-triazole and sodium cyanide: ir 3500, 3330, and 3150 ($-NH_2$), 1675 (amide C=O), 1600 and 1500 (phenyl), and 925, 1005, and 1075 cm^{-1} (triazole). A sample recrystallized from aqueous ethanol had mp 217–219°.

Anal. Calcd for $C_{15}H_{12}N_4O$: C, 68.13; H, 4.57; N, 21.20. Found: C, 68.00; H, 4.51; N, 21.12.

This substance was identified as 1,4-diphenyl-1,2,3-triazole-5-carboxamide by acid-catalyzed hydrolysis; 1.00 g (0.00375 mol) was refluxed for 1 hr in 50 ml of 75% glacial acetic acid containing 10 ml of concentrated sulfuric acid. After conventional work-up, there was obtained 815 mg (79.6%) of recovered amide (mmp 216–218°) and 170 mg (17.1%) of 1,4-diphenyl-1,2,3-triazole-5-carboxylic acid, mp 172–173.5° with gas evolution and resolidification, remelting at 185–186° (lit.[22] mp 177° dec, remelting at 185°), mmp 173–175 and 185–186°.

5-Benzimidoyl-1,4-diphenyl-1,2,3-triazole (VI). To a solution of phenylmagnesium bromide prepared from 2.675 g (0.11 mol) of magnesium and 17.272 g (0.11 mol) of bromobenzene in 55 ml of ether was added a solution of 12.3 g (0.05 mol) of 1,4-diphenyl-1,2,3-triazole-5-carbonitrile in *ca.* 600 ml of ether. Reflux was maintained for 48 hr, after which the mixture was cooled and treated with 20 ml of absolute methanol; stirring was continued for an additional 1 hr. The magnesium salts were separated by filtration and were triturated repeatedly with fresh aliquots of methylene chloride. The combined filtrates were evaporated to leave a white solid. Recrystallization from absolute ethanol gave 14.42 g (89%) of fine, cream-colored needles: mp 149–150°; ir (Nujol) 3260 (NH), 1600 and 1500 (phenyl), 875, 1000, and 1155 cm^{-1} (triazole); nmr ($CDCl_3$) δ 7.55 (m, 15 H, aromatic) and 6.75 ppm (s, 1 H); *m/e* 324. Four recrystallizations from absolute ethanol gave an analytical sample.

Anal. Calcd for $C_{21}H_{16}N_4$: C, 77.74; H, 4.97; N, 17.28. Found: C, 77.68; H, 5.05; N, 17.33.

5-Benzoyl-1,4-diphenyl-1,2,3-triazole Hydrazone (VII). To a hot solution of 10.0 g (0.0309 mol) of VI in 380 ml of absolute ethanol was added 60 ml (1.896 mol) of anhydrous hydrazine[23] and the mixture was heated at reflux. The total time required for complete conversion of VI to VII varied between 20 and 130 hr, which made it necessary to follow each run by tlc. Upon completion, the mixture was cooled and then concentrated under reduced pressure; crystallization was completed overnight at 0°. The white hydrazone was recrystallized from absolute ethanol, affording 9.04 g (81.5%) of white, shiny platelets: mp 169–172°; ir (Nujol) 3400, 3280, and 3200 (2 NH), 1635 (C=N), 1600 and 1500 (phenyl), and 780, 1000, and 1075 cm^{-1} (triazole); nmr ($CDCl_3$) δ 7.6 (15 H, aromatic) and 6.3 ppm (s, 2 H, NH_2). The yields were consistently 72–83% of once recrystallized material and were independent of the specific reaction time. However, when hydrazone formation was attempted on 1 g or less of imine, it was significantly suppressed by a competing side reaction leading to 5-aminobenzyl-1,4-diphenyl-1,2,3-triazole. An analytical sample of VII hydrazone was obtained by three more recrystallizations from absolute ethanol.

Anal. Calcd for $C_{21}H_{17}N_5$: C, 74.31; H, 5.05; N, 20.64. Found: C, 74.26; H, 5.18; N, 20.65.

5-Aminobenzyl-1,4-diphenyl-1,2,3-triazole. In an analogous experiment with 500 mg (0.00155 mol) of VI and anhydrous hydrazine in 25 ml of ethanol, refluxed for 130 hr, the evidently impure crude solid product was taken up in ether and extracted three times with 5% HCl and once with water. The dried (Na_2SO_4) ether layer yielded 302 mg (57.5%) of pure VII. The acidic extracts were neutralized with $NaHCO_3$ and extracted with ether. Evaporation of the dried (KOH) extracts left 115 mg (22%) of white solid, mp 138–139°. This substance formed a base-soluble benzenesulfonamide, and evolved nitrogen with nitrous acid: nmr ($CDCl_3$) δ 7.8 (complex m, 15 H), 5.8 (s, 1 H), and 1.8 ppm (broadened singlet, 2 H); ir (Nujol) 3275 and 3350 ($-NH_2$), 1600, 1500 (phenyl), and 775, 1000, and 1080 cm^{-1} (triazole); *m/e* 326. The nmr signal at 1.8 ppm disappeared after treatment with D_2O. Reduction of VI with $NaBH_4$ gave the identical substance. A sample recrystallized (EtOH) five times had mp 136.5–139.5°.

Anal. Calcd for $C_{21}H_{18}N_4$: C, 77.27; H, 5.56; N, 17.17. Found: C, 77.02; H, 5.60; N, 17.27.

5-Diazobenzyl-1,4-diphenyl-1,2,3-triazole (II). A solution of 9.00 g (0.0265 mol) of VII in 75 ml of methylene chloride and 7.36 ml (0.058 mol) of cyclohexylamine was cooled to −80°, and a solution of 9.34 g (0.029 mol) of (diacetoxyiodo)benzene in 100 ml of methylene chloride was added with stirring while the temperature was maintained between −10 and −5°. Stirring was continued for 2 hr at −10 to −5°. The deep red mixture was then chilled to −30° and filtered to remove cyclohexylammonium acetate, and the precipitate was washed with small portions of chilled methylene chloride until the washings were colorless. The filtrate was concentrated to about one-half the original volume on a rotary evaporator without warming, and was again cooled to −30° for several hours. Filtration removed all residual cyclohexylammonium acetate and excess oxidizing agent, and the solution was then evaporated at room temperature, leaving a bright reddish-brown residue. Trituration with about 30 ml of ether precipitated a brick-red solid, which was washed with a small amount of ether and recrystallized from ether by dissolving it at room temperature and cooling for 48 hr at −30°, yield 5.02 of reddish-brown, irregular crystals. Three additional crops, together 1.285 g, were collected. All four fractions were pure by tlc. An additional 353 mg was obtained by chromatography of the crude filtrate on a water-jacketed column of Florisil, the red material being eluted with a petroleum ether (bp 30–60°)–ether mixture (9:1), total yield of once-recrystallized product 6.76 g (75.5%).

The nmr spectrum of the red solid showed only aromatic protons centered at 7.4 ppm. The infrared (Nujol) had a very strong, sharp peak at 2050 cm^{-1} (N≡N), also absorption at 1600 and 1500 (phenyl) and at 765, 920, and 1000 cm^{-1} (triazole). Spectral evidence thus clearly indicated the red solid to be 5-diazobenzyl-1,4-diphenyl-1,2,3-triazole (II).

The melting point of the diazo compound varied considerably from one fraction to another, and usually was not sharp. Also, when the compound was recrystallized slowly at 0°, two different types and colors of crystals became distinguishable: ruby-red transparent prisms (mp 125° with visible decomposition from 114°) and orange lumps or rosettes (mp 205°, with visible decomposition from 114°). Slow crystallization produced a larger amount of prisms, generally accompanied by some of the orange material. The two were identical with respect to their nmr (m, 7.4 ppm) and ir spectra (2050, 1600, 1500, 1000, 920, 765 cm^{-1}), their tlc values, and their chemical behavior. A solution of red prisms could easily be crystallized at −30° to give only orange rosettes, but the conversion back to prisms was more difficult. Thus, it took five slow recrystallizations, each time removing manually any prisms formed, to collect 140 mg of the latter from 217 mg of rosettes.

A sample was recrystallized at 0° five times; rosettes were removed manually from prisms and the two fractions were analyzed separately.

Anal. Calcd for $C_{21}H_{15}N_5$: C, 74.75; H, 4.48; N, 20.76. Found (prisms): C, 74.66; H, 4.51; N, 20.84. Found (rosettes): C, 74.74; H, 4.51; N, 20.88.

Thermolysis of 1,4-Diphenyl-5-diazomethyl-1,2,3-triazole (I). Solutions ranging in concentration from 0.01 to 0.02 *M* were prepared in carefully dried equipment by dissolving the diazo compound in a substituted benzene substrate, which had previously been flushed with dry nitrogen for a minimum of 1 hr. The resulting bright red or yellow solutions were immersed in an oil bath preheated to 45–55° and stirred mechanically while being kept under a positive pressure of nitrogen. The decompositions were complete after 4 hr. The work-up procedures differed for each substrate.

A. In Toluene. Thermolysis of 1.044 g (0.004 mol) of I in 200 ml of toluene gave a bright yellow solution, which was filtered to remove a very small amount of azine and was concentrated on a rotary evaporator to a viscous yellow oil, which was chromatographed on a column packed with 70 g of Florisil (100–200 mesh). Each fraction was examined by tlc as it was eluted from the column and the ones with similar composition were combined. Six fractions were obtained. The first two contained only small amounts of unidentified materials and were discarded. Fractions 4 and 5 (eluted with chloroform) and 6 (eluted with ethanol) contained only negligible amounts of mixtures of up to six compounds, three of which had been introduced with the diazo compound. No attempts were made to isolate or identify these beyond examining their nmr spectra for the presence of the potential product of C–H insertion, 1-(1,4-diphenyl-1,2,3-triazol-5-yl)-2-phenylethane, which proved to be absent.

Fractions 2 and 3 (eluted with benzene) amounted to 1.28 g (90.6%) of a pale yellow glass (X), which showed one elongated spot on tlc, and contained the three positional iosmers of *x*-methyl-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene: nmr δ 7.85 (m, aromatic, 2 H), 7.32 (m, aromatic, 8 H), 6.14 (m, C═CHC═C), 5.15 (m, C═CHC-), and 3.1 ppm (m, tertiary H, 1 H). The relative area of the combined vinylic signals was 5. The methyl groups appeared as singlets at 1.97, 1.84, and 1.76 ppm, with a combined relative integration of 3. The infrared spectrum (Nujol) had major absorptions at 1601 and 1505 (phenyl) and also at 1076 and 1000 (very strong), and 920 cm^{-1} (triazole).

The ratio of the isomeric cycloheptatrienes was determined in a separate experiment, in which 0.131 g (0.50 mol) of analytically pure 5-diazomethyl-1,4-diphenyl-1,2,3-triazole was thermolyzed in 50 ml of spectral-grade toluene. The viscous distillation residue was extracted with three portions of chloroform, and the extracts were dried ($MgSO_4$) and evaporated to leave 145 mg (89%) of pale yellow, viscous oil, which according to tlc was >95% cycloheptatrienes. The nmr spectrum corresponded to a mixture of 50.0% of 3-methyl-, 27.3% of 2-methyl-, and 22.7% of 1-methyl-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene. The relative amounts were determined from the intensity of the respective methyl signals (2.2:1.2:1.0). The accuracy of these determinations was confirmed by the ratio of the vinylic hydrogens, calculated from the given composition as 3.227 for the hydrogens in the 2, 3, 4, and 5 positions and 1.773 for the 1 and 6 hydrogens; the corresponding multiplets at 6.14 and 5.15 ppm had an intensity ratio of 3.2:1.8.

The chromatographically pure mixture of the three isomers was fractionally crystallized from ethanol–water, the composition of each solid fraction was examined by nmr, and those of similar isomer ratio were combined and recrystallized from ethanol or methanol. After this had been repeated seven times, 60 mg of 1-methyl-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene was obtained free from the other two isomers. Two additional recrystallizations from methanol furnished 35.4 mg of sand-colored, transparent prisms, mp 161–163°.

Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.99; N, 12.91. Found: C, 81.07; H, 5.98; N, 12.87.

B. In Anisole. Decomposition of 0.131 g (0.50 mol) of I in 50 ml of freshly distilled anisole resulted in a yellow solution, which was steam distilled to remove the anisole. The residue was extracted exhaustively with chloroform. The yellow oil (183 mg) obtained after drying (Na_2SO_4) and concentrating the combined extracts was purified further by preparative thin layer chromatography on silica gel, from which 161 mg (94.3%) of very pale yellow, viscous oil was obtained. It gave only one spot on tlc, decolorized bromine in carbon tetrachloride, and reduced aqueous potassium permanganate. Its nmr spectrum was consistent with a mixture of the three positional isomers of *x*-methoxy-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene: δ 7.83 (m, 2 H), 7.37 (m, 8 H), 5.0–6.4 (m, 5 H), 3.63 (s, 3-CH_3O), 3.56 (s, 2-CH_3O), 3.31 ppm (s, 1-CH_3O) superimposed on a broad hump (7-CH) (3.63–3.31 total intensity, 4 H). After the contribution by the C-7 hydrogen was subtracted, the relative areas of the methoxy signals were 1.32:1.47:1.0, corresponding to 34.8% of 3-methoxy-, 38.8% of 2-methoxy-, and 26.4% of 1-methoxy-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene.

In another experiment, 0.522 g (0.002 mol) of I yielded a brown oil, from which was separated 599 mg of pure *x*-methoxy-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene mixture by column chromatography on 25 g of Florisil. This oil was very resistant to crystallization, but after a solution of it in benzene–petroleum ether was left undisturbed at −20° for 5 months, partial crystallization took place. The solid thus obtained had nmr δ 3.31 ppm (s, 1-CH_3O); three recrystallizations from ethanol afforded 26.7 mg of white needles, mp 169–170°, of 1-methoxy-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene.

The oil recovered from the filtrate was again dissolved in benzene–petroleum ether and allowed to crystallize at 0°. The second crop thus obtained was shown by nmr to be a mixture of all three isomers, with the 3-methoxy isomer predominating (about 75%). One recrystallization from ethanol gave pure 3-methoxy-7-(1,4-diphenyl-1,2,2-triazol-5-yl)cycloheptatriene as pale cream-colored needles, mp 134.5–135.5°, nmr δ 3.63 ppm. Both samples showed compatible infrared spectra: 3000, 1625, 1605, 1505, 1080, 1000, and 925 cm^{-1}.

Anal. Calcd for $C_{22}H_{19}N_3O$: C, 77.30; H, 5.61; N, 12.31. Found (3-CH_2O isomer): C, 77.17; H, 5.56; N, 12.34. Found (1-CH_3O isomer): C, 77.38; H, 5.60; N, 12.46.

C. In Isopropoxybenzene. Thermolysis of 0.522 g (0.002 mol) of I in 50 ml of freshly distilled isopropoxybenzene, after steam distillation, extraction of the residue with chloroform, drying, and evaporation, gave 752 mg (92%) of brown oil, about 90% of which showed as one spot by the tlc.

The nmr spectrum was in good agreement with a mixture of isomeric *x*-isopropoxy-7-(1,4-diphenyl-1,2,3-triazol-5-yl)-cycloheptatrienes: δ 7.86 (m, 2 H), 7.32 (m, 8 H), 7.0 (m, 5 H), 3.15 (m, 1 H), 3.28 (m, 1 H), and 1.17 ppm (three overlapping doublets, total 6 H).

When the oil was dissolved in methylene chloride, 4.3 mg of 1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde azine, mp and mmp 298–302°, remained. The filtrate was evaporated and the residual oil was dissolved in a small amount of ethanol and allowed to stand at room temperature for 1 week. A small amount of white crystals had separated; the nmr spectrum suggested that they were an approximately 1:1 mixture of two isomers of *x*-isopropoxy-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene. Two more crops (136 mg) of white prisms, mp 165–169°, were obtained from the ethanolic filtrate. The chemical shifts of the methyl groups were too close to permit unequivocal differentiation of the isomers by nmr. Four recrystallizations of the first crop from ethanol afforded 6.6 mg of fine, white needles, mp 134–137°.

Anal. Calcd for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.28; N, 11.38. Found: C, 77.98; H, 6.26; N, 11.31.

D. In Nitrobenzene. Thermolysis of 0.130 g (0.001 mol) of I in 25 ml of nitrobenzene gave a reddish-brown solution, which was freed from nitrobenzene by steam distillation. The residue was extracted with chloroform, and the extracts were combined, dried (Na_2SO_4), and evaporated to leave a dark brown oil, which on tlc examination revealed the presence of at least nine components, none of which amounted to more than 25% of the total mixture. Separation by preparative tlc on silica gel furnished only the component of highest R_f in reasonably pure form. Recrystallization of this fraction from benzene afforded 20.8 mg (16.8%) of a white solid, mp 172–174°, identified as 1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde[8] (nmr, ir, mixture melting point). Another tlc fraction contained 43 mg of material whose nmr spectrum exhibited olefinic protons with chemical shifts expected for substituted cycloheptatrienes, but attempts at purification were foiled by rapid decomposition.

E. In Fluorobenzene. The mixture from thermolysis of 0.533 g (0.002 mol) of I in 75 ml of fluorobenzene was concentrated under aspirator pressure, leaving a dark brown oil, which was dissolved in methylene chloride and filtered to remove 6 mg of 1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde azine. The fluorine nmr of the filtrate exhibited six structured singlets (sweep width 100 ppm) at 97.5, 101.8, 113.0, 114.9, 115.7, and 117.9 ppm upfield from the external standard, trichlorofluoromethane. The resonances at 113, 115.7, and 117.9 ppm were later proven to be impurities contained in the "reagent-grade" fluorobenzene; they were separated from the main product by dry-column chromatography[24] on alumina.

The major component was contained in three fractions sectioned off the column, although the last one of these was contaminated with four unidentified compounds. The first two fractions contained 473 mg (72%) of chromatographically pure product. Its spectral characteristics were in accord with a mixture of the three isomeric fluoro-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatrienes: ir ($CHCl_3$) 3050 (aromatic CH), 1640 and 1504 (phenyl), and 1000 and 1075 cm^{-1} (triazole); nmr δ 7.9 (m, 4 H), 7.4 (m, 1 H), 6.2–5.33 (m, 5 H), and 3.18 ppm (broad, 1 H). The fluorine nmr exhibited three structured singlets (sweep width 100 ppm) at 97.6, 101.8, and 114.9 ppm upfield from the external standard, trichlorofluoromethane, in a ratio of 2.1:1:1.1, nearly the same ratio as had been found for the equivalent peaks in the crude product mixture.

This mixture of isomeric *x*-fluoro-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatrienes was taken up in a small volume of ethanol and the solution was allowed to crystallize. Three successive crops were collected, amounting to a total of 323 mg. The first of these was recrystallized twice from ethanol, producing small, pale yellow leaflets, mp 141–145°, of analytical purity, but its positional identity remained spectroscopically ambiguous.

Anal. Calcd for $C_{21}H_{16}N_3F$: C, 76.54; H, 4.90; N, 12.76. Found: C, 76.55; H, 4.92; N, 12.76.

Attack of I on Substituted Benzenes. Relative Rates. The thermolyses were conducted in tubes of Vycor glass, 5 mm in diameter and 9–10 cm long. Prior to use they were cleaned with chromic–sulfuric acid solution, followed by 10 *N* sodium hydroxide, and were then rinsed repeatedly with distilled water, baked for 24 hr at about 150°, and stored in a desiccator over phosphorus pentoxide.

The solvent was commercial 1,1,2,2-tetrachloroethane, which after four fractional distillations still contained an impurity of higher R_f; although it amounted to at most 0.5%, its appearance in the vpc trace was prominent, since the solvent–substrate ratio used was larger. Since additional redistillation did not noticeably improve the purity, and the foreign component did not interfere with the vpc traces of the substrates used, the solvent was used in this state.

The aromatic substrates used were reagent-grade benzene, toluene, trifluoromethylbenzene, and phenetole, which were fractionally distilled and stored over sodium sulfate; reagent-grade nitrobenzene, which was steam distilled, dried, and then fractionally distilled; and isopropoxybenzene, which was synthesized from isopropyl bromide and sodium phenoxide, and redistilled (bp 177°). The purity of each solvent was ascertained by vpc.

Solutions were prepared by weighing approximately 0.25 mmol each of benzene and substituted benzene from a 0.24-ml syringe into a 1-ml volumetric flask, which was then filled to the mark with 1,1,2,2-tretrachloroethane, stoppered, and shaken to thoroughly mix the liquids. Half of this solution was withdrawn into a 0.5-ml syringe and added to an ampoule containing 0.0655 g (0.25 mmol) of I. The remaining half was refrigerated in the stoppered flask, until used to assay the amount of the substrates by vpc. The solution was distributed among five reaction tubes, frozen in Dry Ice–acetone, and sealed. All transfers were conducted as rapidly as possible to minimize loss of solvents. The diazotriazole used had been recrystallized from ether–petroleum ether to analytical purity.

Anal. Calcd for $C_{15}N_{11}N_5$: C, 68.94; H, 4.25; N, 26.81. Found: C, 68.91; H, 4.22; N, 26.94.

The samples were allowed to warm to room temperature and were equilibrated in a constant-temperature bath at 50.0 ± 0.1°. Tubes were withdrawn at various time intervals and were stored in Dry Ice–acetone until analyzed; one vial, "t_∞," was not removed until at least 10 hr.

The changes in composition of the samples were determined on an F & M Model 500 gas chromatograph equipped with a Brown recorder and disc chart integrator, using a 0.25 in. × 8 ft column of 5% SE-30 silicone rubber on Chromosorb 60/80 W (He flow rates 50–80 ml/min; initial temperature 30–50°; programs 0–7.9°/min). The average numerical values obtained (each an average of five measurements) were divided by the value for the t_0 sample. The best least-squares fit to a straight line for log ([Ph-G] at t_n/[Ph-G] at t_0) for the substituted substrate against log ([Ph-H] (t_n)/[Ph-H] (t_0) for benzene was caluclated by computer, according to the equation

$$k_{\text{rel}} = \frac{k[\text{Ph}-\text{G}]}{k[\text{Ph}-\text{H}]} = \frac{\log\left([\text{Ph}-\text{G}]_{t_n}/[\text{Ph}-\text{G}]_{t_0}\right)}{\log\left([\text{Ph}-\text{H}]_{t_n}/[\text{Ph}-\text{H}]_{t_0}\right)}$$

The evaluation of the vpc traces of samples containing trifluoromethylbenzene was complicated by the near coincidence of the retention times of the substrate and of an undetermined reaction product which was formed in similar amounts in all experiments, regardless of the aromatic substrate, amounting to about 8%. A correction was made by subtracting the amount formed in experiments without trifluoromethylbenzene.

The overall results are presented in Figure 1 and Table II.

Kinetics of Thermolysis of 5-Diazobenzyl-1,4-diphenyl-1,2,3-triazole (II). The thermolysis rates of II were determined by observing the change in absorbance at 495 nm on a Cary 14 recording spectrophotometer. The validity of Beer's law was confirmed on five standard solutions of II in anisole; molar extinction coefficients were determined to be 69 for anisole solutions, 76 for nitrobenzene solutions, and 63 for dioxane solutions.

Method A. Solutions of II (0.012–0.015 *M*) were immersed in a water bath preequilibrated at the required temperature; 12–15 min was allowed for the solution to warm, after which time the first aliquot was removed and transferred to a cell chilled in ice–water (duration less than 15 sec). Subsequent aliquots were removed in like manner at appropriate time intervals. Absorbances were determined after each sample had cooled to room temperature.

Method B. The solution was apportioned among 12 stoppered tubes which were immersed into the equilibrated water bath. The first tube was withdrawn 10 min after immersion, and one tube each at appropriate time intervals. The sample tubes were stored in ice–water until the spectra could be scanned, for which purpose the contents were allowed to thaw, and were then transferred to the absorbance cell.

The measurements were carried out in every case by scanning the spectrum from 600 to 400 nm and determining the absorbance at the maximum (about 495 nm). Baseline corrections were applied as necessary. Decomposition to completion in *p*-dioxane resulted in a colorless solution; thus there was no interference from products. With the aromatic substrates, however, absorption caused by the yellow products began to overlap with the absorbance at 495 nm after about two half-lives, but they presented no problem during the initial period, during which the kinetic measurements were taken.

The data were evaluated by a computerized least squares fit analysis[25] to determine the coefficients for the best quadratic equation fitted to the sets of logarithm *vs.* time and the standard deviation of the log A values from the calculated straight line. In anisole, at 69.9 ± 0.1°, $k = (9.89 \pm 0.06) \times 10^{-3}$ min^{-1} (two experiments, 11 measured points for each); at 80.0 ± 0.1°, $k = (29.5 \pm 0.9) \times 10^{-3}$ min^{-1}, in nitrobenzene at 70.0 ± 0.1°, $k = 10^{-3}$ min^{-1}, and at 59.9 ± 0.1°, $k = (80.3 \pm 5.2) \times 10^{-3}$ min^{-1}.

1,4-Diphenyl-5-(α-hydroxybenzyl)-1,2,3-triazole. Reduction of 3.5 g of XI was brought about by treatment with 0.234 g of lithium aluminum hydride in 180 ml of tetrahydrofuran at reflux for 1 hr. After conventional work-up, 2.18 g (60%) of white crystals of 1,4-diphenyl-5-(α-hydroxybenzyl)-1,2,3-triazole, mp 172–177°, clearly distinguishable by tlc from the original ketone, was obtained: ir (Nujol) 3300 and 3175 (OH), 1600 and 1503 (phenyl), 1000 and 1075 cm^{-1} (triazole); nmr 7.2 (m, 15), 6.21 (d, 1), and 3.47 ppm (d, 1). When the sample was shaken with D_2O, the 3.47-ppm doublet collapsed to a singlet. This substance was identical with the product of thermolysis of II in dioxane. An analytical sample was prepared by five more recrystallizations from benzene as shiny white needles, mp 177–179°.

Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 76.82; H, 5.13; N, 12.83.

The mother liquors were shown by tlc to consist of a mixture of starting material and product.

Thermolyses of 5-Diazobenzyl-1,4-diphenyl-1,2,3-triazole in Aromatic Solvents. Thermolysis of II. Solutions of II, *ca.* 0.02 *M*, in a given solvent were flushed with dry nitrogen for 30 min to 5 hr and were then heated at 80–85° in an oil bath, with stirring, in apparatus dried by baking for 12 hr, under a positive pressure of nitrogen. Decomposition was allowed to proceed for 4–5 hr, after which no more II was detectable by tlc or ir. Decompositions in benzene required a reflux condenser.

A. In Benzene. The yellow solution resulting from decomposition of 0.450 g of II in 133.4 ml of dry benzene was concentrated *in vacuo* to a yellow oil, which on trituration with ether precipitated 195.5 mg of a white solid: mp 148–198°; ir 1610, 1580, and 1500 (phenyl), 1080, 1005, and 925 cm^{-1} (triazole); nmr δ 7.87 (m, 2), 7.39 (m, 13), and 5.37 ppm (s, 1); mass spectrum *m/e* 310 ($C_{21}H_{16}N_3$). The empirical formula corresponds to α-(1,4-diphenyl-1,2,3-triazol-5-yl)benzyl radical, and the ir and nmr spectra unambiguously indicate the preservation of the 1,4-diphenyl-1,2,3-triazole moiety. Presumably, the compound is the dimer, 1,2-diphenyl-1,2-di(1,4-diphenyl-1,2,3-triazol-5-yl)ethane, $C_{42}H_{32}N_6$, in which the lability of the central bond is high enough to permit complete dissociation of the molecular ion under the conditions used (60 eV, direct inlet at 150–200°). Attempts to obtain a mass spectrum at lower ionization voltages gave unsatisfactory results. The structure assignment of IX is supported by the fact that the same substance was formed regardless of the aromatic decomposition medium; so it could only have been derived from II.

Eight recrystallizations from ethanol gave an analytically pure sample as fine, pure white needles, mp 221–223°.

Anal. Calcd for $C_{42}H_{32}N_6$: C, 81.25; H, 5.19; N, 13.55. Found: C, 81.13; H, 4.97; N, 13.52.

The ethereal filtrate from the foregoing fraction was concentrated and again triturated with ether to produce an additional 75 mg of IX (ir, tlc, mixture melting point). The mother liquors from this second crop were subjected to preparative tlc on silica gel. Nine bands were collected, containing a least seven compounds. The fifth band consisted of two compounds in approximately equal amounts, one of which was IX. Recrystallization from ethanol gave 9.8 mg of IX, increasing the total amount isolated to 412 mg (65.2%).

Bands 3 and 4 contained 53.8 mg of mixtures of compounds, with one material predominating to the extent of 80% as estimated from the relative intensities on tlc. A 20-mg crop (4.5%) of this material, mp 177–180°, was obtained chromatographically pure by crystallization from absolute ethanol. One further recrystallization led to pale yellow prisms of XI, mp 182–184°, identical by mixture melting point, ir, and nmr with authentic material.

Trituration with ether of the material separated in the seventh band precipitated 8.7 mg of X as white needles, mp 261–277° dec; recrystallization from ethanol increased the melting point to 297–301°, mass spectrum *m/e* 618 ($C_{42}H_{30}N_6$). All isolated fractions of X were combined and recrystallized repeatedly from ethanol, affording 5.0 mg of glossy white needles, mp 303–304.5°; it did not decolorize bromine in carbon tetrachloride, which is not unusual for a highly hindered olefin.

Anal. Calcd for $C_{42}H_{30}N_6$: C, 81.53; H, 4.89; N, 13.59. Found: C, 81.33; H, 5.09; N, 13.60.

Approximate estimates of the total amounts of products formed were obtained by examining the various impure fractions by tlc and estimating the proportion of each component from the relative size of the spot on the chromatogram. The residual fractions were deduced to contain approximately 15 mg of XI, 18 mg of IX, and 28 mg of X; adding the actually isolated quantities to these amounts gave 44 mg of XI (6.7%), 271 mg of IX (42.), and 37 mg of X (5.5%). None of the other compounds observed as tlc spots was obtained in quantities sufficient for isolation and identification.

B. In Toluene, Anisole, Isopropoxybenzene, and Nitrobenzene. Thermolyses in these solvents were examined in much the same way as described for benzene, with minor variations in recrystallization and chromatographic techniques. The identity of the various samples of IX, X, and XI with each other was established by mixture melting point, ir, nmr, and tlc retention. The results are recorded in Table III.

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Registry No.—I, 15764-89-3; II, 39974-78-2; III, 50640-05-6; IV, 50640-06-7; VI, 50640-07-8; VII, 50640-08-9; IX, 50640-09-0; X, 50640-10-3; XI, 50640-11-4; 1,4-diphenyl-1,2,3-triazole-5-carboxaldehyde hydrazone, 15764-92-8; bromobenzene, 108-86-1; 1,4-diphenyl-1,2,3-triazole-5-carbonitrile, 15764-95-1; 5-aminobenzyl-1,4-diphenyl-1,2,3-triazole, 50640-12-5; 3-methyl-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene, 50640-13-6; 2-methyl-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene, 50640-14-7; 1-methyl-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene, 50640-15-8; 3-methoxy-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene, 50640-16-9; 2-methoxy-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene, 50640-17-0; 1-methoxy-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene, 50640-18-1; *x*-isopropoxy-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene, 50790-96-0; 3-fluoro-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene, 50640-19-2; 2-fluoro-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene, 50640-20-5; 1-fluoro-7-(1,4-diphenyl-1,2,3-triazol-5-yl)cycloheptatriene, 50640-21-6; 1,4-diphenyl-5-(α-hydroxybenzyl)-1,2,3-triazole, 50640-22-7.

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fluorescent indicator, "dry-column chromatography grade." Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

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[25] We wish to express our sincere thanks to the late Dr. K. Lanini for his patient assistance with the computer program.

Intermediates in Nucleophilic Aromatic Substitution. XII.[1] Kinetic and Equilibrium Study of the Spiro Meisenheimer Complex of 1-(β-Hydroxyethoxy)-2,4-dinitrobenzene

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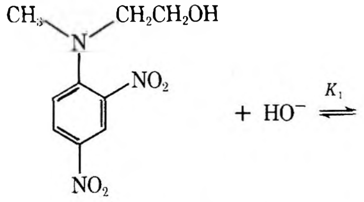
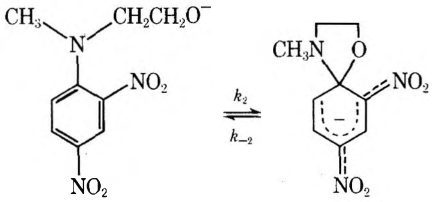
The spiro Meisenheimer complex formed from 1-(β-hydroxyethoxy)-2,4-dinitrobenzene (**4**) in the presence of strong base in aqueous DMSO is considerably more stable than the analogous complex from *N*-β-hydroxyethyl-*N*-methyl-2,4-dinitroaniline (**1**). This difference in stabilities, which becomes more pronounced in DMSO-rich mixtures, is attributed mainly to greater ground-state resonance stabilization in **1**. In water-rich mixtures the rates at which the two spiro Meisenheimer complexes revert to starting materials are almost identical, indicating that the higher stability of the complex derived from the title compound is entirely due to a higher rate of formation. This is shown to be consistent with a complex-like transition state. In DMSO-rich solvents the results indicate a shift toward a more reactant-like transition state in agreement with the Hammond postulate.

We recently published a kinetic study on the formation of the cyclic Meisenheimer complex (**3**) derived from *N*-β-hydroxyethyl-*N*-methyl-2,4-dinitroaniline (**1**) in various mixtures of dimethyl sulfoxide (DMSO) and water.[3] We were particularly concerned with the rate coefficient k_{-2} since it provides a point of reference for the expected rates of leaving-group departure in typical nucleophilic aromatic substitution reactions of amines with 1-X-2,4-dinitrobenzene compounds.[4]



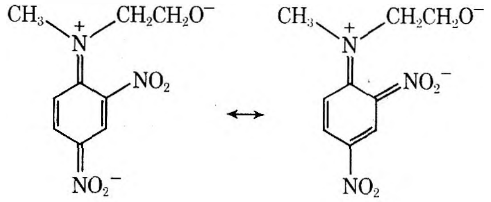
1



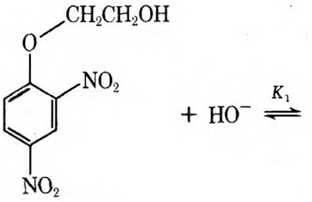
2 **3**

(1)

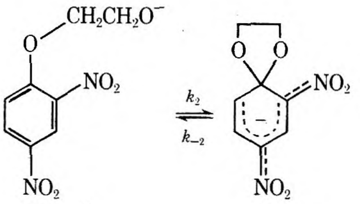
In trying to understand better the factors on which leaving group reactivities depend, we have now investigated the reaction of eq 2. One point of special interest is whether resonance stabilization in **2** (**2a**, **2b**) has a major influence on the rate constants k_2 and k_{-2} of eq 1. Inasmuch as resonance stabilization of this type is expected to be less important in **5**, a comparison between the two systems should be revealing.[5]



2a **2b**



4



5 **6**

(2)

Results

Upon addition of base to a solution of **4** in aqueous DMSO, **6**[6] is formed according to eq 2; the stability of **6** relative to the starting materials increases with increasing DMSO content, a well-known phenomenon in Meisenheimer complex chemistry[7] as well as in many other nucleophilic additions or substitutions.[8]

Absorption spectra in 54% DMSO (v/v) at various base concentrations are shown in Figure 1. Owing to hydrolysis the solutions were not very stable; the spectra shown represent extrapolations to zero time.

If we assume that at [KOH] ≥ 0.5 *M* conversion to **6** is quantitative, one calculates an extinction coefficient of 21,000 at λ_{max} 495 nm. This extinction coefficient is the same as the one determined indirectly (see below) in 50% DMSO (v/v). Spectra taken in 80% DMSO in the presence of tetramethylammonium hydroxide indicate ϵ_6 32,200 at λ_{max} 500 nm; *i.e.*, ϵ_6 is significantly solvent dependent.

Kinetics. The kinetics of the equilibrium formation of **6** were monitored spectrophotometrically in the stopped-flow (SF) or the temperature-jump (TJ) apparatus. In all runs the base was in a large excess over the substrate concentration, assuring pseudo-first-order kinetics throughout. Thus the reciprocal relaxation time is given by eq 3,

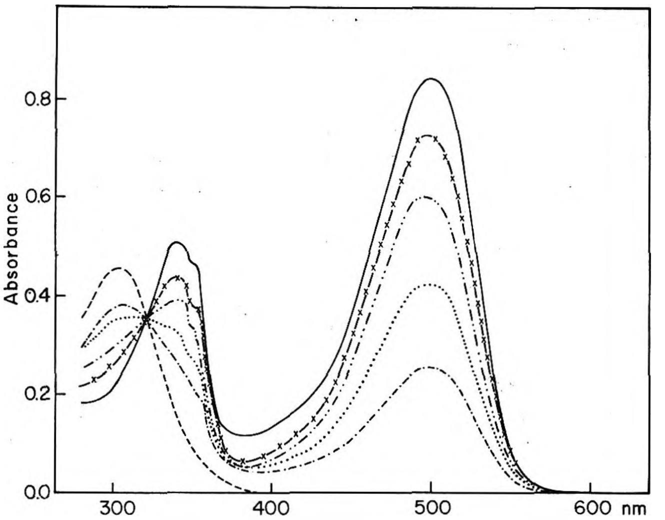


Figure 1. Uv-visible spectra of 4 at various KOH concentrations in 54% DMSO (v/v) (μ = 0.5 M, $[4]_0 = 4.0 \times 10^{-5}$ M): — — —, without base; — · —, 0.006 M; . . . ., 0.0125 M; — · · —, 0.025 M; — x —, 0.05 M; ———, 0.5 M.

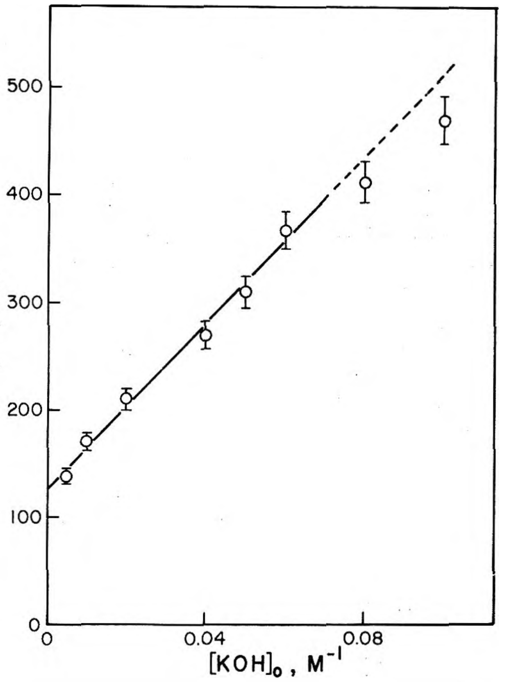


Figure 2. Reaction in 50% DMSO (v/v), μ = 0.5 M, τ^{-1} as function of $[KOH]_0$.

since the acid-base equilibrium $4 \rightleftharpoons 5$ is always rapidly established with respect to the time scale of τ; $[HO^-]_0$ refers to the stoichiometric base concentration.

$$\frac{1}{\tau} = k_2 \frac{K_1[HO^-]_0}{1 + K_1[HO^-]_0} + k_{-2} \qquad (3)$$

In any given solvent the ionic strength was kept constant by adding KCl as necessary. Our results are summarized in Table I.

As confirmed by equilibrium measurements reported below, complex formation is disfavored in 2% DMSO (v/v). Thus τ^{-1}, which is independent of base concentration in this solvent, is equivalent to k_{-2}.

In 20% DMSO (v/v) τ^{-1} increases slightly with base concentration. A plot of τ^{-1} *vs.* $[HO^-]_0$ (not shown) is linear, indicating that $K_1[HO^-]_0 \ll 1$; thus eq 3 simplifies to eq 4 with k_2K_1 = 144 M^{-1} sec^{-1} and k_{-2} = 719 sec^{-1}.

$$\frac{1}{\tau} = k_2K_1[HO^-]_0 + k_{-2} \qquad (4)$$

Table I
Reciprocal Relaxation Times in Various Solvent Mixtures at 25°

% DMSO (v/v)	$[KOH]_0$, M	μ, M	$[4]_0$, M	τ^{-1}, sec^{-1}	Method
2	0.2	1.0	2×10^{-3}	1460 ± 70	TJ
2	0.5	1.0	2×10^{-3}	1460 ± 70	TJ
2	1.0	1.0	2×10^{-3}	1440 ± 70	TJ
20	0.2	1.0	2×10^{-3}	751 ± 35	TJ
20	0.5	1.0	10^{-3}	786 ± 39	TJ
20	1.0	1.0	5×10^{-4}	865 ± 43	TJ
50	0.005	0.5	8×10^{-5}	139 ± 7	SF
50	0.01	0.5	8×10^{-5}	169 ± 9	SF
50	0.02	0.5	2×10^{-5}	210 ± 11	SF
50	0.04	0.5	2×10^{-5}	266 ± 13	SF
50	0.05	0.5	2×10^{-5}	310 ± 15	SF
50	0.06	0.5	2×10^{-5}	367 ± 18	SF
50	0.08	0.5	2×10^{-5}	412 ± 21	SF
50	0.10	0.5	2×10^{-5}	471 ± 23	SF
65	~0.0003	0.46	4×10^{-4}	53 ± 3	TJ
65	0.0015	0.46	2×10^{-5}	97 ± 5	SF
65	0.0025	0.46	2×10^{-5}	139 ± 7	SF
65	0.005	0.46	2×10^{-5}	221 ± 11	SF
65	0.0075	0.46	2×10^{-5}	313 ± 15	SF
65	0.01	0.46	2×10^{-5}	396 ± 20	SF

In 50% DMSO (v/v) the dependence of τ^{-1} on base concentration is much stronger; a plot of τ^{-1} *vs.* $[HO^-]_0$ is shown in Figure 2. The plot is linear at low base concentrations ($K_1[HO^-]_0 \ll 1$) with k_2K_1 = 4020 M^{-1} sec^{-1} and k_{-2} = 124 sec^{-1}, but shows a tendency to curve down at the highest concentrations. Determinations of τ^{-1} at still higher concentrations would have been desirable for purposes of evaluating k_2 and K_1 separately; this was not possible with our equipment for the following reasons. (1) The rates become too fast for the stopped-flow technique. (2) There is no suitable wavelength where the relaxation amplitude in a temperature-jump experiment was satisfactory at $[KOH]_0 > 0.1$ M.[9]

In 65% DMSO (v/v) τ^{-1} increases about ten times more strongly with base concentration than it does in 50% DMSO. For the same reasons as in 50% DMSO it was not possible to determine τ^{-1} at $[KOH]_0 > 0.01$ M; up to this concentration the dependence is linear (plot not shown) with $k_2K_1 = 3.53 \times 10^4$ M^{-1} sec^{-1} and k_{-2} = 50 sec^{-1}.

Equilibrium Measurements. In 2% DMSO k_2K_1 cannot be determined from kinetics, whereas in 20% DMSO the kinetically determined value of k_2K_1 is not very accurate since it is the small slope of a plot of τ^{-1} *vs.* $[KOH]_0$. One can, however, obtain k_2K_1 indirectly from equilibrium measurements.

We carried out such measurements by the spectrophotometric method. At the absorption maximum of 6 there is no other species in the equilibrium which absorbs a significant amount of light. Thus in a 1-cm cuvette Beer's law is given by eq 5.

$$A = \epsilon_6[6] \qquad (5)$$

The equilibrium concentration of 6 in the presence of an excess of base is given by eq 6, where $[4]_0$ is the stoichiometric concentration of 4 and $K_2 = k_2/k_{-2}$. Combining eq 5 with eq 6 affords eq 7.

$$[6] = \frac{K_1K_2[HO^-]_0}{1 + (K_1 + K_1K_2)[HO^-]_0}[4]_0 \qquad (6)$$

$$\frac{A}{\epsilon_6[4]_0} = \frac{K_1K_2[HO^-]_0}{1 + (K_1 + K_1K_2)[HO^-]_0} \qquad (7)$$

Absorption readings in 2, 20, and 50% DMSO (v/v) are summarized in Table II. In 2 and 20% DMSO absorption increases linearly with base concentration (plots not shown), indicating $(K_1 + K_1K_2)[\mathrm{HO}^-]_0 \ll 1$ up to $[\mathrm{KOH}]_0 = 1\ M$. Thus eq 7 simplifies to eq 8. Assuming that ϵ_6 at the respective absorption maxima in 2 and in 20% DMSO is the same (21,000) as the one determined in 50% DMSO, one obtains $K_1K_2 = 4.1 \times 10^{-2}\ M^{-1}$ and thus k_2K_1 $(= K_1K_2k_{-2}) = 59.5\ M^{-1}\ \mathrm{sec}^{-1}$ in 2% DMSO, $K_1K_2 = 0.24\ M^{-1}$ and thus $k_2K_1 = 173\ M^{-1}\ \mathrm{sec}^{-1}$ in 20% DMSO.

$$\frac{A}{\epsilon_6[4]_0} = K_1K_2[\mathrm{HO}^-]_0 \qquad (8)$$

In 50% DMSO a plot (not shown) of A *vs.* $[\mathrm{KOH}]_0$ is curved. For evaluation we invert and rearrange eq 7 and obtain eq 9. A plot of the left-hand side of eq 9 *vs.* $[\mathrm{HO}^-]_0^{-1}$ is shown in Figure 3. By again choosing $\epsilon_6 = 21{,}000$ we obtain the same value for K_1K_2 of 32.1 M^{-1} (reciprocal slope of Figure 3) as from kinetics (K_1k_2/k_{-2}).[10]

$$\frac{\epsilon_6[4]_0}{A} = 1 + \frac{1}{K_2} + \frac{A}{K_1K_2[\mathrm{HO}^-]_0} \qquad (9)$$

In 65% DMSO (v/v) the equilibrium favors **6** over **4** to such an extent that a spectrophotometric equilibrium determination was not attempted since most measurements would have to be made at base concentrations $<10^{-3}\ M$, which are difficult to maintain without buffers.

Table II
Absorbance at λ_{max} in Various Solvent Mixtures at 25°

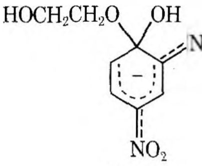
% DMSO (v/v)	$[\mathrm{KOH}]_0$, M	μ, M	$[4]_0$, M	A^a at λ_{max}	A at $\lambda_{max}{}^b$ / $\epsilon_6[4]_0$
2	0.2	1.0	10^{-3}	0.185	0.0088
2	0.4	1.0	10^{-3}	0.370	0.0176
2	0.5	1.0	10^{-3}	0.448	0.0213
2	0.6	1.0	10^{-3}	0.535	0.0255
2	0.8	1.0	10^{-3}	0.703	0.0335
2	1.0	1.0	10^{-3}	0.888	0.0423
20	0.1	1.0	10^{-3}	0.570	0.0271
20	0.3	1.0	5×10^{-4}	0.815	0.0776
20	0.4	1.0	5×10^{-4}	1.037	0.0988
20	0.6	1.0	5×10^{-4}	1.530	0.146
20	0.7	1.0	2×10^{-4}	0.706	0.168
20	0.9	1.0	2×10^{-4}	0.872	0.208
20	1.0	1.0	2×10^{-4}	1.037	0.247
50	0.01	0.5	10^{-4}	0.444	0.212
50	0.02	0.5	10^{-4}	0.871	0.415
50	0.03	0.5	10^{-4}	1.014	0.484
50	0.04	0.5	5×10^{-5}	0.618	0.589
50	0.05	0.5	5×10^{-5}	0.651	0.620
50	0.06	0.5	5×10^{-5}	0.746	0.711
50	0.08	0.5	5×10^{-5}	0.795	0.757
50	0.10	0.5	5×10^{-5}	0.826	0.786

[a] λ_{max} 480 nm in 2 and 20% DMSO, 494 nm in 50% DMSO. [b] ϵ_6 assumed to be 21,000 throughout as determined in 54% DMSO.

Discussion

Table III summarizes all kinetics and equilibrium parameters of this study along with those of the system of eq 1. Note that the values for k_{-2} and K_1K_2 referring to the system of eq 2 have been statistically corrected (experimental k_{-2} divided by 2, experimental K_1K_2 multiplied by 2).

In treating our data we have implicitly assumed that **6** is the only species contributing significantly to the absorption of visible light. In response to a comment by a referee we shall briefly discuss the possibility that formation of **7** might compete with the formation of **6**. This is a real possibility, since Hasegawa and Abe[11] have found that complex **8** is formed in solutions of 2,4-dinitroanisole in aqueous DMSO in the presence of hydroxide ion, preceded by the transient appearance of a 1,3 complex (attack of HO^- on the 3 position).



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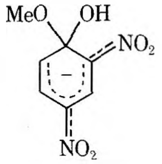

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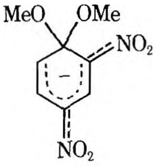

9

The stability constant for **9** in methanol is $K \approx 5 \times 10^{-5}\ M^{-1}$.[12] Based on findings with σ complexes formed between 1,3,5-trinitrobenzene and HO^- or MeO^-, respectively,[13] the stability constant in water of **8**—and by analogy that of **7** as well—is expected to be no greater than that of **9** in methanol, and probably smaller.

Let us now make the hypothesis that the colored species in our study is **7** instead of **6**; the quantity K_1K_2 in Table III would thus take on the meaning of the stability constant, K, of **7**. In 2% DMSO this quantity is $8.2 \times 10^{-2}\ M^{-1}$, which is more than 10^3-fold greater than the upper limit ($5 \times 10^{-5}\ M^{-1}$) expected for the stability constant of **7**. Further, if we were dealing with **7** instead of **6**, the high rate of complex dissociation (*e.g.*, in 2% DMSO $k_{-2} = 725\ \mathrm{sec}^{-1}$) would be difficult to rationalize since expulsion of HO^- from **7** in 2% DMSO is expected to be no greater and probably slower than expulsion of MeO^- from **9** in methanol[13] ($42\ \mathrm{sec}^{-1}$).[12] We conclude that the color in our system is virtually exclusively due to **6**. This conclusion is further supported by the fact that we observe only one relaxation process and that K_1K_2 determined from kinetics in 20% DMSO agrees with K_2K_2 determined spectrophotometrically within the experimental error.

Let us now turn our attention to a comparison of the systems of eq 1 and 2. There are striking differences be-

Table III
Kinetic and Equilibrium Parameters for the Reactions of Equations 1 and 2

DMSO (v/v)	2%	20%	50%	65%
$4 \rightleftharpoons 5 \rightleftharpoons 6$				
k_{-2},^{a} sec^{-1}	725 ± 35	360 ± 18	62 ± 3	25 ± 5
K_1k_2, M^{-1} sec^{-1}	59.5 ± 5^b	173 ± 15^b	$4.01 \pm 0.2 \times 10^3$	$3.53 \pm 0.14 \times 10^4$
K_1K_2,^{a} M^{-1} (kinetic)		0.40 ± 0.08	64.2 ± 6	1410 ± 200
K_1K_2,^{a} M^{-1} (spectr)	$8.20 \pm 0.3 \times 10^{-2}$	0.48 ± 0.02	64.2 ± 6^c	
$1 \rightleftharpoons 2 \rightleftharpoons 3$				
k_{-2}, sec^{-1}	929	650	332	166
K_1k_2, M^{-1} sec^{-1}	4.56^b	4.95^b	19.9^b	156^b
K_1K_2, M^{-1} (spectr)	4.92×10^{-3}	7.60×10^{-3}	5.98×10^{-2}	0.94
$(k_{-2})_6/(k_{-2})_3$	0.78	0.55	0.187	0.150
$(K_1k_2)_6/(K_1k_2)_3$	13.1	35	202	226
$(K_1K_2)_6/(K_1K_2)_3$	16.7	63.2	1075	1500

[a] Statistically corrected. [b] From K_1K_2 (spectr) × k_{-2}. [c] ϵ_6 chosen such as to give K_1K_2 (spectr) = K_1K_2 (kinetic); see text.

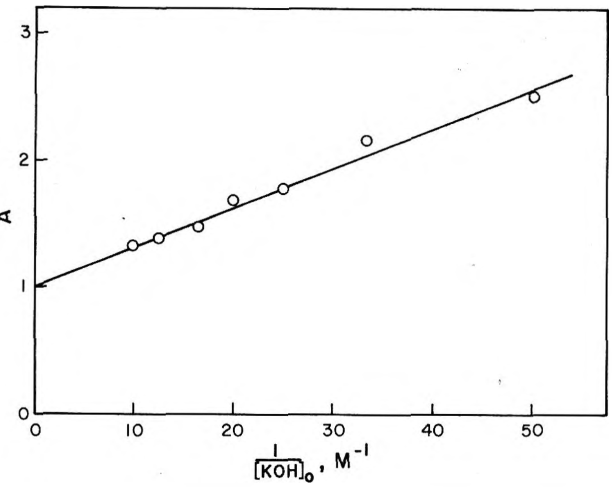

Figure 3. Reaction in 50% DMSO (v/v), μ = 0.5 M, inversion plot according to eq 9.

tween the two systems, both in the absolute values of the kinetic and equilibrium parameters as well as in their solvent dependence. For example, for **6** the effect on k_{-2} of increasing the DMSO content is comparable in magnitude to similar solvent effects on the rate of decomposition of σ complexes between HO^- and 3,5-dinitropyridine[14] or 3,5-dinitrobenzonitrile;[15] for **3** this solvent effect on k_{-2} is much smaller. This suggests that **6** behaves "normally," **3** "abnormally."

Comparing the K_1K_2 values in the two systems, we note that **3** is considerably less stable than **6**. Since K_1, the acid dissociation constant of **1** and **4**, respectively, can be expected to be very similar for both compounds, the higher K_1K_2 value for **6** must mainly reflect a higher K_2 value.[16]

Possible factors accounting for the lower stability of **3** include ground-state resonance stabilization in **2** (**2a**, **2b**), a larger steric strain (eclipsing effects) in the five-membered ring of **3**, and the stabilizing effect of two alkoxy substituents on the sp^3 carbon[18] of **6**.

We believe that the first factor may very well be the most important of the three for the following reasons. When the DMSO content of the solvent is increased, the ratio $(K_1K_2)_6/(K_1K_2)_3$ increases from 16.7 in 2% to 63.2 in 20% to 1075 in 50% to 1500 in 65% DMSO. Assuming that the solvent effect on K_1 is comparable in both systems, these data indicate that the stability of **6** increases more than does the stability of **3**. In other words, the factor responsible for the higher stability of **6** over **3** becomes more important in DMSO-rich mixtures.

Since DMSO is well known to be more effective than water in solvating large dipoles,[8] resonance forms such as **2a** and **2b** may in fact become more important in DMSO-rich mixtures and with it ground-state stabilization of **2**, thus accounting for the solvent effect on $(K_1K_2)_6/(K_1K_2)_3$. It would be more difficult to rationalize the solvent effect on the basis of the two other possible factors (steric strain or sp^3 carbon stabilization).

This interpretation is also consistent with the idea that **6** is the "normal," **3** the "abnormal" compound as suggested earlier.

An interesting question regards the extent to which the transition state is affected by the resonance stabilization. In **2** and in 20% DMSO both **6** and **3** revert to their starting materials at essentially the same rates. This means that it is the forward rate coefficient (k_2) which is entirely responsible for the difference in complex stability between **3** and **6**. We conclude from this that the transition state for the reaction **2** $\rightleftharpoons$ **3** does not benefit from resonance stabilization and thus must closely resemble the complex.

As the DMSO content is increased k_{-2} becomes coresponsible for the lower stability of **3**; in 65% DMSO k_{-2} for **3** is almost seven-fold larger than for **6**. This suggests that in DMSO-rich mixtures there is some resonance stabilization in the transition state; *i.e.*, the transition state must move closer to **2** as the DMSO content increases. Since complex stability increases at the same time, such an effect would be consistent with Hammond's postulate.[19]

Though more data of a similar kind are needed for definite conclusions, this study suggests that developing resonance stabilization in the transition state of the product-forming step in nucleophilic aromatic substitution reactions by amines probably only plays an important role when the intermediate complex is very stable.

Experimental Section

Materials. 1-(β-Hydroxyethoxy)-2,4-dinitrobenzene was prepared according to Blanksma and Fohr,[20] mp 111° after recrystallization from ethanol. DMSO (Baker Analyzed Reagent Grade) and KCl (Mallinckrodt) were used without further purification. Tetramethylammonium hydroxide (Matheson Coleman and Bell) was recrystallized from anhydrous ethanol. KOH solutions were prepared from Titrisol (Merck). Reaction solutions were prepared by dispensing the appropriate amount of DMSO into a volumetric flask, then adding an aqueous solution of the other ingredients, and finally filling to the mark with distilled water.

Rate and Equilibrium Measurements. Kinetic determinations were made on a temperature-jump transient spectrophotometer of Messanlagen Studiengesellschaft, Göttingen, and on a stopped-flow spectrophotometer of Durrum Instruments Corp. Chemical relaxation was monitored between 490 and 530 nm. Spectrophotometric equilibrium measurements were carried out in a modified thermostatted Bechman DU spectrophotometer. Owing to hydrolysis, absorbance readings decreased slowly with time. The values reported in Table II are extrapolated to time zero.

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Registry No.—**1**, 37580-86-2; **3**, 37541-32-5; **4**, 2831-60-9; **6**, 12128-27-7.

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(9) Apart from an apparently rather small enthalpy of reaction, it was not possible to optimize the amplitude by monitoring the relaxation at a wavelength of strong absorption of the disfavored species **4** because of interference with the spectrum of **6** (see Figure 1). There was no such problem with the reaction of eq 1, since **1** has a maximum at 390 nm where the complex **3** has a minimal absorption.[3]

(10) An "inversion plot" according to eq 9 offers the interesting possibility of determining K_2 and K_1 separately provided that K_2 is quite small (K_2 <1) so that the intercept ($1 + K_2^{-1}$) is significantly larger than 1. With ϵ_6 = 21,000 this intercept is, however, 1.02 ±

0.05, *i.e.*, indistinguishable from 1. For the system of eq 1 a similar inversion plot in 65% DMSO had afforded an intercept of 1.35 from which K_2 was calculated.[3] We now have serious reservations about this value because of a possibly erroneous extinction coefficient (ϵ_3). For lack of any better value we were forced to use ϵ_3 determined in 85% DMSO. Our present study indicates that ϵ_6 decreases from 32,200 in 80% DMSO to 21,000 in 50% DMSO. If ϵ_3 depends in a similar way on the solvent as does ϵ_6, the true intercept of said inversion plot would become indistinguishable from 1.

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Equilibrium Additions of Nucleophiles to Carbon–Nitrogen Double Bonds in Nonaqueous Solutions. Addition of Alcohols to Substituted Benzylideneanilines

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Rate and equilibrium constants for the base-catalyzed addition of methanol to benzylideneanilines in methanol-acetonitrile (90:10 v/v) were determined by means of spectrophotometry. The equilibrium constant increases by electron-withdrawing substituents in the aniline ring as well as in the benzylidene ring, showing a correlation with the σ^+ constants. Also the rate constant increases by electron-withdrawing groups, showing a correlation with σ in this case. The solvent deuterium isotope effects are 0.98 for K_0^{MeOH}/K_0^{MeOD} and 0.60 for k_f^{MeOH}/k_f^{MeOD}. The structural change of alcohol leads to the Taft equation for equilibrium constant, K_0: $\log (K_0^X/K_0^{Me}) = -8.2\sigma^* + 0.48E_s$. The rate decreases in the order *n*-BuOH > EtOH > MeOH > *sec*-BuOH > *t*-BuOH > *i*-PrOH, showing no simple correlation. The observed base catalysis, substituent effect, and solvent isotope effect are best explained by a mechanism involving a rate-determining attack by the alkoxide ions on the imino carbon atom. Thermodynamic parameters are calculated.

Equilibrium additions of nucleophiles to C=O bonds have been extensively studied[1] but the studies on the additions to C=N bonds are few except for the hydrolysis of Schiff bases[2-5] and for the additions of amines[5] and of hydrogen cyanide.[6,7] Only a few reports have paid attention to the addition of alcohols to C=N.[2,8,9] Because of the higher basicities[2-4] and lower electrophilicity of C=N than those of C=O,[1] these reactions involve the protonated Schiff bases, where negative ρ values have been observed.[2-7]

The present report describes the base-catalyzed equilibrium addition of alcohols to benzylideneanilines **1**–**11** in which no subsequent reactions such as C—N cleavage in hydrolysis occur.

$R^1C_6H_4CH{=}NC_6H_4R^2$

Compd	R¹	R²	Compd	R¹	R²
1	*p*-NO$_2$	*m*-NO$_2$	**7**	H	*m*-NO$_2$
2	*p*-NO$_2$	*m*-Cl	**8**	H	*m*-Cl
3	*p*-NO$_2$	*p*-Cl	**9**	H	*p*-Cl
4	*p*-NO$_2$	H	**10**	H	H
5	*p*-NO$_2$	*p*-Me	**11**	*p*-Cl	H
6	*p*-NO$_2$	*p*-OMe			

Results

Base-Catalyzed Addition of Methanol. The stoichiometry of equilibrium addition of methanol to benzylideneanilines was confirmed by the decrease in extinction at 340 nm in the uv spectrum and appearance of the CH proton at *ca.* τ 4.5 with a decrease in the CH= proton at τ 1.7 in the nmr spectrum. The addition in neutral methanol solution requires several days to reach an equilibrium, while in the presence of a basic catalyst it is much more rapid. Addition of acetonitrile to the basic equilibrium solution causes the extinction at 340 nm to increase until a new equilibrium position is established, because of the decrease in methanol concentration. Moreover, the value of equilibrium constant, K_0, evaluated in terms of a following stoichiometry from the decrease in extinction of a Schiff base, is consistent with that evaluated from the relative strengths of the CH proton signal *vs.* the -CH= proton signal in the nmr spectrum of the solution. Hence

$$R^1C_6H_4CH{=}NC_6H_4R^2 + MeOH \overset{K_0}{\rightleftharpoons} R^1C_6H_4CH(OMe){-}NHC_6H_4R^2$$

Although rapid solvolysis of Schiff bases occurs in acidic methanol to afford the corresponding benzaldehyde dimethyl acetals and anilines, no solvolysis occurs in alkaline methanol.

Effect of Substituent in Benzylideneanilines. The equilibrium and rate constants for addition of methanol to benzylideneanilines are shown in Table I. *N*-Benzylideneanilines with a single electron-releasing group such as methyl or methoxy have very small equilibrium constants showing only poor addition of the alcohol ($K_0 \leq 10^{-3}\ M^{-1}$ based on ≤1% conversion of Schiff base).

The equilibrium constants show a good correlation with the Brown–Okamoto's σ^+ constant,[10] giving a ρ^+ value of 1.42 (r = 0.993) at 15°, 1.41 (r = 0.994) at 25°, and 1.43 (r = 0.995) at 30° for *N*-(*p*-nitrobenzylidene)(substituted anilines), 1.58 for *N*-benzylidene(substituted anilines), and

Table I
Equilibrium and Rate Constants for the Addition of Methanol to Benzylideneanilines at 25° in Methanol–Acetonitrile (90:10 v/v)[a]

Compound	Registry no.	Substituent		10^3K_0, M^{-1}	$10^5k_f^{\mathrm{MeOH}}$,[b] M^{-1} sec^{-1}	k_f^{MeOH},[c] M^{-1} sec^{-1}
		R¹	R²			
1	10480-07-6	*p*-NO₂	*m*-NO₂	65 ± 1	176 ± 6	6.6
2	10480-21-4	*p*-NO₂	*m*-Cl	31.5 ± 0.5	23.5 ± 0.5	0.88
3	14796-61-3	*p*-NO₂	*p*-Cl	16.4 ± 0.1	9.5 ± 0.1	0.36
4	785-80-8	*p*-NO₂	H	7.1 ± 0.1	1.6 ± 0.2	0.06
5	730-39-2	*p*-NO₂	*p*-Me	3.6 ± 0.2	1.03 ± 0.04	0.04
6	5455-87-8	*p*-NO₂	*p*-OMe	0.6 ± 0.2	~0.04	~0.015
7	5341-44-6	H	*m*-NO₂	23 ± 1	7.5 ± 0.3	0.28
8	7519-65-5	H	*m*-Cl	8.6 ± 0.2	1.35 ± 0.10	0.051
9	780-21-2	H	*p*-Cl	3.5 ± 0.1	0.54 ± 0.06	0.020
10	538-51-2	H	H	1.5 ± 0.05	0.39 ± 0.07	0.015
11	2362-79-0	*p*-Cl	H	2.6 ± 0.2	0.28 ± 0.02	0.011
2		*p*-NO₂	*m*-Cl	32[d]	39[d]	

[a] [KOH] = 0.006 *M*. [b] Apparent second-order rate constants calculated from the concentration of MeOH. [c] Second-order rate constants calculated from experiments at a single KOH concentration. [d] In MeOD–MeCN (90:10 v/v). Solvent deuterium isotope effect is 0.98 for $K_0^{\mathrm{MeOH}}/K_0^{\mathrm{MeOD}}$ and 0.60 for $k_f^{\mathrm{MeOH}}/k_f^{\mathrm{MeOD}}$.

Table II
Base Catalysis for the Addition of Methanol to *N*-(*p*-Nitrobenzylidene)-*m*-chloroaniline (2) at 25° in Methanol–Acetonitrile (90:10 v/v)

KOH, *M*	10^2K_0, M^{-1}	$10^5k_f^{\mathrm{MeOH}}$,[a] M^{-1} sec^{-1}
0.0006	3.15	1.60
0.0012	3.2	3.54
0.0030	3.2	10.5
0.0048	3.2	17.3
0.0060	3.2	23.1

[a] Apparent second-order rate constant based on the concentration of MeOH.

Table III
Equilibrium and Rate Constants for the Addition of Alcohols to *N*-(*p*-Nitrobenzylidene)-*m*-chloroaniline (2) at 25° in ROH–MeCN (90:10)[a]

R in ROH	Registry no.	10^2K_0, M^{-1}	10^5k_f, M^{-1} sec^{-1}
Me	67-56-1	3.2 ± 0.05	23 ± 0.1
Et	64-17-5	2.4 ± 0.1	58 ± 0.1
n-Bu	71-36-3	3.7 ± 0.1	140 ± 8
i-Pr	67-63-0	11 ± 1	1.9 ± 0.1
sec-Bu	78-92-2	7.6 ± 0.2	5.0 ± 0.4
t-Bu	75-65-0	22 ± 1	4.8 ± 1.5

[a] [KOH] = 0.0006 *M*.

0.86 for *N*-(substituted benzylidene)anilines at 25°. An electron-withdrawing group both in the aniline and benzylidene rings increases the equilibrium constants, and the polar effect of the substituent in the aniline ring is a little larger than in the benzylidene ring. On the other hand, the forward rate constants are correlated with σ, giving a ρ value of 2.66 (r = 0.995) at 15°, 2.65 (r = 0.994) at 25°, and 2.80 (r = 0.999) at 30° for *N*-(*p*-nitrobenzylidene)(substituted anilines) and 1.7 for *N*-benzylidene(substituted anilines). An electron-withdrawing group (p-NO$_2$ and p-Cl) in the benzylidene ring also increases the rate constant.

Base Catalysis. The apparent second-order rate constant based on the concentration of methanol is proportional to the concentration of added potassium hydroxide. As methanolic KOH contains a much larger amount of the methoxide ions than the hydroxide ions,[7] the rate equation is $v_f = k_f^{\mathrm{MeO^-}}[\mathrm{C{=}N}][\mathrm{MeO^-}]$, where C=N is benzylideneaniline. The value of $k_f^{\mathrm{MeO^-}}$ for *N*-(*p*-nitrobenzylidene)-*m*-chloroaniline was calculated to be 0.88 M^{-1} sec^{-1} at 25° from the plotted data in Table II.

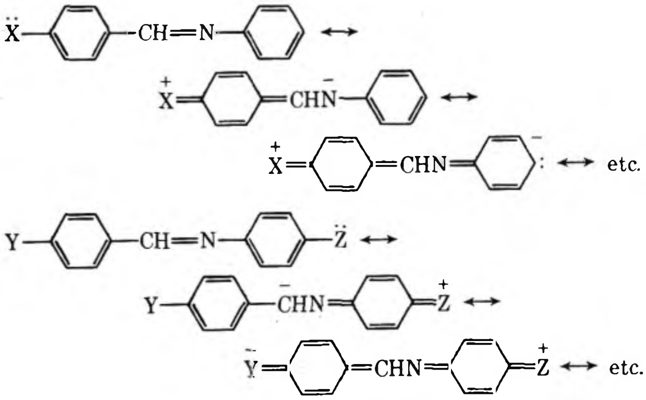
Solvent Isotope Effect. Table I shows that the solvent deuterium isotope effects on the equilibrium constant $K_0^{\mathrm{MeOH}}/K_0^{\mathrm{MeOD}}$ and rate constant $k_f^{\mathrm{MeOH}}/k_f^{\mathrm{MeOD}}$ for the base-catalyzed addition of methanol to *N*-(*p*-nitrobenzylidene)-*m*-chloroaniline (2) are 0.98 and 0.60, respectively.

Effect of Structure of Alcohols. The equilibrium and rate constants with some alcohols are presented in Table III. Application of the Taft equation to the equilibrium constants gave a ρ^* value of −8.2 and a δ value of 0.48 in the Taft equation,[11] $\log (K_0^{\mathrm{X}}/K_0^{\mathrm{ME}}) = \rho^*\sigma^* + \delta E_s$, where σ^* and E_s are polar and steric substituent constants, and ρ^* and δ are polar and steric reaction constants, respectively. The polar effect on the equilibrium constant is larger than the steric effect. Methanol showed a positive deviation from the line. On the other hand, application of the Taft equation to the rate constant is less satisfactory in the case where the steric effect is larger than the polar effect. Thus, the rate constants for primary alcohols are larger than those for secondary and tertiary alcohols.

Effect of Temperature. Thermodynamic properties were calculated from the data at 15, 25, and 30° in methanol-acetonitrile (90:10 v/v) and are shown in Table IV.

Discussion

These reactions are base-catalyzed equilibrium additions. A few examples of such base-catalyzed additions to carbon–nitrogen double bonds have been reported, *e.g.*, the addition of diethyl phosphonate to benzylideneanilines,[12] dehydration of carbinolamine intermediates (the reverse of the addition of water)[13,14] and hydrolysis of some benzylideneanilines with strong electron-withdrawing groups.[2] The observed correlation of the equilibrium constant with σ^+ suggests that the following resonance



X = Z = OMe; Y = NO₂

Table IV
Temperature Effect for the Addition of Methanol to *N*-(*p*-Nitrobenzylidene)-(substituted anilines) in Methanol–Acetonitrile (90:10 v/v)[a]

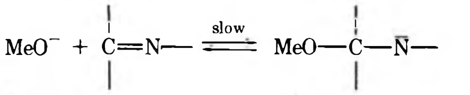
Compd	Substituent R^2	$\Delta F°$, kcal mol^{-1}	$\Delta H°$, kcal mol^{-1}	$\Delta S°$, eu	ΔF^*, kcal mol^{-1}	ΔH^*, kcal mol^{-1}	ΔS^*, eu
1	*m*-NO_2	1.6	1.5 ± 0.3	0 ± 0.8	21.0	8.3 ± 0.5	−44 ± 2
2	*m*-Cl	1.8	3.0 ± 0.3	4.2 ± 0.8	22.1	7.3 ± 0.4	−51 ± 1
3	*p*-Cl	2.2	2.8 ± 0.3	2.1 ± 0.9	22.6	7.8 ± 0.9	−51 ± 3
4	H	2.7	2.7 ± 0.3	0 ± 0.8	23.6	6.9 ± 2.1	−58 ± 7
5	*p*-Me	3.1	2.1 ± 0.9	−3.4 ± 3.1			
6	*p*-OMe	4.2	2.3 ± 3.1	−6.6			

[a] [KOH] = 0.0006 *M*.

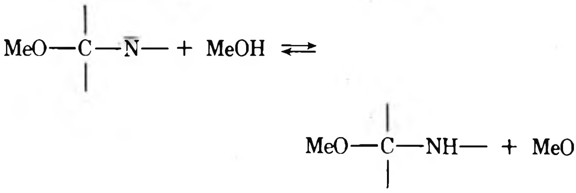
stabilization of benzylideneanilines by both R^1 and R^2 is important to make the equilibrium constant smaller, although benzylideneanilines have been reported to have nonplanar conformations,[15,16] composed of the planar benzylideneamino and anilino parts. Correlation with σ^+ for equilibria for the substituent attached to the benzylidene part is well known,[4,5] but such a correlation with σ^+ for the substituent attached to the anilino part (R^2) is unknown. The former resonance between X and C=N is similar to that in carbonyl compounds, and the latter between Z and N=C resembles that in stilbenes and azobenzenes[17] but not in carbonyl compounds.

The deuterium solvent isotope effect on equilibrium constant, $K_0^{\mathrm{MeOH}}/K_0^{\mathrm{MeOD}} = 0.98$, can be explained by virtually no change in zero-point energies between the O–H and the N–H vibrations,[18] since $\nu_{\mathrm{OH}} = \nu_{\mathrm{NH}} = 3400$ cm^{-1} in methanol and α-methoxybenzylanilines can be assumed.

The observed base catalysis and the positive ρ value can exclude the possibility of the participation of the conjugate acid of the Schiff base. Hence a probable mechanism is



$$\mathrm{MeO^-} + \overset{|}{\underset{|}{\mathrm{C}}}{=}\mathrm{N}{-} \xrightleftharpoons{\text{slow}} \mathrm{MeO}{-}\overset{|}{\underset{|}{\mathrm{C}}}{-}\overline{\mathrm{N}}{-} \qquad (1)$$



$$\mathrm{MeO}{-}\overset{|}{\underset{|}{\mathrm{C}}}{-}\overline{\mathrm{N}}{-} + \mathrm{MeOH} \rightleftharpoons \mathrm{MeO}{-}\overset{|}{\underset{|}{\mathrm{C}}}{-}\mathrm{NH}{-} + \mathrm{MeO^-} \qquad (2)$$

A noncatalyzed mechanism involving preequilibrium formation of methoxide ion and protonated Schiff base from methanol and Schiff base, followed by a slow reaction between these ions, is less plausible because the reaction should be independent of base. Also, the reaction involving such a preequilibrium, followed by a reaction between free Schiff bases and methoxide ion, would require second-order kinetics in Schiff bases, which is not the case.

The value of 0.60 for $k_f^{\mathrm{MeOH}}/k_f^{\mathrm{MeOD}}$ is close to the value of 0.71 for $k^{\mathrm{H_2O}}/k^{\mathrm{D_2O}}$ reported for an attack of hydroxide ions on the Schiff base,[19] which supports the above mechanism. Since potassium hydroxide (a strong base) is used, the concentration of the methoxide ions in methanol is the same as that in methanol-d_1 and hence the value of 0.60 corresponds to the effect of solvent on the methoxide ion attack, that is, desolvation of the methoxide ions may be easier in methanol-d_1 than in methanol, which is a stronger acid than methanol-d_1.[20] It is known that the rate of specific base catalysis is lower in protiated solvent than in deuterated solvent.[21] Hydrogen bonding to the imino nitrogen in the transition state, if any, would be unimportant because it would lead to an isotope effect over unity.

The correlation of rates by σ in contrast to the correlation of equilibria by σ^+ may be explained by the transition state structure of

$$(\mathrm{MeO}^{\delta-}\text{- - - - -}\mathrm{C}{=\!=}\mathrm{N}^{\delta-})$$

Since partial negative charge may appear at the carbon and nitrogen atoms, the electron-releasing resonance by a substituent is not so important for the transition state stability.

The entropy of reaction ($\Delta S° \sim 0$) and the enthalpy of reaction ($\Delta H° \sim 3$) are small. Although it is difficult to explain the changes of entropy and enthalpy of reaction with varying substituent, electron-withdrawing groups tend to increase the enthalpy and entropy of reaction at any rate. On the other hand, the rate is controlled by entropy of activation rather than enthalpy of activation. This trend is the reverse of that for the hydrolysis rate of aromatic amides[22] and anhydrides.[23] The solvation of the transition state may be stronger with an electron-releasing substituent and cause a decrease in the degree of freedom in the transition state.

The equilibrium constant is influenced by polar substituents in alcohols ($\rho^* = -8.2$, $\delta = 0.48$), while the rate constant decreases in the order *n*-$\mathrm{BuO^-}$ > $\mathrm{EtO^-}$ > $\mathrm{MeO^-}$ > *sec*-$\mathrm{BuO^-}$ > *t*-$\mathrm{BuO^-}$ > *i*-$\mathrm{PrO^-}$. No parallelism between equilibrium and rate constants was observed. This order would result from overlapping of steric, polar, and solvent effects. The failure of the Taft relationship for the rates may be ascribed in part to the rate measurement in each alcohol itself, *i.e.*, in a different solvent, because of low conversion in equilibrium in other solvents. For the addition of nucleophiles to the carbonyl compounds, where the steric effect is larger, γ value or a measure of the affinity of nucleophiles for carbon[1] decreases in the order MeOH > EtOH > *i*-PrOH > *t*-BuOH. In contrast, the following reactivity order has been observed for an attack of alkoxide ions on acrylonitrile or butenone, where the polar effect is larger: $\mathrm{MeO^-}$ > $\mathrm{EtO^-}$ > $\mathrm{PrO^-}$ > *i*-$\mathrm{PrO^-}$.[24,25]

Experimental Section

Uv spectra were recorded on a Hitachi spectrophotometer Model 124 and nmr spectra on a JEOL spectrometer Model C-60 HL.

Materials. Substituted benzylideneanilines **1-11** were prepared as reported previously[6,7] and stored as an acetonitrile solution. Alcohols and acetonitrile were purified according to the literature.[26]

Nmr Spectra of the Solution. The nmr spectrum of *N*-benzylidene-*m*-chloroaniline in *tert*-butyl alcohol shows signals of α-*tert*-butoxybenzyl)-*m*-chloroaniline at τ 4.62 (CH) and at 3.3–3.6 (aromatic H) together with signals of *N*-benzylidene-*m*-chloroaniline at τ 1.70 (–CH=). Signals assigned to the NH proton of the adduct are obscure because of the overlap with strong signals of the OH protons. Also the nmr spectrum of *N*-benzylidene-*m*-nitroaniline in methanol shows signals of the CH protons at τ 4.33 together with those of the –CH= protons at τ 1.43. From relative strengths of these two signals the equilibrium constant for *N*-benzylidene-*m*-nitroaniline is calculated to be 0.028 M^{-1} which is close to 0.023 M^{-1} at 25° obtained by uv spectrophotometry. These facts indicate the stoichiometry of the reaction described above.

Rate and Equilibrium Measurements. The reaction was carried out in methanol-acetonitrile (90:10 v/v) and followed in a cell compartment of a spectrophotometer. The reaction was started when methanolic potassium hydroxide (0.1 ml) was added to a thermostated solution of benzylideneanilines (2.9 ml) and the extinction (E) at an appropriate wavelength (320-340 nm) was followed. Because of the excess methanol the equilibrium constant (K_0) was calculated by the following equation

$$K_0 = \frac{E_0 - E_\infty}{E_\infty[\mathrm{MeOH}]}$$

where subscripts 0 and ∞ refer to time 0 and equilibrium state, respectively.

Plot of log ($E_t - E$) *vs.* time t gave a good straight line from which pseudo-first-order rate constant for a reversible reaction, k_{obsd}, was obtained. Using the values of [MeOH], K_0, and k_{obsd}, apparent forward second-order rate constant, k_f^{MeOH}, was calculated by means of the equations

$$k_{\mathrm{obsd}} = \frac{2.303}{t} \log \frac{E_0 - E_\infty}{E_t - E_\infty}$$

and

$$k_f^{\mathrm{MeOH}} = \frac{k_{\mathrm{obsd}} K_0}{[\mathrm{MeOH}]K_0 + 1}$$

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Steroidal Nitrones

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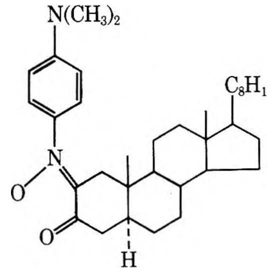
Steroidal 6- and 20-aldonitrones were prepared. 3-Ketonitrones were also prepared, and, in the case of Δ^4-3-ketonitrones, stereoisomers were separated and configurations assigned on the basis of uv and nmr spectroscopy.

Bambury, *et al.*, have published several reports on heterocyclic containing nitrones having antimicrobial activity.[1] Nitrone groups increase water solubility and the ability of a molecule to penetrate cell membranes.[2] For these reasons, we extended our work to the steroid field, and report here some of our findings on the preparation of 6-aldonitrones, 20-aldonitrones, and 3-ketonitrones.

Several steroidal nitrones are reported as intermediates in the Kröhnke reaction.[3] For example, the ketonitrones **1**[4] and **2**[5] were prepared and converted to the corresponding α-diketones. Similarly, the 21-aldonitrones **3**,[6] **4**,[6] and **5**[7] were prepared and converted to the 21-aldehydes. Other examples of steroid-like nitrones in which the nitrone is an integral part of the ring system, such as **6**,[8] **7**,[8] and **8**,[9] have also been reported. Subsequent to the completion of this work, Barton and coworkers[10] reported the conversion of 3-ketonitrones **9** *via* a Beckmann-type rearrangement to amides **10**, but no details for preparing **9** were given.



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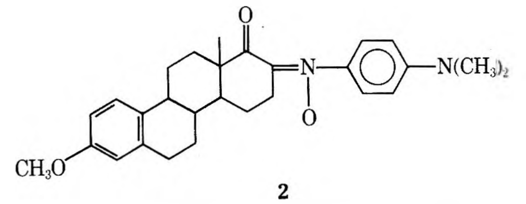

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6-Aldonitrones. Steroidal 6-carboxaldehydes are readily available from Vilsmeier-Haack formylation of the corresponding 3-enol ethers **11** according to Burn, *et al.*[11] Experimentation showed that nitrone formation was best accomplished by heating a mixture of **12**, *N*-alkylhydroxylamine salt, and sodium bicarbonate in aqueous methanol containing pyridine. The resulting nitrones **13** are crystal-

Table I
Aldonitrones and Ketonitrones

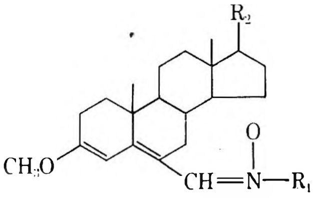
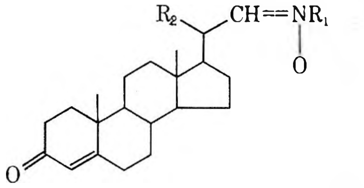
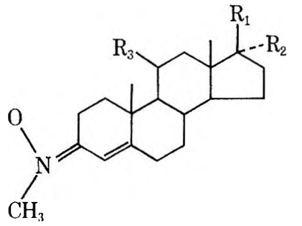
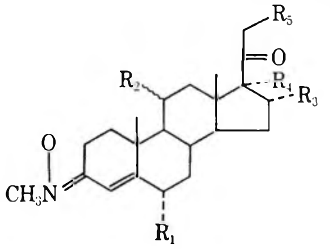
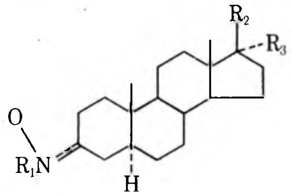
Compd	R_1	R_2	R_3	R_4	R_5	Misc	Mp, °C	Yield, %	Isomer	Formula[f]
										
14	CH_2CH_2OH	OH H					231–232 dec	67.6		$C_{23}H_{35}NO_4$
15	CH_3	OH H					244.5	68.0		$C_{22}H_{33}NO_3$[h]
16	CH_2CH_2OH	$COCH_3$ H					124–127	30.4		$C_{25}H_{37}NO_4 \cdot H_2O$
17	CH_3	$COCH_3$ H					247–249	55.8		$C_{24}H_{35}NO_3 \cdot {}^1/_4H_2O$
18	CH_2CH_2OH	O[a]					248–249	7.5		$C_{23}H_{31}NO_5 \cdot {}^1/_4H_2O$
19	CH_3	O[a]					242–244 dec	13.7		$C_{22}H_{29}NO_4$[g]
										
22	CH_2CH_2OH	CH_3					189–191	66.9		$C_{24}H_{37}NO_3$
23	CH_3	CH_3					178–180	35.6		$C_{23}H_{35}NO_2 \cdot {}^1/_2H_2O$
24	$CH(CH_2OH)$- CH_2CH_3	CH_3					173–176	64.2		$C_{26}H_{41}NO_3$
25	CH_2CH_2OH	CH_3[b]					217–218	4.5		$C_{24}H_{35}NO_3 \cdot {}^1/_4H_2O$
26	CH_2CH_2OH	CH_3[b]					187, 210	10.4		
27	CH_3	CH_3[b]					182.5–185	19.3		$C_{23}H_{33}NO_2$[i]
28	CH_3	CH_3[c]					197–199 dec	22.0		$C_{24}H_{38}N_2O_2 \cdot H_2O$
29	CH_2CH_2OH	H[b,d]					214–215 dec	70.2		$C_{23}H_{31}NO_4$[j]
30	CH_3	H[b,d]					229–230 dec	68.4		$C_{22}H_{29}NO_3$
										
37	OH	H	H			${}^1/_4H_2O$	234–235 dec	18.5[e]	Syn	$C_{20}H_{31}NO_2 \cdot {}^1/_4H_2O$
38	OH	H	H			${}^1/_4H_2O$	170–171 dec	3.3	Anti	$C_{20}H_{31}NO_2 \cdot {}^1/_4H_2O$
39	OH	H	H			${}^1/_4H_2O$ NCH_2CH_2OH	180–182.5	42.2	Anti/syn 50:50	$C_{21}H_{33}NO_3 \cdot {}^1/_4H_2O$
40	OH	CH_3	H			${}^1/_4H_2O$	184–186	23.8	Syn	$C_{21}H_{33}NO_2 \cdot {}^1/_4H_2O$
41	OH	CH_3	H			${}^1/_2H_2O$	187–189	6.0	Anti	$C_{21}H_{33}NO_2 \cdot {}^1/_2H_2O$
42	OH	$C{\equiv}CH$	H				234–235 dec	26.3	Syn	$C_{22}H_{31}NO_2$
43	OAc	H	H			Δ^6	189–190 dec	23.8	Syn	$C_{22}H_{31}NO_3$
	OAc	H	H			Δ^6	187–188 dec		Anti	
44	OH	H	H			19-nor	217–218 dec	60.5	Syn	$C_{19}H_{29}NO_2$
45	O		H				202–203 dec	12.4	Syn	$C_{20}H_{29}NO_2$
										
46	H	H	H	H	H		152–154			$C_{22}H_{33}NO_2$
47	H	H	H	H	H		185–186 dec		Anti	$C_{22}H_{33}NO_2$
48	H	α-OAc	H	H	H		210–212 dec		Syn	$C_{24}H_{35}NO_4$
	H	α-OH	H	H	H		231–232 dec		Syn	$C_{22}H_{33}NO_3$[g]
49	H	H	H	OH	H		245–247 dec	67.2	Anti/syn 20:80 Anti	$C_{22}H_{33}NO_3$[g]

Table I (*Continued*)

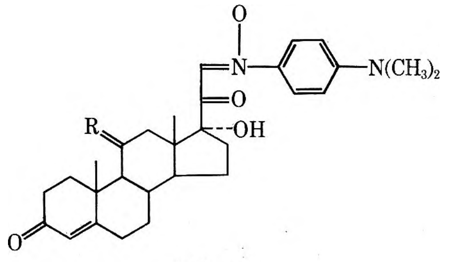
Compd	R_1	R_2	R_3	R_4	R_5	Misc	Mp, °C	Yield, %	Isomer	Formula[f]
50	H	H	H	OAc	H		197–198	31.8	Syn	$C_{24}H_{35}NO_4$
	H	H	H	OAc	H		195–197 dec	10.0	Anti	$C_{24}H_{35}NO_4$
51	H	H	H	H	OAc		162–165	8.0	Syn	$C_{24}H_{35}NO_4$
52	H	β-OH	H	OH	OH	$^1/_4H_2O$	259–260 dec	45.8	Anti/syn 50:50	$C_{22}H_{33}NO_5 \cdot {}^1/_4H_2O$
53	H	β-OH	H	OH	OH	NCH_2CH_2OH	220 dec	20.0	Syn	$C_{23}H_{35}NO_6$
54	CH_3	H	CH_3	H	H		185–187	24.4	Syn	$C_{24}H_{37}NO_2$
55	α-CH_3	H	H	OAc	H		209–212 dec		Syn	$C_{25}H_{37}NO_4$
56	α-CH_3	H	H	OAc	H		168–170 dec		Anti	$C_{25}H_{37}NO_4$
57	CH_3	H	H	OAc	H	Δ^6	203 dec	32.2	Syn	$C_{25}H_{35}NO_4$
	CH_3	H	H	OAc	H	Δ^6	197–201	12.1	Anti	$C_{25}H_{35}NO_4$



58	CH_3	O					150–152	65.0		$C_{20}H_{31}NO_2 \cdot {}^1/_2H_2O^k$
59	CH_3	OH	H				196–198	43.3		$C_{20}H_{33}NO_2 \cdot {}^1/_2H_2O$
60	CH_2CH_2OH	OH	H				195–197	73.7		$C_{21}H_{35}NO_3 \cdot H_2O$
61	CH_3	OH	CH_3				210–213	39.1		$C_{21}H_{35}NO_2$
62	CH_2CH_2OH	OH	CH_3				115–117	44.8		$C_{22}H_{37}NO_3 \cdot 1{}^1/_2H_2O^{g,l}$

[a] 11-Oxo. [b] 17(20)-Ene. [c] 3-*N*-Methylnitrone. [d] 1-En-11β-ol. [e] Yield raised to 74.2% (0.1 *M* scale) in another run. [f] C, H, and N analyses were within 0.3% of calculated values. [g] C analysis was within 0.4% of calculated value. [h] Calcd: C, 73.50. Found: C, 72.97. [i] Calcd: C, 77.70. Found: C, 77.26. [j] Calcd: C, 71.66. Found: C, 71.22. [k] Calcd: C, 73.59. Found: C, 73.14. [l] Calcd: H, 10.33. Found: H, 9.96.

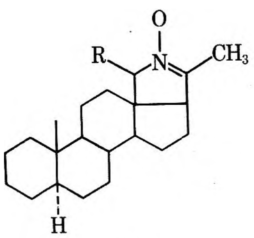
line solids with ultraviolet maxima at 238–240 (ε 9000–9600) and 333–334 nm (ε 14,700–17,600) and nuclear magnetic resonance (nmr) signals for the imino proton at δ 7.1–8.2. This compares with ultraviolet maxima at 219–221 (ε 10,000–12,000) and 319–323 nm (ε 14,000–16,000) and nmr signals for the aldehyde proton at δ 10.2 for the parent aldehydes. It is interesting that the 17β-acetoxy group was hydrolyzed under these conditions using a hydrochloride salt of the hydroxylamine. Table I lists the compounds prepared in this series.



3, R = O

4, R = OH, H

5, R = H_2



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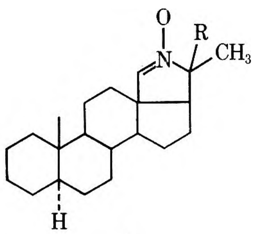

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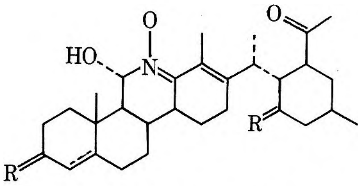
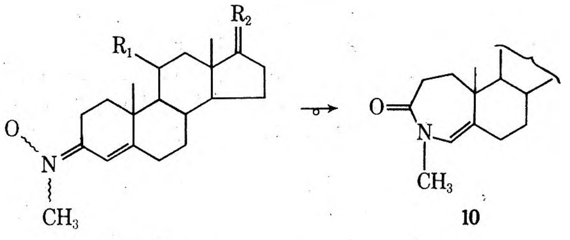
R = H, OH

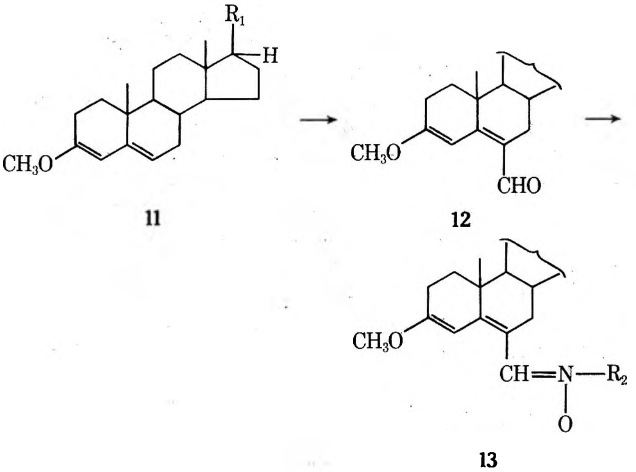


8a, R = O Δ^4

b, R = AcO, H 5α



9 **10**

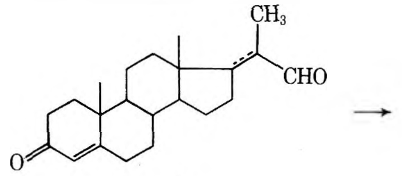


11 **12** **13**

Table II

N-Oxide	Assigned structure	Uv max	Nmr, ppm: Proton adjacent oxide oxygen	Nmr, ppm: Proton away from oxide oxygen
Nonsteroids	Anti	211, 228, 304 (higher)		2.38
	Syn	205, 221.5, 228	2.16 (higher field)	
Δ^4 steroids	Anti	242–243, 293–296 (higher)		6.65–6.85
	Syn	288–292	6.00–6.38 (higher field)	

20-Aldonitrones. Several steroidal 20-carboxaldehydes are commercially available or available by a simple one-step oxidation. These aldehydes **20** were readily converted to the corresponding nitrones **21** by the methods described above. The nitrones are crystalline compounds readily purified by silica gel column chromatography.



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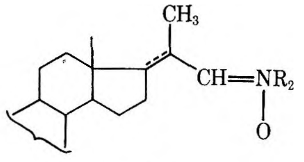

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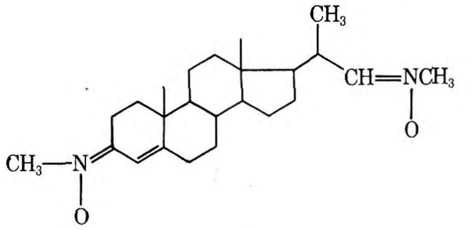

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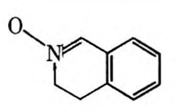
Reaction of 3-oxopregn-4-ene-20-carboxaldehyde with an excess of *N*-methylhydroxylamine hydrochloride gave, in addition to the expected aldonitrone **23**, a second compound which had no carbonyl absorption bands in its infrared spectrum and had two NCH_3 signals in its nmr at 3.70 and 3.72 ppm. Elemental analyses corresponded to $C_{24}H_{38}N_2O_2 \cdot H_2O$, which confirmed the structure as dinitrone **28**. Table I lists the compounds prepared in this series.

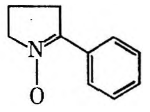
3-Ketonitrones. Reaction of aliphatic ketones with *N*-alkylhydroxylamines is reported to be sluggish and the resultant ketonitrones are hygroscopic, unstable species.[12] For example, the *N*-methyl nitrone of cyclopentanone is reported as very hygroscopic and is instantly hydrolyzed by water and decomposed by ethanol.[13] To the contrary, we have found the 3-ketonitrones to be readily formed, stable, and only slightly hygroscopic. The 3-ketonitrones were generally prepared by refluxing overnight a mixture of steroid, alkylhydroxylamine salt, and sodium bicarbonate in absolute ethanol in the dark. There seems to be some difference in which acid salt is used in the reaction. In the case of *N*-methylhydroxylamine, where both the hydrochloride and oxalate salts were available, the hydrochloride reacted more rapidly, giving a more stereochemically pure product. The reaction proved quite versatile for 3-keto steroids except dihydroprogesterone, which was inexplicably refractory.

Silica gel chromatography of the crude product separated, in several cases, stereoisomeric pairs of nitrones. Isomerism in nitrones has been previously reported,[12] and ultraviolet spectra have been used to determine syn and anti configurations. However, this method of analysis is still tenuous, since there is no confirmatory evidence for generalization.

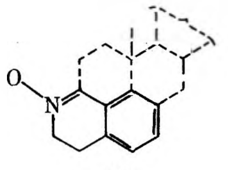
Nitrone **31** with the phenyl group and the oxygen atom fixed in the anti configuration absorbs at 211, 228, and 304 nm, while nitrone **32** absorbing at 205, 221.5, and 288 nm is rigidly held in the syn configuration. In other words, the higher absorbing isomer is anti and the lower absorbing isomer is syn. These two compounds are redrawn in **31a** and **32a**, respectively, with a partial steroid skeleton superimposed in dotted lines to show the relationship of these two compounds to the steroidal nitrones **33** and **34**. In our steroidal pairs, one isomer absorbed at 288–292 nm and the other at 242–243 and 293–296 nm. The 293–296 nm absorbing isomers were tentatively assigned the anti configuration (**33**) and the other isomer the syn configuration (**34**) assuming for the moment that assignments by ultraviolet maxima are valid.



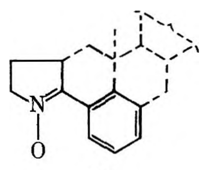
31
anti



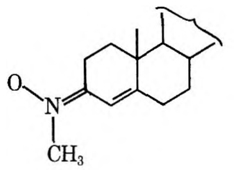
32
syn



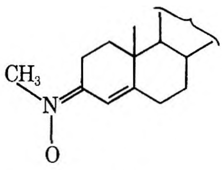
31a



32a

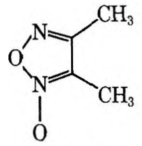


33



34

The proton nmr spectrum of dimethylfurazan oxide (**35**) consists of two peaks at 2.16 and 2.38 ppm, while that of dimethylfurazan consists of a single peak at 2.31 ppm.[14] The highfield peak at 2.16 ppm was associated with the methyl group adjacent to the *N*-oxide oxygen.[15] Similarly, in assigning chemical shifts of the 4 and 7 protons in benzofurazan oxide (**36**) the higher field peak was assigned to the proton adjacent to the *N*-oxide oxygen (7 proton).[16]



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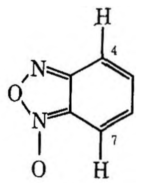

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Thus, one would expect to find that C_4 vinyl proton of **34** at higher field than the corresponding proton of **33**. Also, one would expect the *N*-methyl group in **34** to be somewhat more deshielded than its counterpart in **33** and, therefore, at lower field. This is indeed the case. The steroids assigned to the anti configuration by uv maxima have C_4-proton peaks at 6.65–6.85 ppm, while the other isomer has peaks at 6.00–6.28 ppm. Further, the assigned anti isomers have *N*-methyl peaks at 3.67–3.70 ppm while the other isomer has peaks at 3.71–3.84 ppm. These data, summarized in Table II, confirm the stereochemical sssignments made for the isomers and corroborate the use of uv maxima for distinguishing between conjugated syn and anti nitrone pairs.

Table I lists the androstene, the pregnene nitrones, and the saturated 3-ketonitrones prepared. The latter compounds were homogeneous by tlc analysis and had no outstanding spectral characteristics. Thus, although these nitrones, too, must exist as stereoisomeric pairs, they were not detected. Biological testing of the nitrones found them less active than the parent ketones.

Experimental Section[17]

***N*-(2-Hydroxyethyl)-α-(17β-hydroxy-3-methoxyandrosta-3,5-dien-6-yl)nitrone (14). General Procedure for 6- and 20-Aldonitrones.** A mixture of 17-acetoxy-3-methoxyandrosta-3,5-diene-6-carboxaldehyde (30.1 g, 81 mmol), $NaHCO_3$ (40 g), and *N*-(2-hydroxyethyl)hydroxylamine oxalate (25 g, 0.116 mol) in MeOH (1 l.)–H_2O (50 ml)–pyridine (15 ml) was stirred under reflux in the dark for 22 hr. The hot reaction mixture was filtered and the filtrate was concentrated to a yellow paste. The resulting solid (43 g) was crystallized from aqueous MeOH to give **14** (23.5 g).

17α-Methyl-3-methyliminoandrost-4-en-17β-ol *anti*- and *syn*-*N*-Oxide (40 and 41). General Method for 3-Ketonitrones. A mixture of methyltestosterone (30.6 g, 0.1 mol), $NaHCO_3$ (35 g), and *N*-methylhydroxylamine oxalate (18.9 g, 0.1 mol) in absolute EtOH (75 ml) was stirred overnight in the dark under reflux. The reaction mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel (350 g), collecting 250-ml fractions and eluting with Me_2CO (1 l.), Me_2CO–5% MeOH (1 l.), and Me_2CO–10% MeOH (7 l.). Fractions 11–16 were combined and concentrated and the residue was crystallized from acetone–ether–hexane to give **40** (8.0 g). Fractions 28–33 were combined and concentrated and the residue was triturated with ether to give **41** (2.0 g).

Acknowledgment. The authors wish to thank Dr. Vladimir Petrow for suggesting this problem and to his helpful discussions throughout the course of this work.

Registry No.—**12** (R_2 = OH), 50276-51-2; **12** (R_2 = OAc), 5490-78-8; **14**, 50324-69-1; **15**, 50324-70-4; **16**, 50324-71-5; **17**, 50324-72-6; **18**, 50324-73-7; **19**, 50324-74-8; **19** 6-carboxaldehyde derivative, 50323-68-7; **20** (R_2 = CH_3), 24254-01-1; **22**, 50324-77-1; **23**, 50324-78-2; **24**, 50324-79-3; **25**, 50324-80-6; **25** 20-carboxaldehyde derivative, 50323-70-1; **27**, 50324-81-7; **28**, 50324-82-8; **29**, 50324-83-9; **29** 20-oxo derivative, 50324-76-0; **30**, 50324-84-0; **37**, 50324-85-1; **37** 3-oxo derivative, 58-22-0; **38**, 50324-87-3; *syn*-**39**, 50324-88-4; *anti*-**39**, 50324-89-5; **40**, 50324-90-8; **40** 3-oxo derivative, 58-18-4; **41**, 50324-92-0; **42**, 50324-93-1; **42** 3-oxo derivative, 434-03-7; *syn*-**43**, 50324-95-3; *anti*-**43**, 50324-96-4; **43** 3-oxo derivative, 2352-19-4; **44**, 50324-98-6; **44** 3-oxo derivative, 434-22-0; **45**, 50325-00-3; **45** 3-oxo derivative, 63-05-8; *syn*-**46**, 50325-01-4; **46** 3-oxo derivative, 57-83-0; **47**, 50325-02-5; **48** (R_2 = α-OAc), 50325-03-6; **48** (R_2 = α-OAc) 3-oxo derivative, 2268-98-6; **48** (R_2 = α-OH), 50325-05-8; **48** (R_2 = α-OH) 3-oxo derivative, 80-75-1; *syn*-**49**, 50276-50-1; *anti*-**49**, 50325-07-0; **49** 3-oxo derivative, 68-96-2; *syn*-**50**, 50276-49-8; *anti*-**50**, 50324-68-0; **50** 3-oxo derivative, 302-23-8; **51**, 50325-08-1; **51** 3-oxo derivative, 56-47-3; *syn*-**52**, 50325-10-5; *anti*-**52**, 50325-12-7; **52** 3-oxo derivative, 50-23-7; **53**, 50325-14-9; **54**, 50323-53-0; **54** 3-oxo derivative, 1816-78-0; **55**, 50323-55-2; **55** 3-oxo derivative, 71-58-9; **56**, 50323-57-4; *syn*-**57**, 50323-58-5; *anti*-**57**, 50278-60-9; **57** 3-oxo derivative, 595-33-5; **58**, 50323-60-9; **58** 3-oxo derivative, 846-46-8; **59**, 50323-62-1; **59** 3-oxo derivative, 521-18-6; **60**, 50323-64-3; **61**, 50323-65-4; **61** 3-oxo derivative, 521-11-9; **62**, 50323-67-6; *N*-(2-hydroxyethyl)hydroxylamine oxalate, 50323-86-9; *N*-methylhydroxylamine oxalate, 7665-00-1; *N*-methylhydroxylamine hydrochloride, 593-56-6; *N*-(2-hydroxyethyl)hydroxylamine hydrochloride, 24395-54-8.

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[17] All melting points were determined in open capillary tubes on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 521 grating spectrophotometer using KBr pellets. Ultraviolet spectra were recorded on a Perkin-Elmer 350 spectrophotometer in ethanol. Nmr spectra were run on a Varian A-60A with Me_4Si as an internal standard. The standard drying agent used was $MgSO_4$ and the solvents were removed under vacuum on a rotary evaporator.

Steroidal Alkaloids. CLXI.[1] Stereospecific Synthesis of (22*R*)- and (22*S*)-22-Aminocholesterol

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The stereospecific syntheses of the two epimeric 22-aminocholesterols from the two known epimeric 22-hydroxycholesterols *via* tosylate → azide → amine are described. These amines are also obtained by the reduction of 22-ketocholesterol oxime.

Recent reviews,[2,3] describing the biogenesis of pregnenolone from cholesterol, feature the importance of a C-22 hydroxylated species. Therefore it seemed interesting to synthesize 22-substituted derivatives of cholesterol in

Table I

	Change, %			
	Nonsaponfiable lipids		Cholesterol	
Concn of **3**, *M*	Acetate	Mevalonate	Acetate	Mevalonate
1×10^{-4}	−3	+19	−99	−95
1×10^{-5}	+4	+10	−77	−66
1×10^{-6}	+7	+2	−20	−10

order to study their activity on the biogenesis of cholesterol.

As starting material we used the known 22-ketocholesterol (**1**) prepared according to a published procedure[4] from methyl 3β-acetoxy-23,24-bisnorchol-5-enate. The benzoate of **1** was reduced with sodium borohydride and the mixture of the two isomeric alcohols **5** (22*R*) and **7** (22*S*) was separated[5] by fractional crystallizations and transformed into their tosylates. The 22*S*-tosylate **8** was displaced with sodium azide in hexamethylphosphoric triamide at room temperature, giving a quantitative yield of the azide **12** (22*R*) with inversion of configuration. Under these conditions, no elimination products could be observed. However, when the 22*R*-tosylate **6** was treated in identical fashion, the 22*S*-azide **9a** (85%), together with a small amount of elimination product **9b**[6,7] (15%), was obtained. The reduction of these azides **9a** and **12** with lithium aluminum hydride in ether under reflux yielded the desired 22*S*-(**10**) and 22*R*-amines (**13**).

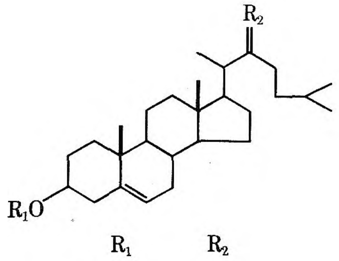
It has already been pointed out by Barton, *et al.*,[8] that the C-22 oxygenated sterols of the 22*S* configurations are more levorotatory than their analogs of the 22*R* configuration. We have observed similar properties for 22*R*- and 22*S*-sterols bearing a nitrogen substitution at C-22. Having established the absolute configuration of the 22-aminocholesterols, we were interested in the determination of the stereoselectivity of the reduction of 22-ketocholesterol (**1**) and of 22-ketocholesterol oxime (**3**) by lithium in ethylamine. At this point it should be reiterated that a number of authors[9-11] have claimed that the 22-oxo group of 22-oxocholesterol is particularly hindered and unable to react with the common carbonyl reagents. We have now obtained the crystalline oxime **3** and the hydrazone **4** of 22-oxocholesterol (**1**). The reduction of the oxime **3** with lithium–ethylamine led to a mixture of the epimeric amines 22*R* (**13**) and 22*S* (**10**) in a ratio of 3:2, respectively. The stereospecific synthesis described above allows the unambiguous assignment of configuration to the reduction products of the oxime. The alcohol amines **10** and **13** were selectively benzoylated at the amino function to give the amides **15** and **16**, respectively. The nmr spectra of the (22*R*)- and (22*S*)-*N*-benzoates reveal a difference in their 21-methyl resonance. The doublet assigned to the 21-methyl, which is only partially visible, is shifted downfield for the (22*S*)-benzamide to 63 Hz, while the 22*R* product gives a value of 59 Hz. The reduction of 22-ketocholesterol (**1**) with lithium in ethylamine gives a mixture of epimeric alcohols 22*R* and 22*S* in a ratio of 3:2[12] (separable on silver nitrate treated silica thin layer plates).

The mass spectra of C-22 nitrogen-substituted compounds were studied. It is known[13] that the basic nitrogen of amines readily retains the positive charge and induces fragmentation of the C–C bond at the α position to the nitrogen. Thus a base peak of *m/e* 100 is obtained from the spectra of the 22-aminocholesterols. However, the hydrazone **4** does not fragment in this fashion, but undergoes two McLafferty rearrangements. The first rearrangement leads to the ion *m/e* 358, which undergoes a second rearrangement to give the base peak of *m/e* 86. The same holds for the oxime **3**, exhibiting the analog peaks of *m/e* 359 and 87, respectively.

Assays[14] for inhibition of cholesterogenesis reveal the oxime **3**[15] to be an active inhibitor at 1×10^{-5} but not at 1×10^{-6} *M*. The data (Table I) show that the site of inhibition was at a late stage in the biosynthetic pathway, *i.e.*, after the formation of squalene.

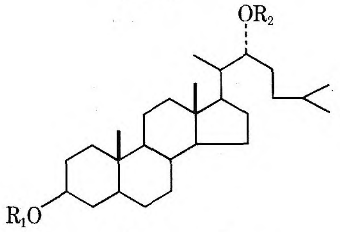
Experimental Section

Melting points are uncorrected. The rotations were measured in chloroform solution (*c* ~1). The nmr spectra were obtained in



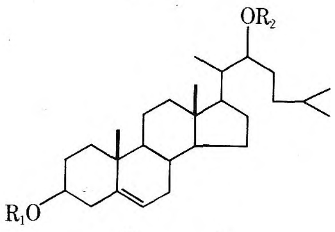
	R1	R2
1	H	O
2	COC_6H_5	O
3	H	NOH
4	H	NNH_2

(22*R*)



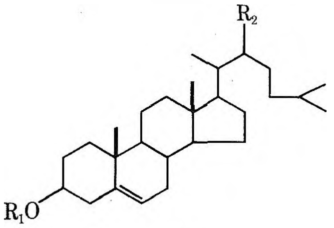
	R1	R2
5	COC_6H_5	H
6	COC_6H_5	OTs

(22*S*)

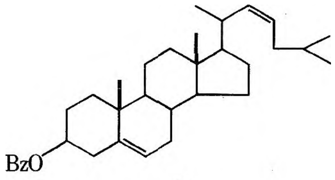


	R1	R2
7	COC_6H_5	OH
8	COC_6H_5	OTs

(22*S*)

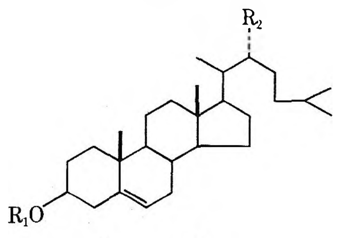


	R1	R2
9a	COC_6H_5	N_3
10	H	NH_2
11	H	NHAc
15	H	$NHCOC_6H_5$



9b

(22*R*)



	R1	R2
12	COC_6H_5	N_3
13	H	NH_2
14	H	NHAc
15	H	$NHCOC_6H_5$

deuteriochloroform solution with tetramethylsilane as the internal standard on a 60-MHz Varian A-60 spectrometer. The chemical shifts are expressed in parts per million. The mass spectra were obtained on an Associated Electronics Industry AEI MS 9 spectrometer. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

22-Oxocholesterol Oxime (3). To a solution of 1.411 g of 22-ketocholesterol (1) in 10 ml of pyridine was added 2 g of hydroxylamine hydrochloride, and the solution was heated to 90° for 36 hr. After cooling, the oxime was extracted with methylene chloride, which gave 1.420 g of crude product. After tlc and crystallization from ethanol there was obtained 609 mg of oxime: mp 178°; $[\alpha]^{22}_{\mathrm{D}}$ −73°; nmr δ 0.72 (18-CH_3), 1.01 (19-CH_3), 1.11 (doublet, $J = 7$ Hz, 21-CH_3); mass spectrum *m/e* (rel intensity) M 415 (48), M − 17 (53), M − C_3H_7 372 (56), M − C_4H_8 359 (22), M − C_4H_8 − 15 334 (33), C_4H_9ON 87 (100).

Anal. Calcd for $C_{27}H_{45}NO_2$: C, 78.02; H, 10.91; N, 3.37. Found: C, 78.30; H, 10.88; N, 3.45.

(22*R*)-22-Azidocholesterol Benzoate (12). To the solution of 200 mg of (22*S*)-22-hydroxycholesterol 3-benzoate (7) in 3 ml of pyridine was added 100 mg of toluenesulfonyl chloride and the solution was kept at 23° for 4 days. After addition of water the tosylate 8 was extracted with methylene chloride and worked up as usual.[16] The 250 mg of crude product was dried in a desiccator over phosphorus pentoxide and then added to the solution of 1 g of sodium azide in 30 ml of freshly distilled hexamethylphosphoric triamide. After the mixture was stirred for 3 hr at room temperature, water was added and the azide was extracted with benzene. The benzene layer was dried and evaporated *in vacuo.* The crude residue of 195 mg gave mp 174°. An analytical sample was obtained after two recrystallizations from acetone which gave 95 mg: mp 179°; $[\alpha]^{23}_{\mathrm{D}}$ +6°; ir 2084 cm^{-1} (N_3); mass spectrum *m/e* (rel intensity) M − C_6H_5 COOH 409 (100), M − C_5H_{11} 460 (4), M − C_5H_{11} − N_2 432 (14), M − C_6H_5COOH − $C_6H_{12}N_3$ 283 (11), $C_6H_{12}N$ 98 (81).

Anal. Calcd for $C_{34}H_{49}O_2N_3$: N, 7.90. Found: N, 7.64.

(22*R*)-22-Aminocholesterol (13). To the solution of 86 mg of azide 12 in 6 ml of ether was added 60 mg of lithium aluminum hydride and the mixture was heated under reflux for 2 hr. After usual[16] work-up there was obtained 71 mg of crude amine, which was recrystallized from ether–hexane. A sample gave a single spot on a silica tlc developed with ethanol. The pure material had mp 140°, $[\alpha]^{22}_{\mathrm{D}}$ −37°, mass spectrum M 401 (trace), *m/e* 100.

Anal. Calcd for $C_{27}H_{47}ON$: C, 80.73; H, 11.80; N, 3.49. Found: C, 80.43; H, 11.80; N, 3.27.

(22*S*)-22-Azidocholesterol Benzoate (9a). This compound was prepared under similar conditions as described for the preparation of its epimer 12. From 144 mg of alcohol 5 there was obtained 107 mg of crude azide, which upon purification gave 62 mg of pure 22*S*-azide **9a** and 11 mg of olefin **9b**, originating from the elimination of the 22*R*-tosylate 6. The azide **9d**, recrystallized from acetone–methanol, gave material which appeared uniform on tlc, and had mp 166°; $[\alpha]_{\mathrm{D}}$ −19°; ir 2084 cm^{-1} (N_3); mass spectrum similar to that of its 22*R* epimer 12.

Anal. Calcd for $C_{34}H_{49}O_2N_3$: N, 7.90. Found: N, 7.64.

The olefin **9b**, which was not further characterized, showed in its nmr spectrum three olefinic protons between 5.20 and 5.65 ppm (H-6, H-22, and H-23); mass spectrum *m/e* (rel intensity) M − C_6H_5COOH 366 (100), M − C_6H_5COOH − C_8H_{15} 255 (21).

(22*S*)-22-Aminocholesterol (10). This compound was produced as described for 13. The 22*S*-amine 10 was recrystallized from petroleum ether (bp 30–60°), mp 144°, $[\alpha]_{\mathrm{D}}$ −45°. On silica thin layer plates (methanol) the 22*S*-amine 10 is less polar than the 22*R*-amine 13. The mass spectrum of 10 is very similar to that of 13 while their nmr spectra are identical.

Anal. Calcd for $C_{27}H_{47}ON$: N, 3.49. Found: N, 3.31.

(22*S*)-22-Benzoylaminocholesterol (15). To the solution of 50 mg of the amine 10 in 2 ml of benzene and 2 ml of methylene chloride was added 15 ml of a 5% aqueous Na_2CO_3 solution. While stirring, 0.3 ml of benzoyl chloride was added, and the mixture was stirred magnetically for 1 hr. The methylene chloride extract gave 60 mg of amide 15, which when recrystallized from benzene gave a single spot on tlc: mp 202°; $[\alpha]_{\mathrm{D}}$ −45°; nmr δ 0.72 (18-CH_3), 1.0 (19-CH_3), 1.05 (doublet, partially visible, 21-CH_3); mass spectrum *m/e* (rel intensity) M 505 (2), M − C_6H_{11} 434 (2), $C_6H_5CONHC_6H_{12}$ 204 (100), C_6H_5CO 105 (7).

(22*R*)-22-Benzoylaminocholesterol (16). This was prepared in the same fashion as 15. The amine 13 (50 mg) gave the amide 16 (55 mg), which was recrystallized from benzene–ethyl acetate and appeared pure on tlc: mp 215°; $[\alpha]_{\mathrm{D}}$ −25°; nmr δ 0.70 (18-CH_3), 1.0 (19-CH_3), 0.97 (partially visible doublet, 21-CH_3); the mass spectrum very closely resembles the spectrum of cholesterol 15.

(22*S*)-22-Acetylaminocholesterol (11). To the saturated methanolic solution of 70 mg of the amino alcohol 10 a few drops of acetic anhydride (slight excess) was added. The product was crystallized from methanol to give 52 mg of amide, single spot on tlc: mp 256°; $[\alpha]_{\mathrm{D}}$ −48°; nmr δ 0.70 (18-CH_3), 1.02 (19-CH_3), 0.95 (partially visible doublet, 21-CH_3); mass spectrum *m/e* (rel intensity) M 443 (0.5), M − C_5H_{11} 372 (0.5), $CH_3CONHC_6H_{12}$ 142 (100), 142 − 42 = 100 (36).

(22*R*)-22-Acetylaminocholesterol (14). This compound was prepared as described for 11. The amide crystallized from methanol: mp 215°; $[\alpha]_{\mathrm{D}}$ −31°; nmr δ 0.68 (18-CH_3), 1.02 (19-CH_3), 0.92 (partially visible doublet, 21-CH_3); mass spectrum very similar to that of its epimer 11.

(22*R*)- and (22*S*)-22-aminocholesterol (10 and 13). To the solution of 315 mg of 22-ketocholesterol oxime (3) in 20 ml of ethylamine, 200 mg of lithium was added in small portions at a rate which maintained the blue color. The excess lithium was destroyed with a few drops of methanol after 2 hr. The thus formed amines were extracted with methylene chloride and the organic phase was washed with water and saline and finally evaporated to dryness *in vacuo.* The residue gave 306 mg of crude amines which could be separated by tlc into 108 mg of 22*R*-amine 13 and 75 mg of 22*S*-amine 10, both identical with the amines obtained by stereospecific synthesis described above: 10, mp 144°, $[\alpha]_{\mathrm{D}}$ −45°; 13, mp 142°+ $[\alpha]_{\mathrm{D}}$ −37°.

22-Ketocholesterol Hydrazone (4). The solution of 360 mg of ketone 2 and 1 ml of hydrazine hydrate in 3 ml of absolute ethanol was heated under reflux for 48 hr. The extraction with methylene chloride gave 370 mg of crude hydrazone, which contained a trace of starting material. The mixture was purified by thin layer chromatography, which gave 209 mg of hydrazone as a uniform band. Recrystallization from hexane gave 135 mg of 4: mp 146°; $[\alpha]_{\mathrm{D}}$ −68°; nmr δ 0.72 (18-CH_3), 1.01 (19-CH_3), 1.14 (doublet, partially visible, 21-CH_3); mass spectrum *m/e* (rel intensity) M 414 (6), M − 15 399 (6), M − C_3H_7 371 (10), M − C_4H_8 358 (15), M − C_4H_8 − 15 343 (11), $C_4H_{10}N_2$ 86 (100).

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Registry No.—**1**, 19243-30-2; **2**, 17976-38-4; **3**, 50921-59-0; **4**, 50921-60-3; **5**, 17954-94-8; **7**, 17954-95-9; **9a**, 50921-61-4; **10**, 50921-62-5; **11**, 50921-63-6; **12**, 50921-64-7; **13**, 50921-65-8; **14**, 50921-66-9; **15**, 50921-67-0; **16**, 50921-68-1; hydroxylamine hydrochloride, 5470-11-1.

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(10) F. S. Prout and Z. F. Chmielewicz, *J. Org. Chem.*, 24, 308 (1959).
(11) K. Tsuda and R. Hayatsu, *J. Amer. Chem. Soc.*, 81, 5987 (1959).
(12) Reduction with sodium borohydride gave a ratio of 1:4, lithium tri-*tert*-butoxyaluminum hydride gave exclusively the 22*S* product, while the reduction with sodium in isopropyl alcohol gave the alcohols in a ratio of 3:2, respectively.
(13) W. Vetter, P. Longevialle, F. Khuong-Huu-Lainé, Q. Khuong-Huu, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 1325 (1963).

(14) The cholesterol synthesis was tested *in vitro* by a rat liver homogenate preparation. A pooled liver homogenate was incubated simultaneously with acetate-^{14}C and mevalonate-^{3}H in the presence of different concentrations of 22-oxocholesterol oxime and the incorporation into nonsaponifiable lipids and cholesterol was measured.

(15) Other compounds in this series have not been assayed as yet.

(16) For procedure compare R. C. Nickolson and M. Gut, *J. Org. Chem.*, **37**, 2119 (1972).

New Monoterpenes from *Artemisia filifolia* (Torrey). Structure, Synthesis, Rearrangements, and Biosynthesis[1a]

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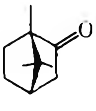
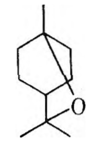
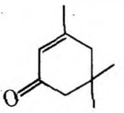
The steam distillate of the leaves and stems of sand sage [*Artemisia filifolia* (Torrey)] contains two new monoterpene lactones, filifolide A and filifolide B. These have been characterized as 1(*R*),5(*S*)-(−)-5-hydroxy-2,2,4-trimethylcyclohex-3-ene-1-carboxylic acid γ-lactone (**8**) and 1(*R*),3(*S*)-(+)-3-hydroxy-2,2,4-trimethylcyclohex-4-ene-1-carboxylic acid γ-lactone (**9**). Other major constituents of the distillate are the cyclobutanone (−)-filifolone, (−)-camphor, 1,8-cineole, and isophorone. Minor constituents are piperitenone, borneol, (−)-verbenone, and 3,3,5-trimethylcyclohex-2-ene-1,4-dione (**13**). The chloroform extract of the plant contains the monoterpene 1(*R*)-(+)-5-keto-2,2,4-trimethylcyclohex-3-ene-1-carboxylic acid (**14**), the flavone acacetin, and the sesquiterpene lactone colartin. In addition to the synthesis of lactones **8** and **9**, another new monoterpene lactone was prepared, 2-hydroxy-α,α,3-trimethylcyclopent-3-ene-1-acetic acid γ-lactone (**2**).

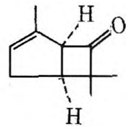
Sand sage [*Artemisia filifolia* (Torrey)] has been used by Hopi Indians and early white settlers as a medicinal plant.[1b] It grows at elevations ranging from 4000 to 6000 ft in the state of Arizona. The strong "cough medicine" fragrance of the plant, particularly after a rainfall, prompted us to investigate the steam distillate of the plant.

Preliminary studies[2] showed a relatively high (1% wet weight) percentage of steam volatile oil. The major constituents were separated by gas–liquid chromatography and identified as (−)-camphor, 1,8-cineole, and isophorone. The structure of the fourth constituent was subsequently shown[3] to be the cyclobutanone (−)-filifolone.

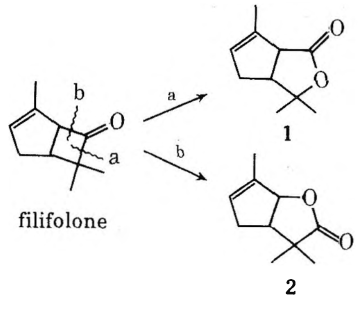

(−)-camphor


1,8-cineole


isophorone

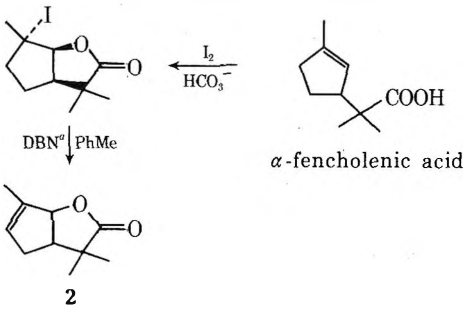

(−)-filifolone

A fifth fraction appeared to be a 1:1 mixture of two monoterpene lactones (filifolide A and filifolide B), both having the molecular formula $C_{10}H_{14}O_2$. Catalytic hydrogenation of the lactone mixture gives a neutral and an acid fraction, indicating an allylic lactone system.[4] Structures **1** and **2** were originally proposed for the two lactones on the assumption that these could have arisen by a simple Baeyer–Villiger oxidation of filifolone. The present report is chiefly concerned with the structures of filifolides A and B.



filifolone

Scheme I
The Synthesis of Lactone 2

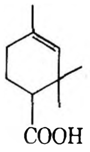


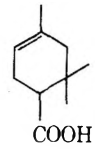
^{a}DBN = 1,5-diazabicyclo[4.3.0]non-5-ene.

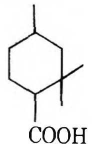
Results

Lactones. Compound **1** (carvenolide) has been reported by Wallach more than 70 years ago.[5] Its structure was recently confirmed[6] and its nmr spectrum[6] was shown to be different from those of filifolides A and B. Compound **2** had not been previously reported; so its synthesis was carried out, as shown in Scheme I. The spectral data for lactone **2** did not coincide with either filifolide A or B from *A. filifolia;* hence neither structure **1** or **2** was tenable.

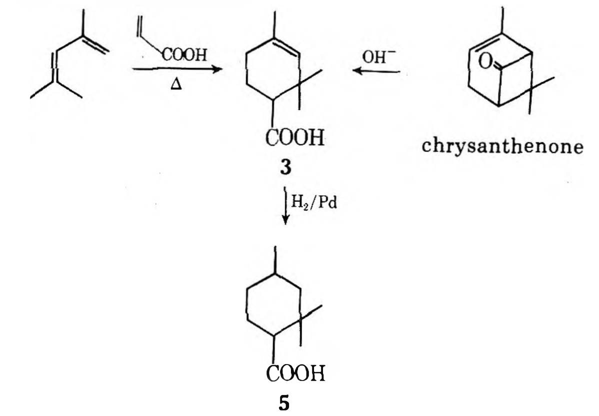
A careful reexamination of the hydrogenation reaction gave us the first clue to the structures of filifolides A and B. Surprisingly, both lactones underwent hydrogenolysis to yield two unsaturated carboxylic acids, both $C_{10}H_{16}O_2$, which on further hydrogenation gave the single acid, $C_{10}H_{18}O_2$. Their respective structures were deduced from nmr spectra reported[7] for **3** and **4** and from the hydrogenation product **5**.


3

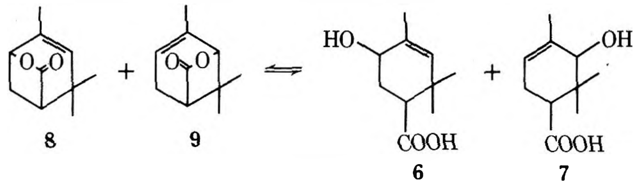

4


5

Compounds 3 and 5 were prepared by two independent routes[7,8] and shown to be identical with the hydrogenation products of filifolides A and B. Thus, 3 and 4 should represent the basic carbocyclic structures of the lactones, less the oxygen function.



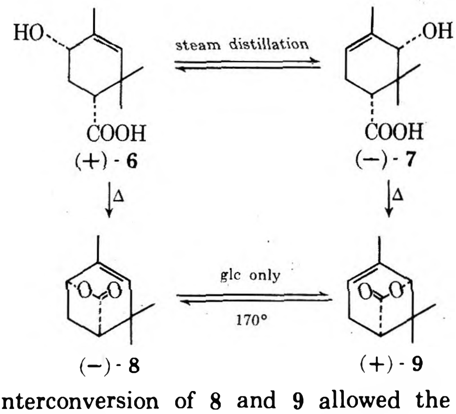
Alkaline hydrolysis of the lactone mixture gave two acids, which were separated by fractional crystallization. One of these was identified as 5-hydroxy-2,2,4-trimethylcyclohex-3-ene-1-carboxylic acid (6)[9] and the other acid was assigned the structure 7, based on spectral evidence. When 6 and 7 were heated separately, they gave lactones A and B, respectively. Therefore, structures 8 and 9 could be tentatively assigned to the filifolides A and B.



The final confirmation of the lactone structures was obtained by independent synthesis. Lactone 8 was prepared by two methods, the first of which established the absolute configuration of the enantiomer in the plant, *i.e.*, (−)-8.

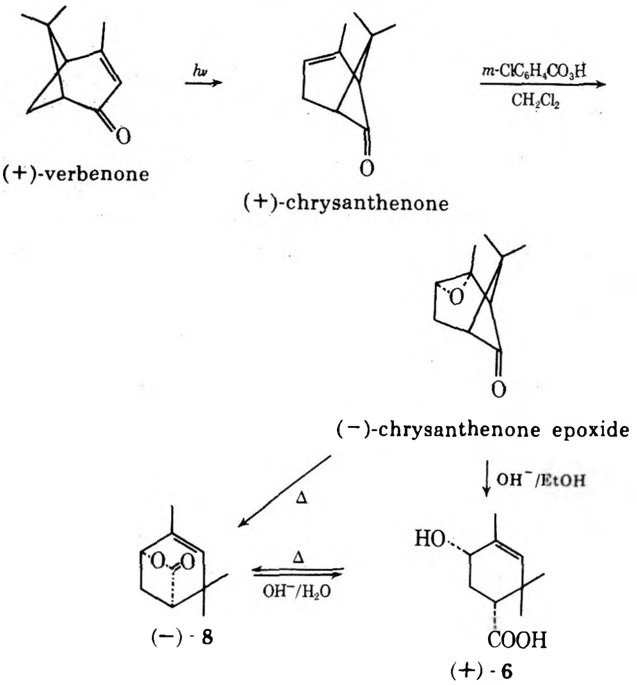
Lactone B (9) proved more difficult to synthesize, because epoxidation of one of the intermediates (10) was not stereospecific and resulted in a mixture of epoxides (11 and 12), as in Scheme II, method 3.

Lactones (−)-8 and (+)-9 occur in the steam distillate of the plant material in approximate ratio of 5:1, respectively. However, if the steam distillate is subjected to gas-liquid chromatography at 170°, the ratio is invariably 1:1. If filifolide A is injected into the glc apparatus, a 1:1 mixture occurs. However, if A is steam distilled, no interconversion takes place. On the other hand, hydroxy acids 6 and 7 are readily interconverted by steam distillation. This behavior is summarized below.

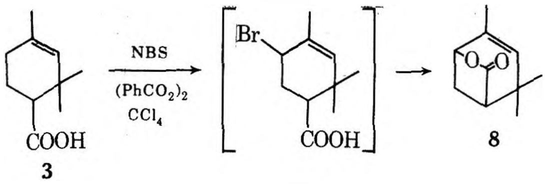


Scheme II

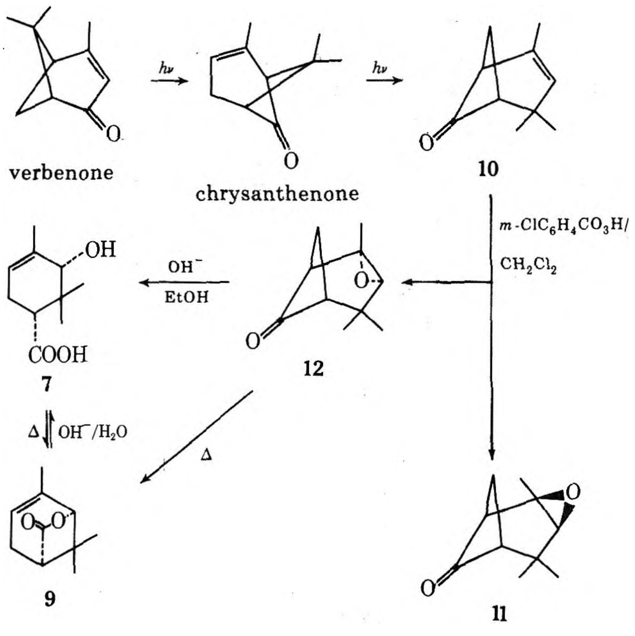
Method 1



Method 2



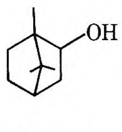
Method 3



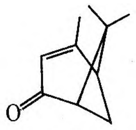
The interconversion of 8 and 9 allowed the absolute configuration of lactone 9 from *A. filifolia* to be determined, since the absolute configuration of (−)-8 was known. The 1:1 (approximately) mixture of lactones 8 and 9 obtained upon preparative glc of (−)-8 was found to have a specific rotation approximately equal to the sum of the specific rotations of (−)-8 and (+)-9 found in *A. filifolia*. This demonstrated that the thermolysis product of (−)-8 is (+)-9, that very little racemization of 8 or 9 was occurring during glc, and that (+)-9 from *A. filifolia* has the absolute configuration shown above.

Neither **6** nor **7** were found in the chloroform extract of the plant, thus excluding the possibility that lactones **8** and **9** could be artifacts of the steam distillation process.

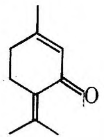
Minor Constituents of *A. filifolia.* Because of the unique carbocyclic system represented by isophorone and lactones **8** and **9**, we were interested in looking for possible biosynthetic precursors in the plant. We carried out an analysis of the minor constituents of the steam distillate and identified borneol, (−)-verbenone, piperitenone, and ketoisophorone (**13**). Of these, compound **13** is the only one with the 1,1,3-trimethylcyclohexane structure.[10] It should also be noted that (−)-verbenone occurs in the plant, whereas (+)-verbenone is the synthetic precursor to lactones **8** and **9** as described above.



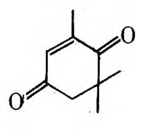
borneol



(−)-verbenone

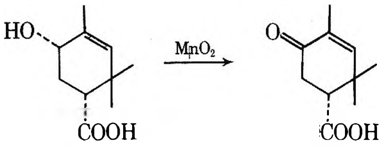


piperitenone



13

The acidic fraction of the chloroform extract was also examined for possible carboxylic acid precursors. The extract yielded a keto acid, (+)-**14**, whose structure was established by MnO_2 oxidation of compound **6**. Compound **14** has not been reported previously as a natural product.

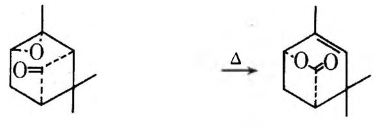


(+)-**6** (+)-**14**

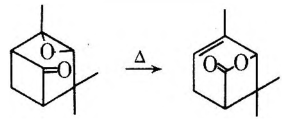
Also found in this fraction was the flavone acacetin.[11] From the neutral chloroform extract the sesquiterpene lactone colartin[12] was isolated.

Discussion

Rearrangements. In the course of the preparation of lactones **8** and **9**, we noted a remarkable thermal rearrangement.

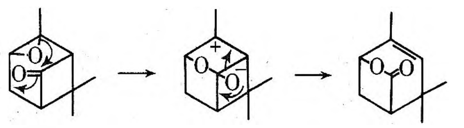


(−)-chrysanthenone epoxide (−)-**8**

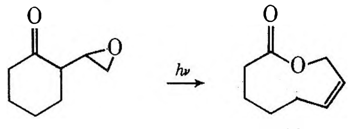


12 **9**

Such a $[_{\sigma}2_s + {}_{\sigma}2_s]$ cycloaddition-type reaction is symmetry forbidden[13] if concerted (*i.e.*, ground state). Thus, the rearrangement probably occurs in a stepwise fashion; the following example is just one of many possible mechanisms.

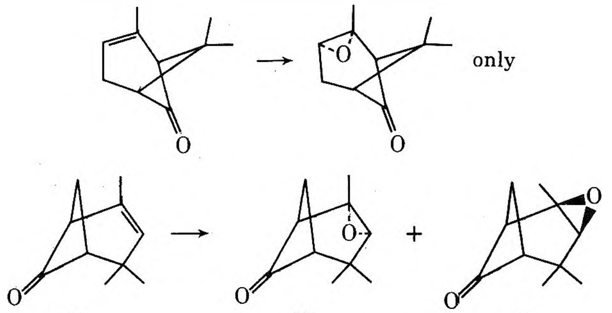


The driving force probably comes from the rupture of the strained cyclobutanone ring system. The reaction may have synthetic applications to other β-epoxy ketone systems. A closed related reaction has recently been carried out by Carlson,[14] the photocatalyzed conversion of **15** to **16**.



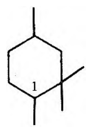
15 **16**

The influence of steric factors was pronounced in the epoxidation of chrysanthenone. In this reaction, only the cis (with respect to the ketone function) epoxide was obtained. On the other hand, epoxidation of compound **10** led to a mixture of cis and trans epoxy ketones.



10 **12** **11**

Biosynthetic Implications. The occurrence of large amounts of isophorone in the plant tissue is unusual, although it has been reported recently[15-17] in small amounts in other species. The carbon skeleton **17** is found in five of the monoterpenes of *A. filifolia*, namely **8**, **9**, **13**, **14**, and isophorone. Altogether they constitute 40% of the monoterpene fraction and represent an important biosynthetic pathway. Presumably, they arise from a common precursor, but one not normally associated with terpene biosynthesis.



17

The head-to-middle coupling of two isoprenyl pyrophosphate units can account for all of the "irregular" constituents of *A. filifolia.* This mechanism has been proposed[18] for the biosynthesis of lavandulol and related monoterpenes. The stereochemistry at C-1 of **17** in the *A. filifolia* monoterpenes is consistent with that reported by Epstein[18,19] for open-chain analogs of lavandulol in other *Artemisia* species.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were measured on a Cary recording spectrophotometer, Model 14. Infrared (ir) spectra were recorded on Perkin-Elmer Models 137 and 337. Nmr spectra were measured on Varian Associates A-60A, T-60, and HA-100 instruments and peak positions are given in δ values, using tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer Model RMU-6E mass spectrometer. Optical rotations were measured on a Cary Model 60 recording spectropolarimeter by scans from 5800 to 6000 Å, selecting the value of 5893 Å as the sodium D line. Gas chromatography (glc) was carried out on a Varian Aerograph Model 90-P, using a Varian Aerograph Model 20 strip chart recorder. The columns used for glc were 15% SE-30 on Chromosorb P, 20 ft × 0.375 in. aluminum tubing (hereafter referred to as column I); 20% Carbowax 20M on Chromosorb W (acid-washed), 5 ft × 0.25 in. copper tubing (hereafter referred to as column II); and 18% SE-30 on Chromosorb P, 6 ft × 0.25 in. copper tubing (hereafter referred to as column III).

Steam Distillation of the Plant Material. Whole, wet plant material gathered 2 miles southeast of Willcox, Ariz., on Oct 31, 1969, and Aug 6, 1970, was steam distilled as follows. A 2- to 8-kg portion of wet plant was placed in a 10-gallon milk can and the can was half filled with water. A special top with a vertical exit tube was then clamped on the milk can. To this vertical metal tube were then attached three condensers in series. The drum was heated with a Meeker burner until about 4 l. of distillate (cooled in ice) had been collected. This process takes about 4 hr. A visible yellow layer of oil was present on top of the water in the distillate. The steam distillate was extracted with ether and dried over anhydrous sodium or magnesium sulfate, and the solvent was carefully removed *in vacuo* to give the steam-volatile oil as the residue. In some experiments chloroform was used in place of ether as the solvent for the extractions. A total of seven such steam distillations was carried out. The average yield based on wet plant material was 0.8%.

Fractional Distillation of the Steam Distillate. The steam distillate (steam-volatile oil) of *Artemisia filifolia* was distilled *in vacuo* through a 600-mm vacuum-jacketed Vigreux column. The pertinent data are included in Table I.

α-Fencholenic Acid (α,α,3-Trimethylcyclopent-2-ene-1-acetic Acid. α-Fencholenic acid was prepared from (±)-fenchone.[20,21] Much longer reaction times than reported were required in our experiments, especially in the conversion of α-fencholenic acid amide to the acid. α-Fencholenic acid was also prepared from (±)-filifolone.[22] The infrared [(neat) 3100 (very broad) and 1705 cm^{-1}], nmr [(CCl_4) δ 11.69 (br s, -COOH), 5.20 (br s, H-2), 1.6–3.0 (complex, H-1, -4, -4′, -5, -5′), 1.73 (br s, C-3 methyl), and 1.08 (s, α-methyls)], and mass [m/e 168 (M^+), 107, and 81 (base, $- (\cdot C_3H_7 + CO_2)$)] spectra of our material were consistent with those reported[22] for α-fencholenic acid.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.08; H, 9.80.

Lactone 2 (2-Hydroxy-α,α,3-trimethylcyclopent-3-ene-1-acetic Acid γ-Lactone). α-Fencholenic acid was converted to its iodolactone with iodine and sodium bicarbonate.[22]

The iodolactone (1.8 g, 0.0060 mol) of α-fencholenic acid was dissolved in toluene (15 ml). To this solution was added 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 1.5 g, 0.012 mol) and the reaction mixture was stirred under reflux for 50 min. The mixture was cooled, diluted with water (100 ml), and extracted with ether (2 × 100 ml). The ether extracts were combined and washed with 5% hydrochloric acid (2 × 100 ml), water (100 ml), saturated sodium thiosulfate (4 × 100 ml) until colorless, and then water (100 ml). The ether solution was dried over anhydrous magnesium sulfate and evaporated to yield 1.2 g of a yellow oil. Nmr analysis revealed this oil to be *ca.* 80% lactone 2; it was subjected to preparative glc (column III, column temperature 170°). The major peak was collected (there appeared to be some thermal decomposition of 2) resulting in pure lactone 2 as a colorless oil, mp ~10° (0.70 g, 0.0042 mol, 70%). The nmr [(CCl_4) 5.60 (br s, H-4), 5.04 (br d, J = 4 Hz, H-2), 2.77 (dd, J = 4, 7 Hz, H-1), 2.38 (m, H-5, -5′), 1.82 (d, J = 1 Hz, C-3 methyl), and 1.24 and 1.12 (both s, α-methyls)], ir [(neat) 1760 cm^{-1}] and mass [m/e 166 (M^+), 122 ($-CO_2$), 107 (base, $-(CO_2 + \cdot CH_3)$), and 91] spectra were in accord with structure 2.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.11; H, 8.63.

Hydrogenolysis of *A. filifolia* Lactones 8 and 9. Carboxylic Acids 3 and 4. Several similar experiments were performed; therefore, only one shall be described in detail here. The products from all such experiments differed only in the relative ratios of 3:4. That is, lactone 9 underwent hydrogenolysis more readily than lactone 8. Therefore, shorter reaction times gave a 3 + 4 mixture richer in acid 4 than did longer reaction times.

The *A. filifolia* lactone mixture (8 + 9) purified by fractional distillation (1.21 g, 0.00730 mol) was dissolved in absolute ethanol (10 ml). To this was added 10% palladium on carbon (0.050 g) and the resulting suspension was hydrogenated at atmospheric pressure and room temperature for 17 hr. The amount of hydrogen absorbed (215 ml) calculates for slightly more than that required (194 ml) for 1 mol of H_2/mol 8 + 9. The ethanolic mixture was then filtered through Celite, diluted with 5% aqueous sodium hydroxide (100 ml), and extracted with ether (2 × 100 ml). Sodium bicarbonate solution was found to be an ineffective solvent for these β,β-disubstituted (sterically hindered) carboxylic acids (3 and 4). Glc analysis of the ether extract revealed cineole, isophorone, camphor, dihydrofilifolone, and unreacted lactones 8 and 9.

A work-up of the sodium hydroxide extract yielded 0.987 g of acidic product as a yellow oil. The nmr spectrum of this oil showed it to consist of a 3:1 mixture of 3:4. The yield of the 3 + 4 mixture was calculated to be 0.00528 mol (72.2%).

Table I
Fractional Distillation of the *A. filifolia* Steam Distillate

Fraction	Bp, °C	Wt, g	Composition[a]
1	30–46	17.0	Ci:C:F:I (11:1:1:1)
2	48–62	44.3	C:F:I (8:1:1)
3	64–71	6.3	C:I:L:O (20:20:1:7)
4	72–81	9.1	I:L:O (3:3:4)
5	84–90	12.2	L:O (3:2)
6	91–109	9.0	>80% L + some IGA[b]
7	110–118	20.5	>90% IGA[b]

[a] Determined by glc and nmr; Ci = 1,8-cineole, C = camphor, F = filifolone, I = isophorone, L = lactones 8 + 9, O = others. [b] IGA = isogeranic acid, a thermal decomposition product of filifolone.

Hydrogenation of the Carboxylic Acid Mixture 3 + 4 from *A. filifolia*. Carboxylic Acid 5 (2,2,4-Trimethylcyclohexane-1-carboxylic Acid). The mixture of carboxylic acids of formula $C_{10}H_{16}O_2$, obtained by hydrogenolysis of the *A. filifolia* lactones (above) (0.30 g, 0.0018 mol), was dissolved in 95% ethanol (10 ml). To this was added platinum oxide (0.050 g) and the resulting suspension was subjected to hydrogenation at atmospheric pressure and room temperature for 48 hr. After removal of the catalyst and evaporation of the solvent there remained 0.29 g of a pale yellow oil which could not be made to crystallize. The crude hydrogenation product was purified by its partial conversion to the anilide. The sodium hydroxide extract of the anilide reaction mixture was acidified and extracted with ether, yielding 0.055 g (0.00032 mol, 63%) of crystalline 5, mp 59–69°. Recrystallization from acetic acid–water gave pure 5 as colorless, tiny flakes, mp 83–84° (lit.[23] mp 81–82°). The acid prepared in this way had nmr [(CCl_4) 11.66 (br s, -COOH), 1.3–2.2 (complex, H-1, -3, -3′, -4, -5, -5′, -6, -6′), 1.03 and 0.98 (both s, C-2 methyls), and 0.89 (d, J = 6.5 Hz, C-4 methyl)], ir [($CHCl_3$ 2960 (very broad) and 1710 cm^{-1}] and mass [m/e 170 (M^+) and 83 (base)] spectra in accord with structure 5. In addition, 5 was independently prepared (described later) and shown to be identical with the material described here by identical spectra (ir, nmr) and an undepressed (82–84°) mixture melting point.

Carboxylic Acid 3 (2,2,4-Trimethylcyclohex-3-ene-1-carboxylic Acid). Carboxylic acid 3 was prepared by the thermal Diels–Alder reaction between 2,3-dimethyl-1,3-pentadiene and acrylic acid[7,8,24] and also by the hydrolysis of chrysanthenone.[7] In these reactions, or in their work-up, we observed some isomerization of the product (3) to 4, as noted by Erman.[7] Hence, the observed melting points of our specimens of 3 were about 10° lower than the reported[7] 84–85°. The nmr spectrum, however, of the acid prepared here was identical with that reported[7] for 3, excepting peaks due to the impurity 4. The ir [($CHCl_3$) 3000 (very broad) and 1710 cm^{-1}] and mass [m/e 168 (M^+), 153 ($- \cdot CH_3$) 123, 107 (base) 96, 81, and 67] spectra were in accord with structure 3.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 70.98; H, 9.47.

Hydrogenation of Synthetic 3. Carboxylic Acid 5. The hydrogenation and subsequent work-up of synthetic 3 were carried out in the same way as the hydrogenation of acids 3 and 4 obtained by hydrogenolysis of *A. filifolia* lactones 8 and 9. Synthetic 5 had mp 83–84° (lit.[23] mp 81–82°).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.47; H, 10.59.

Hydrolysis of the *A. filifolia* Lactones 8 and 9. Isolation of Hydroxy Acids 6 and 7 [1(*R*),5(*S*)-(+)-5-Hydroxy-2,2,4-trimethylcyclohex-3-ene-1-carboxylic Acid and 1(*R*),3(*S*)-(−)-3-Hydroxy-2,2,4-trimethylcyclohex-4-ene-1-carboxylic Acid)]. Fraction 6 from the second distillation (see Table I) of the *A. filifolia* steam distillate (9.0 g, 80% 8 and 9) was dissolved in ether (100 ml) and the ethereal solution was washed with 5% aqueous sodium hydroxide (2 × 100 ml) to remove isogeranic acid. After washing with water (100 ml), drying over anhydrous magnesium sulfate, and evaporation of the ether *in vacuo,* there remained 7.5 g of the mixture of lactones 8 and 9. Nmr integration revealed this mixture to consist of 85% 8 and 15% 9. The latter mixture was then placed with potassium hydroxide (4.5 g) in water (150 ml) and refluxed for 140 min. The reaction mixture was cooled, diluted with water (200 ml), and extracted with ether (2 × 100 ml). The ether extracts were combined, dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to yield 2.9 g of unreacted lactones as a yellow oil. The still-basic aqueous phase was then acidified with hydrochloric acid and extracted with ether (3 × 100 ml). The ether extracts were combined and dried over anhydrous magnesium sulfate and the solvent was removed *in vacuo*. This resulted in 4.5 g of a yellow oil which crystallized on standing. The latter was found by nmr to consist of a 10:1 mixture of **6**:**7**.

Fractional Crystallization of 6 and 7. The crude crystalline mixture of **6** and **7** (4.5 g) from above was recrystallized from carbon tetrachloride. The first crop of crystals (2.3 g) collected was pure **6**, mp 134–136°. Recrystallization from cyclohexane gave colorless plates, mp 140–141° (lit.[9] mp 140°). This sample of (+)-**6** [1(*R*),5(*S*)-(+)-5-hydroxy-2,2,4-trimethylcyclohex-3-ene-1-carboxylic acid] from *A. filifolia* was optically active, $[\alpha]^{24}\mathrm{D}$ +33.8° (c 0.5, $CHCl_3$). The infrared [(KBr) 3350, 3000 (very broad), and 1685 cm^{-1}], nmr [($CDCl_3$ + 3 drops DMSO − d_6) δ 5.07 (br s, H-3), 4.00 (br t, *J* = 7 Hz, H-5), 2.43 (dd, *J* = 3, 12 Hz, H-1), 1.9–2.2 (m, H-6, -6′), 1.67 (s, C-4 methyl), and 1.11 and 0.97 (both s, C-2 methyls)], and mass [*m/e* 184 (M^+), 166 (− H_2O), 122, and 107 (base, − (H_2O + CO_2 + $\cdot CH_3$))] spectra were consistent with structure **6**.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H. 8.75. Found: C, 65.20; H, 8.68.

The mother liquor from which pure **6** was crystallized yielded a second crop of crystals (0.8 g). This was shown by nmr to consist of a 3:1 mixture of **7**:**6**. This material was recrystallized three times from carbon tetrachloride and once from benzene, giving pure (>98%) (−)-**7** (0.16 g) as colorless prisms, mp 134–136°. The hydroxy acid (−)-**7** [1(*R*),3(*S*)-(−)-3-hydroxy-2,2,4-trimethylcyclohex-4-ene-1-carboxylic acid] prepared in this way was optically active, $[\alpha]^{24}\mathrm{D}$ −58.0° (c 0.9, $CHCl_3$). The nmr [(CCl_4 + 3 drops DMSO-d_6) δ 5.30 (br s, H-5), 3.47 (br s, H-3), 2.24 (m, H-1, -6, -6′), 1.70 (s, C-4 methyl), and 1.00 and 0.93 (both s, C-2 methyls)], ir [(KBr) 3230, 2970 (very broad), and 1680 cm^{-1}] and mass [*m/e* 184 (M^+), 166 (− H_2O), 123, 107 (− (H_2O + CO_2 + $\cdot CH_3$)) and 84 (base)] spectra were consistent with structure **7**.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64,95; H, 8.63.

Regeneration of Lactone (−)-8 [1(*R*),5(*S*)-(−)-5-Hydroxy-2,2,4-trimethylcyclohex-3-ene-1-carboxylic Acid γ-Lactone] from the Hydroxy Acid (+)-6. The pure carboxylic acid **6** (1.84 g, 0.0100 mol) from *A. filifolia*, mp 140–141°, $[\alpha]^{24}\mathrm{D}$ +33.8°, was heated (neat) in a glass tube in an oil bath at a temperature of 160–175° for 60 min. After this time, the reaction mixture was washed out of the tube with ether (50 ml). The ethereal solution was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to provide 1.64 g (0.00988 mol, 98.8%) of the lactone **8** as a pale yellow oil. This material was homogeneous by glc and its nmr spectrum showed no extraneous peaks. Lactone **8** prepared in this way was optically active, $[\alpha]^{24}\mathrm{D}$ −33.2° (c 0.4, $CHCl_3$). The nmr [(CCl_4) δ 5.10 (br s, H-3), 4.40 (m, H-5), 2.3 (m, H-1, -6, -6′), 1.80 (d, *J* = 1 Hz, C-4 methyl), and 1.08 (s, C-2 methyls)], ir [(neat) 1770 and 1670 cm^{-1}] and mass [*m/e* 166 (M^+), 107 (base, − (CO_2 + $\cdot CH_3$)), 69, and 41] spectra were consistent with structure **8**.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.12; H, 8.41.

Regeneration of Lactone (+)-9 [1(*R*),3(*S*)-(+)-3-Hydroxy-2,2,4-trimethylcyclohex-4-ene-1-carboxylic Acid γ-Lactone] from the Hydroxy Acid (−)-7. This experiment was performed exactly as was the preceding experiment. The carboxylic acid **7** (0.100 g, 0.00543 mol) from *A. filifolia*, mp 134–136°, $[\alpha]^{24}\mathrm{D}$ −58°, when heated at 160–175° for 1 hr provided, after work-up, 0.0901 g (0.00543 mol, 100%) of lactone **9** as a pale yellow oil. This material was homogeneous by glc and its nmr spectrum showed no extraneous peaks. Lactone **9** prepared in this way was optically active, $[\alpha]^{24}\mathrm{D}$ +43.8° (c 1.2, $CHCl_3$). The nmr [(CCl_4) δ 5.43 (m, H-5), 3.87 (br s, H-3), 2.3 (m, H-1, -6, -6′), 1.80 (s, C-4 methyl), and 1.20 and 1.10 (both s, C-2 methyls)], ir [(neat) 1770 and 1650 cm^{-1}] and mass [*m/e* 166 (M^+), 123, 107 (− (CO_2 + $\cdot CH_3$)), 95, 83, and 43 (base)] spectra were consistent with structure **9**.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.19; H, 8.51.

Photolysis of (+)-Verbenone. Preparation of (+)-Chrysanthenone. Photolysis of (+)-verbenone at a temperature of 50° gave largely racemic products. Therefore, a large fan was used to cool the Hanovia 450 broad spectrum mercury arc lamp employed for the photolysis. This brought the temperature down to 34°. Under these conditions, (+)-verbenone[25] (partially active, $[\alpha]^{24}\mathrm{D}$ +93.7°, 37% optically pure) (10.28 g, 0.0685 mol) in cyclohexane (250 ml), in two Vycor vessels, was photolyzed for 21.0 hr. After this time, a glc analysis showed the composition of the reaction mixture to be 40.7% chrysanthenone, 58.2% verbenone, and only traces (<2%) of other products. The cyclohexane was then removed *in vacuo* to provide 11.2 g of a yellow oil. The latter was distilled under vacuum (7 mm) through a 250-mm vacuum-jacketed Vigreux column. Four fractions were collected (Table II).

Table II

Fraction	Bp, °C	Wt, g	Composition[a]
1	74–76	0.04	88% C, 12% V
2	76.5–77	2.57	87% C, 13% V
3	77.5–79.5	1.30	80% C, 20% V
4	80–82	0.85	60% C, 40% V
Pot residue		4.8	80% V + some IGA, I, P

[a] By glc and nmr analysis. C = chrysanthenone; V = verbenone; I = isopiperitenone; P = piperitenone; IGA = isogeranic acid, a thermal decomposition product of chrysanthenone.

Chrysanthenone, from distillation fraction 2, was optically active, $[\alpha]^{24}\mathrm{D}$ +31° (*c* 3.7, $CHCl_3$) (corrected for 13% verbenone). This corresponds to an optical purity of 29%, based upon a specific rotation of +108° for pure chrysanthenone.[26] Racemic chrysanthenone was also prepared from verbnone by photolysis at 50°. This material was purified by distillation and preparative glc and had an ir spectrum identical with the reported[27] for chrysanthenone. The nmr spectrum of the pure racemic chrysanthenone was identical with the spectrum reported[26] and also identical with that recorded for the partially optically active material described above, excepting peaks due to the impurity, verbenone, in the latter.

Oxidation of (+)-Chrysanthenone. Preparation of (−)-Chrysanthenone Epoxide. To (+)-chrysanthenone (from distillation fraction 2, above, containing 13% verbenone) (1.08 g, 0.00720 mol) in chloroform (30 ml) was added 85% *m*-chloroperbenzoic acid (1.46 g, 0.00733 mol, based upon 85% purity) and sodium bicarbonate (0.61 g, 0.0072 mol). The resulting mixture was stirred at room temperature under anhydrous calcium chloride for 2 hr. The mixture was then diluted with water (50 ml) and chloroform (50 ml) and shaken and the organic layer was separated. The chloroform solution was washed with 5% sodium hydroxide (2 × 50 ml) and then water (50 ml), dried over anhydrous magnesium sulfate, and concentrated *in vacuo* to provide 1.18 g (0.00710 mol, 99%) of a yellow oil. This was shown by nmr analysis to be chrysanthenone epoxide, contaminated only with verbenone (13 mol %). This material was optically active, $[\alpha]^{24}\mathrm{D}$ −26° (c 4.8, $CHCl_3$) (corrected for 13 mol %, 12% by weight, verbenone). If the chrysanthenone epoxide prepared here is 29% optically pure, as was its precursor, (+)-chrysanthenone, then the specific rotation (unreported) of pure (−)-chrysanthenone epoxide is −90°. The nmr spectrum of this sample was identical, excepting peaks due to verbenone, with that of racemic chrysanthenone epoxide prepared from pure racemic chrysanthenone: nmr (CCl_4) δ 3.17 (br s, 1 H) and 2.75 (m, 1 H, protons α to ketone carbonyl), 1.9–2.4 (complex, 3 H, methylene and epoxide methine), 1.37 (s, 3 H, CH_3CO–), 1.30 and 1.10 (both s, 3 H, *gem*-dimethyls).

Thermolysis of (−)-Chrysanthenone Epoxide. (−)-Lactone 8. (−)-Chrysanthenone epoxide, $[\alpha]^{24}\mathrm{D}$ −26° (still containing 13 mol % verbenone) (0.1683 g, 0.001013 mol), was heated (neat) in a glass tube in an oil bath at 170–180° for 20 min. An nmr spectrum of the product showed it to be lactone **8**, contaminated only with verbenone (13 mol %, 12% by weight). This material was a pale brown oil (0.1648 g, 0.000993 mol, 98%) and was optically active, $[\alpha]^{24}\mathrm{D}$ −8.1° (c 1.8, $CHCl_3$) (corrected for 13 mol % verbenone). This calculates for an optical purity of 24%. The nmr spectrum of this material was identical (except for verbenone peaks) with that of pure **8** prepared as described elsewhere.

Hydrolysis of (−)-Chrysanthenone Epoxide. (+)-6. (−)-Chrysanthenone epoxide, $[\alpha]^{24}\mathrm{D}$ −26° (0.44 g, 0.00265 mol), was refluxed with potassium hydroxide (2.0 g) in 95% ethanol (20 ml) and water (2 ml) for 2 hr. The mixture was then cooled, diluted with water (75 ml), washed with chloroform (2 × 50 ml), acidified, and reextracted with chloroform (2 × 50 ml). The latter chloroform extracts were combined, washed with water (50 ml), dried over anhydrous magnesium sulfate, and evaporated to give 0.0824 g of a pale yellow oil. This oil later crystallized after trituration with ether. The crystals (0.0532 g, 0.000289 mol, 10.9%) were recrystallized from benzene to colorless platelets, mp 136–

Table III

Retention time, min^a	Compd	Rel peak area	Yield g	Yield %
0.9	1,8-Cineole	35	1.7	26
2.0	Filifolone	10	0.48	7.4
2.6	Camphor	30	1.5	23
3.2	Isophorone	40	1.9	29
4.0	Borneol + **13** (1:1)	2	0.070	1.1
4.7	(—)-Verbenone	1	0.041	0.63
8.6	Piperitenone	2	0.066	1.0
10.2	**8** and **9**	10	0.50	7.7

^{a} Flow rate = 100 ml/min, column = 178°, detector = 220°, injector = 210°.

138°. An nmr spectrum of this material was identical with that of 6 prepared as previously described. This sample of the hydroxy acid 6 was optically active, $[\alpha]^{24}\text{D}$ +8.2° (*c* 0.56, $CHCl_3$). This calculates for an optical purity of 24%.

Bromination of the Acid 3. Preparation of Lactone 8. 2,2,4-Trimethylcyclohex-3-ene-1-carboxylic acid (3, 2.1 g, 0.012 mol) was dissolved in carbon tetrachloride (40 ml), to which was then added *N*-bromosuccinimide (3.1 g, 0.017 mol) and benzoyl peroxide (0.20 g, 0.00083 mol). The mixture was stirred and refluxed under nitrogen for 22.5 hr. Work-up in the usual way afforded no acidic products (except *m*-chlorobenzoic acid). The neutral fraction, after evaporation of the solvent, gave 1.5 g of a yellow oil. An nmr examination of this oil revealed 27% lactone 8, along with at least two unidentified products. This oil was combined with the oils obtained in the same way from two other brominations of 3 to give a total of 4.0 g of crude lactone 8. Short-path distillation at reduced (0.3 Torr) pressure gave 1.1 g (0.0066 mol, 20%) of pure 8, as a colorless oil, bp 79-83°. The nmr and ir spectra of 8 prepared in this way were identical with those of 8 from *A. filifolia*.

Photolysis of Chrysanthenone. Preparation of the Ketone 10 (2,4,4-Trimethylbicyclo[3.1.1]hept-2-en-6-one). Chrysanthenone, obtained by photolysis of verbenone, was photolyzed in substantially the same way, but at 50°. The products were the same as those reported by Erman.[26] The products were collected by preparative glc on column I or column II. The ketone 10 obtained in this way (average yield 20%) had nmr [(CCl_4) δ 5.00 (br s, H-3), 2.8 (m, H-1, -5), 1.9-2.8 (complex, H-7, -7′), 1.76 (d, J = 1.5 Hz, C-2 methyl), and 1.09 (s, C-4 methyls)], ir [(neat) 1780 and 1650 cm^{-1}] and mass [*m/e* 150 (M^+), 122 (− CO), 108, 107 (base), 93, 91, and 80] spectra consistent with those reported.[26]

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.10; H, 9.21.

Oxidation of 10. Preparation of Epoxide 12. To the ketone 10 (0.157 g, 0.00105 mol) in dichloromethane (3 ml) was added *m*-chloroperbenzoic acid (0.21 g, 0.00122 mol) in dichloromethane (15 ml). The reaction mixture was then stirred under anhydrous calcium chloride at room temperature for 20 hr. After work-up there was obtained 0.112 g (0.000675 mol, 64.3%) of crude epoxide product as a pale yellow oil. Nmr analysis of this oil revealed the presence of the two stereoisomeric epoxides 11 and 12, by glc analysis in the ratio 1:3, respectively. Preparative glc of the 11 and 12 mixture on column I resulted in 0.0420 g (0.000253 mol, 25.1%) of pure 12. The nmr [(CCl_4) δ 3.10 (m, H-1), 2.52 (s, H-3), 2.5 (m, H-5), 1.8 (m, H-7, -7′), 1.43 (s, C-2 methyl), and 1.17 and 1.07 (both s, C-4 methyls)], ir [(neat) 1780 cm^{-1}] and mass [*m/e* 166 (M^+), 123, and 107 (base)] spectra of this material were in accord with structure 12.

Epoxide 12, under the conditions of the mass spectroscopy (inlet temperature 200°), isomerizes largely to lactone 9.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.99; H, 8.57.

Pure epoxide 11 was obtained in amounts too small for adequate structural data to be gathered.

Thermal Rearrangement of Epoxide 12. Preparation of Lactone 9. Pure epoxide 12 (0.0420 g, 0.000253 mol) was heated (neat) in an nmr tube in an oil bath at 160-175° for 12 min. The tube was cooled and weighed (0.0419 g, 0.000252 mol, 99.7%) and the nmr spectrum was recorded. The latter was found to be representative of pure 9, with no extraneous peaks. The infrared spectrum of this sample was identical with that of 9 isolated from *A. filifolia.*

Solvolysis of Epoxide 12. Preparation of Hydroxy Acid 7. Epoxide 12 (0.050 g, 0.00030 mol) was hydrolyzed in the same way as was chrysanthenone epoxide. The usual work-up afforded 0.042 g of a brown oil. The latter was chromatographed over silica gel (20 × 350 mm) and elution with ether gave crystalline 7 (0.029 g, 0.00017 mol, 58%), mp 120-126°. Recrystallization from cyclohexane gave pure 7 (0.022 g) as colorless cubelets, mp 134-136°. That this was identical with the 7 from *A. filifolia* was shown by an undepressed (133-136°) mixture melting point and identical ir and nmr spectra.

Preparative Glc of the *A. filifolia* Steam Distillate. Isolation of (−)-Verbenone, Borneol, Piperitenone, and the Enedione 13. The total steam distillate of *Artemisia filifolia* (6.5 g) was subjected to preparative glc on column II as summarized in Table III.

Identities of these compounds were established by spectral comparisons with authentic specimens and confirmed by mixture melting points of derivatives.

3,5,5-Trimethylcyclohex-2-ene-1,4-dione (13). This compound was prepared from isophorone by the method of Isler.[10] In the last step of the synthesis, activated manganese dioxide was used in place of chromic acid.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.27; H, 8.12.

Isolation of Acacetin and Keto Acid (+)-14. *Artemisia filifolia* was extracted with chloroform by percolation and the extract was separated into neutral and acidic fractions by sodium hydroxide extraction thereof. Chromatography of the acidic fraction over silicic acid gave 2% acacetin and 0.4% keto acid (+)-14 (yields based upon amount of acidic fraction). The latter was recrystallized from benzene to colorless cubelets, mp 106-108°, $[\alpha]^{24}\text{D}$ +128° (*c* 1.0, $CHCl_3$). Identity of each of these two compounds was established by taking a mixture melting point with a synthetic specimen (see below).

Acacetin. Synthetic acacetin was prepared from anisic anhydride and phloracetophenone by the method of Robinson and Venkataraman,[11] mp 260-262° (lit.[11] mp 262°).

Anal. Calcd for $C_{16}H_{12}O_5$: C, 65.60; H, 4.25. Found: C, 65.31; H, 4.49.

The diacetate had mp 200-202° (lit.[28] mp 202-203°).

Preparation of the Keto Acid (+)-14 [1(*R*)-(+)-5-Keto-2,2,4-trimethylcyclohex-3-ene-1-carboxylic Acid]. The hydroxy acid 6 ($[\alpha]^{24}\text{D}$ +33.8°, from *A. filifolia*) (0.70 g, 0.0038 mol) was dissolved in dichloromethane (100 ml) to which was then added active manganese dioxide (5.0 g, 0.063 mol), prepared according to Ball, Goodwin, and Morton.[29] The resulting suspension was stirred under anhydrous calcium chloride for 24 hr, after which time the reaction mixture was filtered through Celite and the filtrate was evaporated to provide 14 (0.55 g, 0.0030 g, 79%) as a yellow oil, which soon crystallized, mp 101-104°. Recrystallization from benzene afforded pure 14 (0.42 g, 0.0023 mol, 60%) as colorless cubelets, mp 107-109°. The reported melting point[9] for racemic 14 is 107°. The material prepared in this way had nmr [($CDCl_3$) δ 9.6 (br, -COOH), 6.38 (br s, H-3), 2.4-3.0 (complex, H-1, -6, -6′), 1.77 (s, C-4 methyl), and 1.33 and 1.13 (both s, C-2 methyls)], ir [(KBr) 3000 (very broad), 1720, and 1660 cm^{-1}], and mass [*m/e* 182 (M^+) and 137 (base, − (·H + CO_2))] spectra in accord with structure 14. This material was optically active, $[\alpha]^{24}\text{D}$ +128° (*c* 1.05, $CHCl_3$).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.64; H, 8.06.

Isolation of Colartin. The neutral chloroform extract of *A. filifolia* was chromatographed over silicic acid and elution with 1:1 benzene-chloroform, decolorization, and repeated recrystallizations from hexane gave a 1% yield of pure colartin as colorless, tiny flakes, mp 107-108°, $[\alpha]^{24}\text{D}$ +19.4° (*c* 0.88, $CHCl_3$).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.06; H, 9.67.

A sample of crude colartin[30] (4 mg), mp 81-94°, had an infrared spectrum identical with that of the material from *A. filifolia*. Recrystallization of this authentic specimen from hexane gave colorless, tiny flakes, mp 106-107°. That the material isolated from *A. filifolia* was in fact colartin was confirmed by an undepressed (106-108°) melting point of a mixture of natural and authentic specimens.

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Registry No.—2, 50585-68-7; 3, 13746-43-5; 4, 50585-69-8; 5, 50585-70-1; (+)-6, 50585-59-6; (−)-7, 50585-60-9; (−)-8, 50585-61-0; (+)-9, 50585-62-1; 10, 50585-71-2; 11, 50585-63-2; 12, 50763-18-3; 13, 1125-21-9; (+)-14, 50585-64-3; acacetin, 480-44-4; colartin, 24493-40-1; 1,8-cineole, 470-82-6; (−)-camphor, 464-48-2; filifolone, 4613-37-0; isophorone, 78-59-1; α-fincholenic acid, 32082-53-4; α-fincholenic acid iodolacetone, 4627-35-4; (+)-chrysanthenone, 38301-80-3; (−)-chrysanthenone epoxide, 50763-19-4; (+)-verbenone, 18309-32-5.

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Mechanism of Cystine Racemization in Strong Acid

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Cystine (1) is the only naturally occurring amino acid which is racemized to a significant extent under the conditions commonly used for hydrolysis of proteins. A study of the mechanism of the racemization of cystine in refluxing 6 N HCl is reported. Various analog studies show that the racemization mechanism involves the formation of an acid enol which is stabilized by the inductive effect of a partially or fully charged β-heteroatom. In general, the requisite charge density may be induced through resonance as in the case of S-(2,4-dinitrophenyl)-L-cysteine or through protonation as in the case of 2,3-diaminopropionic acid, both of which racemize in acid at rates comparable to that of cystine. However, in the case of cystine, enolization does not occur in the intact molecule as a result of disulfide protonation. Rather, the intermediates in a concurrent, acid-catalyzed, disulfide interchange reaction are implicated as the species which undergo racemization.

All of the α-amino acids undergo some racemization during acid hydrolysis of protein, and the degree to which the various amino acids racemize has been quantitated by tritium incorporation experiments.[1] In the case of every naturally occurring amino acid but one, cystine (1), the rate of racemization is vanishingly slow under normal hydrolysis conditions. Cystine, on the other hand, is almost completely racemized after 120-hr exposure to refluxing 6 N HCl. When cystine, the first amino acid discovered, was initially isolated from kidney stones in 1810,[2] it was obtained in a relatively high state of optical purity, as the isolation did not involve extended heating in strong acid. It was not until 89 years after its discovery that cystine was isolated from horn hydrolysate[3] and shown to be the source of much of the sulfur known to be present in protein. In this very early work, the rotation of the cystine isolated was found to be dependent upon the duration of hydrolysis. In 1902,[4] the correct structure of cystine was elucidated and it was shown to be racemized completely by heating in hydrochloric acid. The existence of D, L, and meso forms was proposed in the inactive material, and all three forms were isolated in 1933.[5]

Somewhat surprisingly, in none of the above work or in other studies of this unique racemization[6] is there comment or speculation about the mechanism of the reaction. In the course of preparing a sample of DL-cystine for a separate study, our curiosity was aroused by the anomalous rate at which L-cystine racemized in acid, and we have examined this reaction with the objective of understanding its mechanism.

The decrease in rotation of a solution of cystine in refluxing 6 N HCl is first order in amino acid and has a half-life of about 20 hr. Unfortunately, dependence of the rate on acid concentration could not be fully investigated because of the rapid decomposition of cystine which occurs in more dilute, refluxing acid. Specifically, it was found that in refluxing 1 or 3 N HCl rather rapid decomposition occurred to give cysteine, alanine, glycine, and other products, production of which occurred rapidly enough to render racemization rate measurements meaningless. The extent of decomposition which occurred during racemization experiments was monitored by amino acid analysis and it was found that in 5 N or stronger HCl, decomposition occurred only very slowly.

The effect of the conjugate base of the mineral acid on racemization rate was investigated by comparing the results of experiments conducted in HCl, HBr, and H_2SO_4 at 110° (sealed tube) and constant H_0. Though these acids have widely variant anion nucleophilicities, the rate of racemization was essentially constant for all three. This observation may be interpreted to indicate that nucleophilic attack by the conjugate base is not involved in the rate-determining step of the racemization reaction.

In order to establish the effect of various structural parameters on the rate of racemization, a variety of analog amino acids were subjected to refluxing 6 *N* HCl. The tabulated results of these experiments appear in Table I, in which the amount of racemization is indicated as per cent decrease in optical activity over 20 hr, approximately the optical half-life of cystine under these conditions.

Cysteine (2) and *S*-methylcysteine (3) do not undergo appreciable racemization under the standard conditions. These amino acids differ from cystine to the extent that they do not incorporate either a disulfide linkage or a second intramolecular α-amino acid group. Hence, their lack of reactivity implicates one of these two structural parameters in the cystine molecule.

If the inclusion of a companion intramolecular α-amino acid function is the key to the reactivity of cystine, replacement of one of the disulfide sulfur atoms by a methylene group should have no effect on racemization rate and should result in a structure that would racemize significantly more rapidly than normal amino acids. In fact, such a compound, cystathionine (4), was prepared. Neither cystathionine or the analogous lanthionine (5) racemize appreciably faster than alanine. In addition, the ω-carboxy amino acids aspartic (9) and glutamic (10) do not racemize nor does the ϵ-amino acid, lysine (11). These results clearly indicate that inclusion of an ω-amino or carboxyl group, or both, is not sufficient to activate the molecule toward the acid-catalyzed racemization which cystine undergoes.

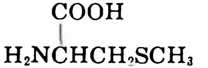
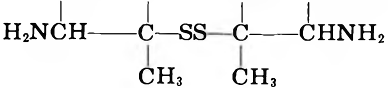
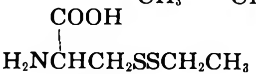
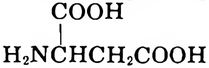
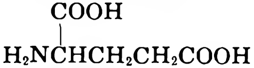
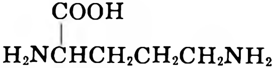
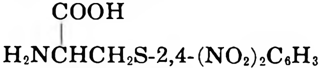
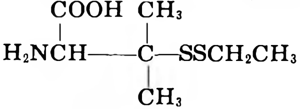
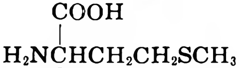
The results above implicate the disulfide linkage as the activating structural parameter. Hence, a number of structural analogs of cystine, which include the disulfide linkage, were prepared for testing. Homocystine (6), in which the disulfide linkage is insulated from the chiral carbons by two methylene groups, does not racemize to a significant extent. Penicillamine disulfide (7), which can be considered a β-tetramethyl analog of cystine, does not racemize.

The inability of penicillamine disulfide to racemize under conditions which result in rapid racemization of cystine could be the result of steric inhibition of the mechanism or could result from absence of the β hydrogens present in cystine. If, for example, enamine formation was the source of the racemization, replacement of the β hydrogens by methyl groups would prevent the occurrence of reaction.

In order to ascertain whether the racemization of cystine involved the β protons, L-cystine was refluxed in 6 *N* $DCl-D_2O$. After 70 hr (3+ half-lives), nmr analysis of the isolated cystine showed that over 80% exchange had occurred at the α position but no measurable exchange (less than 3%) had occurred at the β position. Clearly, racemization does not involve an enamine-like intermediate or any other structure which requires rehybridization of the β carbon. It would appear, therefore, that penicillamine disulfide does not racemize either because of some steric inhibition or because of the inductive effect of the β-methyl groups.

In order to gain further insight into the question of steric inhibition to racemization in penicillamine disulfide, *S*-(ethylthio)-L-cysteine (8) was subjected to the reaction conditions. This unsymmetrical disulfide incorporates the requisite disulfide linkage and retains the unsubstituted β carbons. When 8 was refluxed in 6 *N* HCl, a loss of rotation occurred at a rate similar to that of cystine. However, amino acid analysis of the reaction mixture showed that only 20% of the starting amino acid remained after 55 hr and that a large amount of cystine had been produced. Extraction of the reaction mixture with methylene chloride yielded diethyl disulfide, indicating that a disulfide interchange reaction had occurred.

Table I
Amino Acid Racemization Rates

No.	Compd	% loss optical rotation at 20 hr[a]
1	 $H_2N\overset{COOH}{C}HCH_2SSCH_2\overset{COOH}{C}HNH_2$	50[b]
2	 $H_2N\overset{COOH}{C}HCH_2SH$	0
3	 $H_2N\overset{COOH}{C}HCH_2SCH_3$	0[b]
4	 $H_2N\overset{COOH}{C}HCH_2SCH_2CH_2\overset{COOH}{C}HNH_2$	5[b,c]
5	 $H_2N\overset{COOH}{C}HCH_2SCH_2\overset{COOH}{C}HNH_2$	5[b,d]
6	 $H_2N\overset{COOH}{C}HCH_2CH_2SSCH_2CH_2\overset{COOH}{C}HNH_2$	5[b]
7	 $H_2N\overset{COOH}{C}H—\overset{CH_3}{\underset{CH_3}{C}}—SS—\overset{CH_3}{\underset{CH_3}{C}}—\overset{COOH}{C}HNH_2$	0[b]
8	 $H_2N\overset{COOH}{C}HCH_2SSCH_2CH_3$	*b, f*
9	 $H_2N\overset{COOH}{C}HCH_2COOH$	5[b]
10	 $H_2N\overset{COOH}{C}HCH_2CH_2COOH$	5[b]
11	 $H_2N\overset{COOH}{C}HCH_2CH_2CH_2NH_2$	0
12	 $H_2N\overset{COOH}{C}HCH_2NH_2$	86[b]
13	 $H_2N\overset{COOH}{C}HCH_2CH_2NH_2$	5
14	 $H_2N\overset{COOH}{C}HCH_2S\text{-}2,4\text{-}(NO_2)_2C_6H_3$	38[b,e]
15	 $H_2N\overset{COOH}{C}H—\overset{CH_3}{\underset{CH_3}{C}}—SSCH_2CH_3$	*b, f*
16	 $H_2N\overset{COOH}{C}HCH_2CH_2SCH_3$	5
17	 $H_2N\overset{COOH}{C}HC_6H_5$	17
18	 $H_2N\overset{COOH}{C}HCH_2C_6H_5$	0

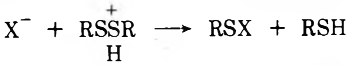
[a] Estimated error in rotation measurements is ±5%. [b] Amino acid analyses were performed on the refluxed solution at 20 hr or longer to determine amount of decomposition; no decomposition occurred unless specified. [c] Approximately 40% decomposition had occurred at 72 hr. [d] Meso isomer was detected by amino acid analysis. [e] 11% decomposition, yielding ammonia, at 20 hr; 45% loss of optical activity. [f] Disulfide interchange occurred; rotation data not meaningful.

The loss of optical rotation could not be attributed to racemization of the unsymmetrical disulfide, however, as we found that the interchange reaction is rapid compared to loss of rotation. In fact, within 1 hr, an equilibrium mixture of disulfides is produced. By chance, the molecular rotation of 8 (234°) is almost exactly half that of cystine (466°) in 6 *N* HCl. Therefore, conversion of two molecules of 8 into one molecule of cystine by disulfide interchange would not in itself cause a change in the magnitude of the measured rotation if no racemization occurred during the interval required for interchange. This reaction might be considered to have simply produced a solution of cystine which then racemized at its normal rate.

The experiment described above led to attempts to determine whether there is a mechanistic relationship between the disulfide interchange reaction and racemization. The mechanism of disulfide interchange in acid is not clearly understood. Initially, it was proposed that the reaction proceeded *via* a sulfenium ion mediated chain reaction.[7] More recent work[8] suggests that this mechanism is incorrect, as some evidence indicates that the rate-determining step involves nucleophilic displacement by acid anion on a sulfur activated by a prior electrophilic attack. In addition, homolytic cleavage and a resulting radical mechanism are known to occur under some conditions.[9] None of these mechanisms are consistent with all of the data; perhaps all are operative.

$$\text{initiation} \quad \mathrm{RSSR} + \mathrm{H}^+ \longrightarrow \mathrm{RSH} + \mathrm{RS}^+ \qquad (1)$$

$$\text{interchange} \quad \mathrm{RS}^+ + \mathrm{R'SSR'} \longrightarrow \mathrm{RSSR'} + \mathrm{R'S}^+ \qquad (2)$$



$$\mathrm{X}^- + \mathrm{RS}\overset{+}{\underset{\mathrm{H}}{\mathrm{S}}}\mathrm{R} \longrightarrow \mathrm{RSX} + \mathrm{RSH} \qquad (3)$$

In any case, cystine and most other disulfides are certainly undergoing some interchange reaction in acid solution. Demonstration of this interchange in a symmetrical disulfide such as cystine would require an isotopic labeling experiment, which has not been carried out. It has been shown, however, that *N,N'*-bis(2,4-dinitrophenyl)-cystine interchanges with cystine itself[10] and we have demonstrated the rapid interchange of cystine with diethyl disulfide. There is little doubt that interchange occurs upon heating cystine in acid. The question of a mechanistic relationship between this interchange reaction and racemization led to a new series of experiments.

Since it seemed that the disulfide linkage and/or its associated interchange intermediates might be in some way the source of the species prone to racemization, we attempted to uncouple the interchange and the racemization. That is, a set of experiments was designed to determine whether racemization could occur without interchange and vice versa.

Since the existence of a free radical interchange mechanism has not been eliminated, we attempted to inhibit a presumed homolytic interchange in order to study the effect of interchange inhibition on racemization rate. When 10 mol % of hydroquinone was added to *S*-(ethylthio)-L-cysteine (8) and the resulting solution was refluxed in 6 *N* HCl in the absence of air and light, the interchange rate was the same as that observed for a sample refluxed open to the air, in the light, and without the radical scavenger. Though this type of experiment is not completely conclusive, it must be interpreted to mean that either the interchange is not primarily free radical in mechanism or that our inhibition conditions were inadequate.

It has been noted in an earlier experiment that penicillamine disulfide does not racemize at a rate even near that of cystine. Yet penicillamine disulfide (7) differs from cystine only by inclusion of the β-methyl groups. Since β hydrogens are not necessary for the racemization is indicated by the isotope-exchange experiment, it was postulated that the methyl groups might, in some way, prevent the interchange reaction and thereby the racemization. We found that penicillamine disulfide (7) does, in fact undergo disulfide interchange but at a rate much slower than that of cystine. This was demonstrated by refluxing each of these disulfides in 6 *N* HCl to which a quantity of diethyl disulfide had been added. At intervals, the reaction mixtures were analyzed (by amino acid analysis) for the production of the corresponding unsymmetrical disulfides, the concentration of which, as a function of time, was a measure of interchange rate. It was found that cystine undergoes interchange with diethyl disulfide about ten times as fast as penicillamine disulfide does.

We have shown then, that the exchange rate and the racemization rate have a certain correlation. That is, penicillamine disulfide racemizes more slowly than cystine, and it also exchanges more slowly than cystine. This observation does not prove a direct relationship between the two reactions; however, a common intermediate may be involved in both racemization and interchange, with the activation energy for the interchange being lower than that for racemization.

A crossover experiment was conducted to determine whether the presence of the intermediates in the interchange reaction (*e.g.*, sulfenium ions) could induce racemization *via* intermolecular reaction. This experiment consisted of refluxing mixtures of racemic cystine with L-alanine, with L-cysteine, and with *S*-methyl-L-cysteine. In none of these three cases was there any evidence of an increased racemization rate. Therefore, the interchange intermediates are not capable of promoting racemization *via* an intermolecular reaction.

Both of the postulated ionic mechanisms for disulfide interchange in acid, though different, involve an intermediate in which the cysteinyl residue bears a full or partial positive charge on the sulfur atom. Thus, it is possible that the electron-withdrawing inductive effect of a charged sulfur atom at the β position might be sufficient to increase the acidity of the α proton enough to lead to racemization. The likelihood of such a proposal is buoyed by the fact that the proton on the chiral carbon is already exposed to the inductive effect of protonated, geminal amino and carboxyl groups. Thus, the combination of strong electron-withdrawing groups ($\mathrm{NH_3}^+$, S^+, COOH)[11] and the potential for stabilization of the conjugate base by acid enol formation may well be responsible for the rapid racemization of cystine. However, since one would not expect the disulfide to be more basic than the thio ether,[12] and since neither *S*-methyl-L-cysteine, the corresponding thioether, or cysteine, the corresponding mercaptan, racemize under conditions which racemize cystine, simple protonation of the β sulfur cannot be the source of the charged intermediate. This intermediate must then arise as a result of the interchange reaction, a path uniquely available to disulfides.

The hypothesis above would predict that 2,3-diaminopropionic acid (12) should racemize as rapidly as cystine, if not faster. Consistent with the hypothesis, 2,3-diaminopropionic acid was found to racemize at a dramatic rate. In addition, the insulating effect of a single methylene group, as in 2,4-diaminobutyric acid (13), renders the molecule inert to racemization. This observation is consistent with the similar observations on cystine and homocystine. It is also consistent with the observation that phenylglycine (17) racemizes while phenylalanine (18) does not. In the case of **17**, the acid enol is stabilized by phenyl conjugation, resulting in rapid racemization. In **18**, insulation by the methylene group is sufficient to confer optical stability.

The extent to which the sulfur must carry charge is demonstrated in the observation that *S*-(2,4-dinitrophenyl)-L-cysteine (14) racemizes at a rate only slightly slower than that of cystine. Since cysteine itself does not racemize, it is difficult to postulate a mechanism that does not depend upon the influence of the charged sulfur. It would seem that the rate may be dependent upon the degree of charge induction and that the actual cystine intermediate must have a degree of charge somewhere between that induced by the 2,4-dinitrophenyl group and the full charge on the protonated nitrogen of 2,3-diaminopropionic acid.

In summary, it is proposed that in refluxing 6 *N* HCl, cystine is undergoing fairly rapid disulfide interchange and that some intermediate in this exchange reaction carries at least a partial positive charge on sulfur. The combined inductive effect of geminal carboxyl and protonated amino groups together with the added boost from this charged sulfur renders the α proton sufficiently acidic to allow acid enol formation, resulting in racemization. The racemization reaction is far slower than the interchange reaction but factors which increase or decrease the interchange rate likewise affect the racemization rate.

Experimental Section

Melting points are uncorrected. Amino acid analyses were performed on a Beckman Model 120C amino acid analyzer. Optical rotations were obtained on a Bendix ETL-NPL automatic polarimeter, Type 143A, using an all-glass 2-cm cell. Elemental analyses were performed by the Analytical Laboratory, University of California, Berkeley.

Materials. L-Methionine, L-cystine, D-penicillamine, L-cysteine, L-aspartic acid, L-glutamic acid, L-2,4-diaminobutyric acid, L-lysine, and L-phenylglycine were obtained from commercial sources and used as supplied. The following amino acids were synthesized by standard literature procedures.

D-Penicillamine disulfide (7) was prepared by O_2 oxidation of D-penicillamine,[13] mp 199–201° (lit.[14] mp 204–205°).

S-Methyl-L-cysteine (3) had mp 240° (lit.[15] mp 247–248°), $[\alpha]^{20}{}_{\rm D}$ − 10° (*c* 1, 1 *N* HCl) [lit.[13] $[\alpha]^{20}{}_{\rm D}$ − 9.6° (*c* 1, 1 *N* HCl)].

L-Lanthionine (5) was prepared from serine and cysteine, mp 297–299° (lit.[16] mp 293–295°), $[\alpha]^{20}{}_{\rm D}$ + 6° (*c* 1, 1 *N* NaOH) [lit.[16] $[\alpha]^{20}{}_{\rm D}$ + 6° (*c* 1, 1 *N* NaOH)].

L-Cystathionine (4) had $[\alpha]^{20}{}_{\rm D}$ − 21.5° (*c* 1, 1 *N* HCl) [lit.[17] $[\alpha]^{20}{}_{\rm D}$ − 23.5° (c 1, 1 *N* HCl)].

S-(2,4-Dinitrophenyl)-L-cysteine hydrochloride (14) was prepared from cysteine and 2,4-dinitrofluorobenzene at pH 4.2.[18] Further purification was necessary by cation-exchange chromatography (Bio-Rad AG50W-X8, H^+ form, 200–400 mesh), mp 180–181° (lit.[18] mp 182–184°), $[\alpha]^{20}{}_{\rm D}$ + 82° (*c* 1, 6 *N* HCl).

L-Homocysteine had mp 255–265° (lit.[19] mp 281–284°), $[\alpha]^{20}{}_{\rm D}$ + 69° (*c* 1, 1 *N* HCl) [lit.[19] $[\alpha]^{20}{}_{\rm D}$ + 79° (c 1, 1 *N* HCl)].

L-2,3-Diaminopropionic acid (12) was purified by cation-exchange chromatography (Bio-Rad AG50W-X8, H^+ form, 200–400 mesh), $[\alpha]^{20}{}_{\rm D}$ + 22.5° (*c* 1, 1 *N* HCl) [lit.[20] $[\alpha]^{20}{}_{\rm D}$ + 25° (c 1, 1 *N* HCl)].

S-(Ethylthio)-L-cysteine (8) was prepared by reaction of cysteine with diethyl sulfenyl thiocarbonate.[21] Cysteine hydrochloride monohydrate (8.73 g, 50 mmol) was added to 100 ml of ethanol–water (2:1). To this solution was added diethyl sulfenyl thiocarbonate (8.4 g, 50 mmol) dissolved in 50 ml of ethanol and the reaction mixture was stirred vigorously under nitrogen at room temperature after 3 drops of triethylamine was added. Stirring was continued for 5 hr followed by evaporation of the solvent and crystallization of the residue from aqueous ethanol, yield 5 g, mp 190–193°, $[\alpha]^{20}{}_{\rm D}$ + 129° (*c* 1.5, 6 *N* HCl).

Anal. Calcd for $C_5H_{11}NO_2S_2$: C, 33.1; H, 6.1; N, 7.7; S, 35.4. Found: C, 33.2; H, 6.1; N, 7.7; S, 35.2.

Ethyl penicillamine disulfide (15) was prepared essentially as 8, in methanol at 50° for 7 hr, from D-penicillamine hydrochloride (5.07 g, 27 mmol) and diethyl sulfenyl thiocarbonate (4.53 g, 27 mmol) and was crystallized from ethanol–ether, mp 148–151°, $[\alpha]^{20}{}_{\rm D}$ + 111° (*c* 1, 1 *N* HCl).

Anal. Calcd for $C_7H_{16}NO_2S_2Cl$ (0.6 mole fraction as HCl salt): C, 36.7; H, 6.8; N, 6.1. Found: C, 36.9; H, 7.1; N, 5.9.

$DCl–D_2O$ was prepared essentially as described,[22] except that both SO_2 traps were at Dry Ice temperature and the $DCl–D_2O$ was boiled to remove residual SO_2. Nmr of the $DCl–D_2O$ solution showed it to be as isotopically pure as the D_2O used in the hydrolysis, 99.8%.

Table II
Rates of Disulfide Interchange with $CH_3CH_2SSCH_2CH_3$

Time, min	% of cystine (1) interchanged	% of penicillamine disulfide (7) interchanged
0	0	0
5	10	1
10	24	4
20	39	9
77	42	27
192	42	51

Racemization Rate Studies. In a typical experiment, 100 ml of 6 *N* HCl in a round-bottom flask equipped with reflux condenser was brought to reflux (110°) in a thermostated (120°) oil bath. The flask was removed from the bath and cooled to about 100°, and about 1.0 g of the amino acid was added; immediately the flask was returned to the oil bath, whereupon refluxing ensued within a few minutes. All of the amino acid dissolved within the first few minutes and, as soon as solution was effected, a 5-ml aliquot was removed and cooled to room temperature in an ice bath, and the initial rotation measured. Subsequent aliquots were obtained and their rotations were measured in a similar manner.

Rates of Disulfide Interchange. The relative rates of disulfide interchange between cystine (1) and penicillamine disulfide (7) and diethyl disulfide were measured in the following manner. Disulfide 1 (0.25 g) or 7 (0.31 g) was placed in 25 ml of 6 *N* HCl and the solution was brought to reflux (110°) in a thermostated (120°) oil bath. At time $t = 0$, pure diethyl disulfide (1.1 g) was injected by syringe into the refluxing solution and the flask was shaken. Some of the diethyl disulfide dissolved, but the solution remained heterogeneous. An aliquot of the aqueous solution was removed at the appropriate time, cooled to about 0°, diluted (1:20 in pH 2.2 buffer), and immediately placed on the column of the amino acid analyzer. The results of these disulfide interchange studies are given in Table II.

Registry No.—**1**, 56-89-3; **2**, 52-90-4; **3**, 1187-84-4; **4**, 6899-07-6; **5**, 922-55-4; **6**, 462-10-2; **7**, 20902-45-8; **8**, 17885-24-4; **9**, 56-84-8; **10**, 56-86-0; **11**, 56-87-1; **12**, 4033-39-0; **13**, 1758-80-1; **14**, 23815-63-6; **15**, 38261-80-2; **16**, 63-68-3; **17**, 2935-35-5; **18**, 63-91-2; diethyl sulfenyl thiocarbonate, 30453-25-9; L-cysteine hydrochloride, 52-89-1; D-penicillamine hydrochloride, 2219-30-9; diethyl disulfide, 110-81-6.

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Occurrence of Gas Phase Ammonolysis during Chemical Ionization Mass Spectrometry

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Ammonolysis of base-sensitive bonds such as lactone, ester, and amide bonds has been found to occur under chemical ionization mass spectrometry conditions. This reaction occurs in the mass spectra of (1) the antimycin A complex, (2) a synthetic precursor of antimycin A_3, and (3) proline dipeptides. The role that ammonolysis in CI played in the structural elucidation of the minor components of the antimycin A complex is discussed. The conditions in the ion source of the mass spectrometer ensure that a several hundredfold excess of ammonia over sample is maintained during the course of vaporizing the sample.

While investigating the antimycin A complex[1b-8] by mass spectrometry, we compared the electron ionization (EI) and chemical ionization (CI) mass spectra of this complex. Instead of the typically "clean" CI spectrum that one normally obtains when ammonia is used as a reagent gas[9-12] (proton affinity of NH_3 207 ± 3 kcal/mol[13]), as many peaks were found in the CI spectrum with ammonia as the reagent gas as in the EI spectrum. This can only be rationalized by the occurrence of gas phase ammonolysis: new compounds (amides) are formed in the ion source which then subsequently are protonated by the ammonia ion–molecule reaction products[12] to produce protonated molecular ions. Accordingly, we investigated the occurrence of gas phase ammonolysis in the CI spectra of (1) the antimycin A complex, (2) a synthetic precurser of antimycin A_3[14,15] which does not contain any homologs, and (3) a series of proline dipeptides.

The observance of gas phase ammonolysis products was especially useful in the case of the antimycin A complex. This complex is composed of a mixture of homologous compounds, due to the presence of two alkyl side chains (structure I). While investigating the EI spectra of this complex, we found that each molecular species consists of one to four components.[16] These constituents are extremely difficult to separate.[5,6] With methane as a reagent gas for CI, adduct ions were obtained which differed by 28 amu (just as every other homolog did), whereas ammonia helped to establish the molecular ions, as each molecular species is indicated by $[M + 1]^+$ and $[M + 18]^+$ ions.[12]

Results and Discussion

The Antimycin A Complex. Figure 1a contains the EI mass spectrum of the antimycin A complex (I). Scheme I rationalizes the genesis of the indicated ions. These data have also been confirmed by the mass spectra of II–V.

Figure 1b contains the CI spectrum of I. By comparing the two mass spectra it is apparent that all of the ions in the molecular ion region of the EI spectrum have shifted 1 and 18 amu in the CI spectrum. This shift provides sufficient information to determine which molecular components are present in the complex by the analysis of the $[M + H]^+$ and $[M + NH_4]^+$ ions shown in Table I. The quantity $(R_3 + R_4)$ is a convenient representation of the sum of the number of carbon atoms present in the two aliphatic side chains, R_3 and R_4, as shown in Scheme II.

The "shift" of fragment ions by either 17 or 18 amu is the indication that ammonolysis is occurring. The intact molecule (I) contains five potential sites where ammonolysis of a base-sensitive bond may occur—two lactone, one ester, and two amide bonds. For example, the amide bond next to the nine-membered ring is one of the potential sites. If ammonolysis takes place, the ion found at *m/e* 164 would "shift" 17 amu (owing to the addition of an $-NH_2$ moiety followed by protonation) to form the molecular ion u at *m/e* 181. In Figure 1b, we observe the appropriate shift.

Table I

No. of carbons $(R_3 + R_4)$	*m/e* $(M + 1)^+$	*m/e* $(M + 18)^+$
5	479	
6	493	510
7	507	524
8	521	538
9	535	552
10	549	566
11	563	580
12	577	594

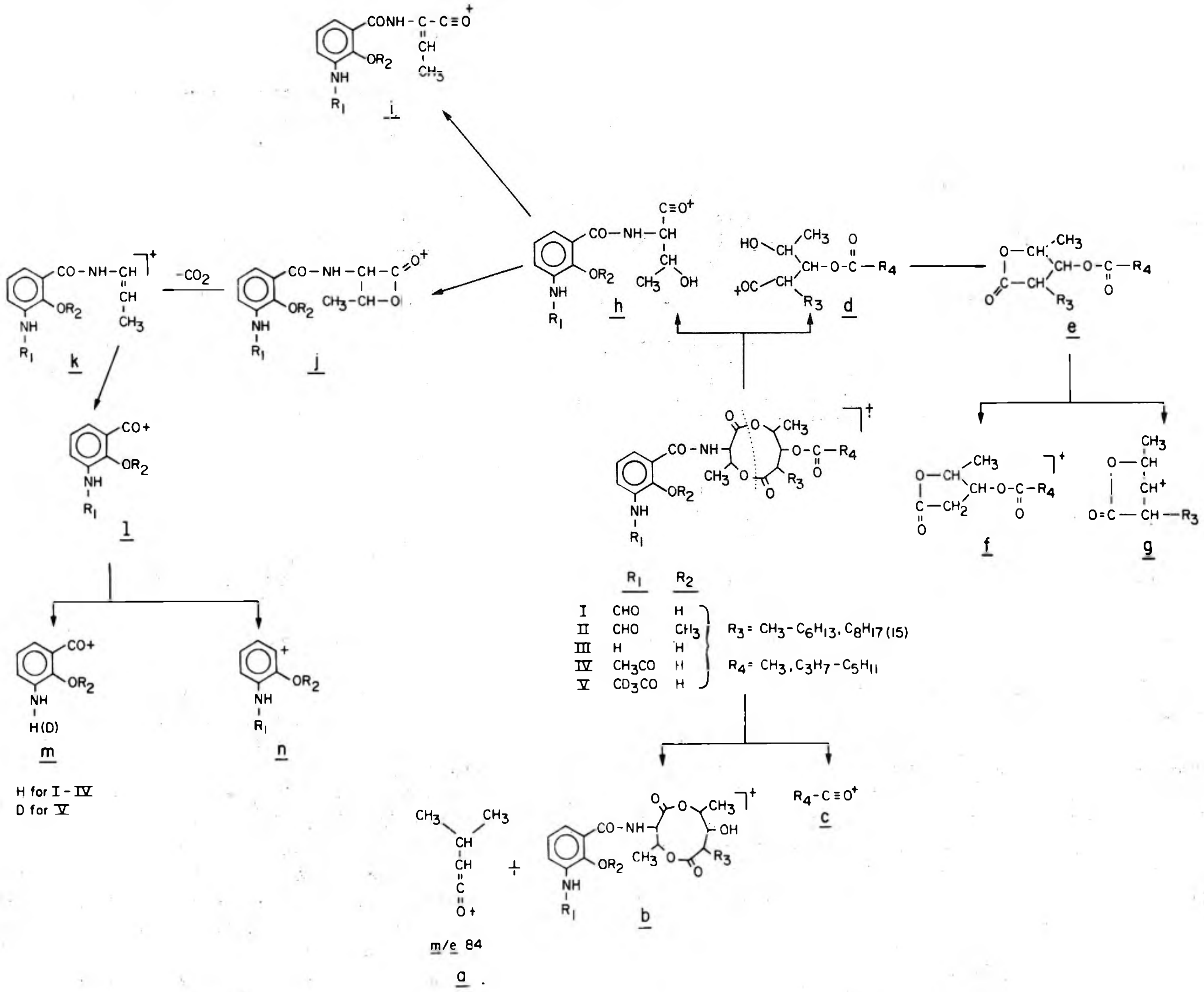
An interesting reaction occurs with the asymmetrically disubstituted dilactone ring of antimycin A. The two extremely labile lactone bonds both undergo ammonolysis to form two hydroxy amides, which after protonation form the molecular ions r and s (see labeled peaks in Figure 1b). In order to obtain corroborative evidence that ammonolysis is occurring, the CI spectrum was also run with ND_3 as the reagent gas, whereupon the appropriate shift in mass occurred. (For example, *m/e* 274 → 278 is a shift of 4 amu and is composed of two deuteriums on the $-ND_2$ group from the reagent gas, the deuterium on the -OD group, and a deuterium to deuterate the molecule.)

The other moiety formed after ammonolysis of the dilactone ring and protonation is the molecular ion s, *m/e* 282, which readily loses NH_3 to form the more stable lactone t at *m/e* 265.

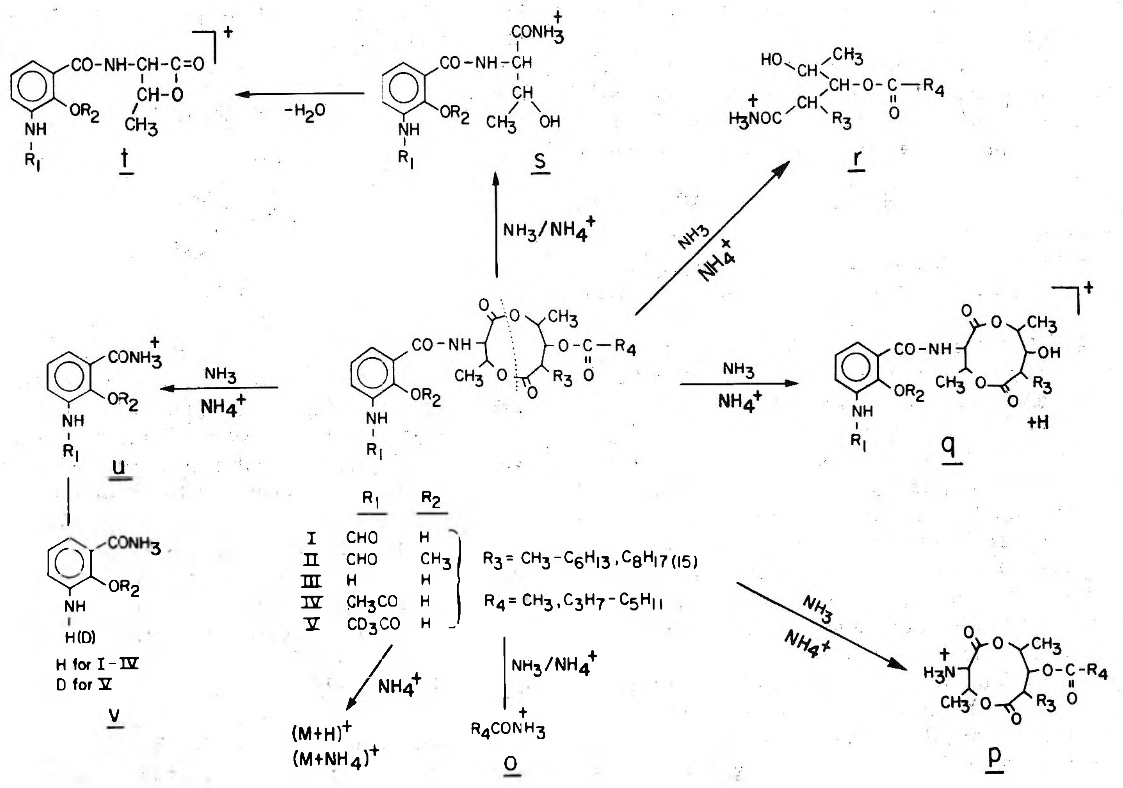
The ions which are found in Figure 1b do not represent extensive fragmentation of the molecule, but rather, every peak in this mass spectrum represents a molecular ion. That some of these ions are still low in abundance is due to their low concentration in the antimycin A complex.[1b] Generally the abundance of these ions is much greater in the CI spectrum (as compared to the corresponding ions in the EI spectrum) because they do represent nonfragmented molecular ions. With ammonia as a reagent gas, the sensitivity toward nitrogen-containing compounds (or conjugated compounds) is higher in that these compounds represent stronger Brønsted acids than the reactant ion NH_4^+.

Ammonolysis can be shown to occur in a base-labile compound that cleaves into two moieties of different molecular weights followed by the detection of both species. A model compound containing no homologs was reported during the total synthesis of antimycin A_3 and its diastereoisomer.[14,15] This compound is the benzoxycarbonyl derivative of the dilactone ring in structure I and is (−)-(3*S*,4*R*,7*S*,8*S*,9*R*)-3-benzyloxycarboxamido-7-butyl-4,9-di-

Scheme I



Scheme II



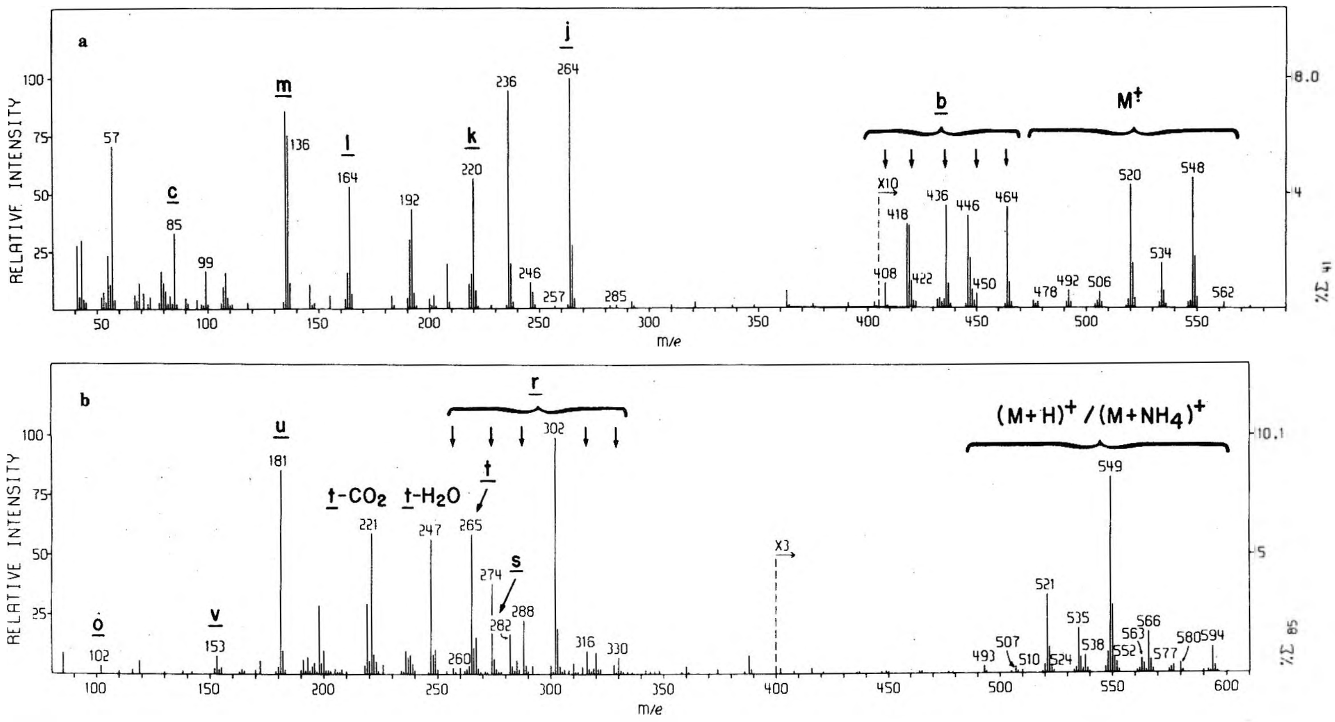


Figure 1. (a) EI mass spectrum of antimycin A complex (I); (b) CI (NH_3) mass spectrum of antimycin A complex (I).

methyl-1,5-dioxa-8-isovaleryloxycyclononane-2,6-dione (VI, Scheme III).

The *m/e* values and the relative intensities from the CI mass spectrum of VI with ND_3 as the reagent gas are given in Scheme III. The molecular weight (M) of VI is 491 amu. With ND_3 as the reagent gas, exchange of the amide hydrogen occurs quantitatively. Deuteration then produces the ion at *m/e* 494 (5%), while addition of ND_4^+ produces the base peak at *m/e* 514. Opening of the dilactone ring only at one point and subsequent deuteration yields the two molecular ions w and x at *m/e* 514, coincident in mass with the $[M + ND_4]^+$ ions (see Scheme III).

Ammonolysis of the amide bond in VI followed by deuteration produces ion y at *m/e* 361 (20%). The other product of this reaction is the unstable carbamic acid ester (ion z), which is not found.

The base-sensitive dilactone ring of VI undergoes ammonolysis to generate, after deuteration, ions aa (80%) and ab (15%) at *m/e* 278 and 258, respectively. (Some of the ion current at *m/e* 278 may be due to the addition of ND_4^+ to ab.)

Ammonolysis of the aliphatic ester bond of VI does not seem to occur owing to the absence of ions ac and ad. This could be explained by the greater stability of the aliphatic ester bond in comparison to the more base-labile dilactone ring.

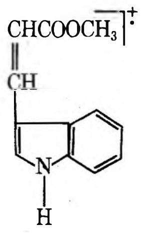
It is interesting to make some general observations concerning the spectra in Figures 1a, 1b, and 2 and Scheme III. For example, the more abundant ion species in the EI spectrum (Figure 1a) are due to the aromatic portion containing ions, such as those occurring at *m/e* 264, 220, 164, and 136, whereas the aliphatic ions (Scheme I, d, e, f, and g) are quite small. On the other hand, the situation is quite different in the CI spectrum (Figure 1b). For example, r in Scheme II accounts for the family of abundant ions at *m/e* 260, 274, 288, 302, 316, and 330 in Figure 1b.

The characteristic abundant ions of the EI spectra reflect the presence of the aromatic portion in the antimycin A complex. An ion structure such as j (Scheme I) could quite easily be ionized by the removal of an electron.

In CI, however, with NH_3 as the reagent gas, protonation can occur only with a molecule having a higher proton affinity than NH_3. This means that the corresponding molecule to ion r has a higher proton affinity than NH_3, and therefore is more abundant (see Figure 1b) in CI as opposed to EI (Figure 1a).

Proline Dipeptides. The CI mass spectra (with NH_3) of the following eight dipeptides N^{α}-acetyl-Pro-X-methyl ester, where X = glycyl, alanyl, seryl (-OMe), leucyl, methionyl, phenylalanyl, tyrosyl (-OMe), and tryptophyl residues, showed that ammonolysis of the peptide bond occurs, too. For purposes of illustration, the Pro-Trp dipeptide will serve as an example.

The EI mass spectrum of *N*-acetylprolyltryptophanmethyl ester (VIII) is given in Figure 2a. The molecular ion occurs at *m/e* 357 and $[M - 31]^+$ at *m/e* 326. The large ion at *m/e* 201 occurs *via* a McLafferty rearrangement of the β hydrogen on the Trp side chain resulting in ion ae.



ae, *m/e* 201

The other ions are represented in the fragmentation pattern given in Figure 2a. The small ion at *m/e* 157 is due to cleavage of the N^{α}–C^{α} bond at the Trp residue, with migration of two hydrogen atoms, which then would eliminate ammonia to produce the amino acyl fragment at *m/e* 140.[16]

In each one of the CI mass spectra of the dipeptides with NH_3 as the reagent gas, the ion at *m/e* 157 was dominant. As cleavage of the N^{α}–C^{α} bond is energetically unfavorable under CI conditions with ammonia as the reagent gas, ammonolysis of the peptide bond occurred to produce ions af and ag.

The CI mass spectrum of VII, with ND_3 as the reagent gas, is presented in Figure 2b. The $[M + D]^+$ ion is observed at *m/e* 361. The molecular weight is 357 amu.

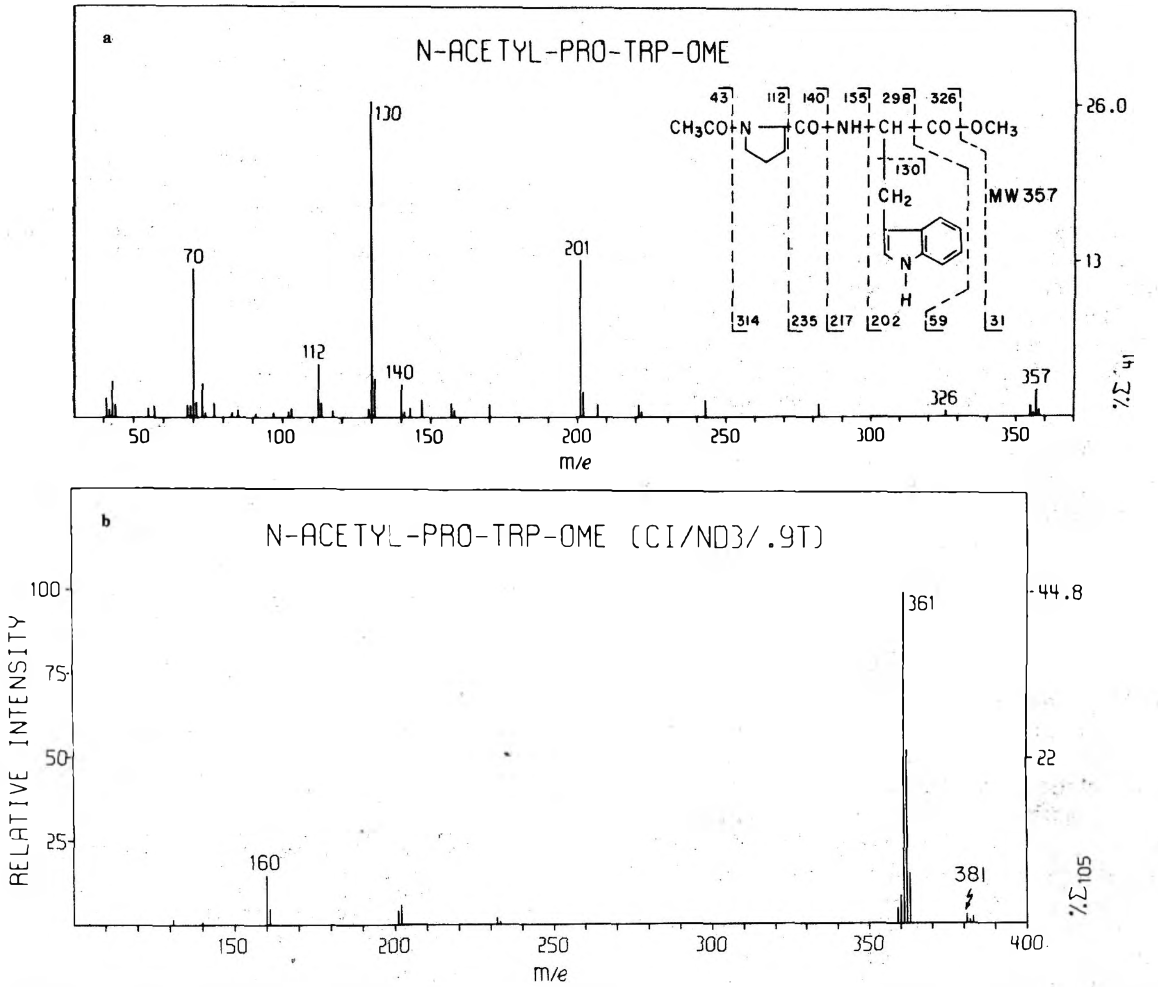
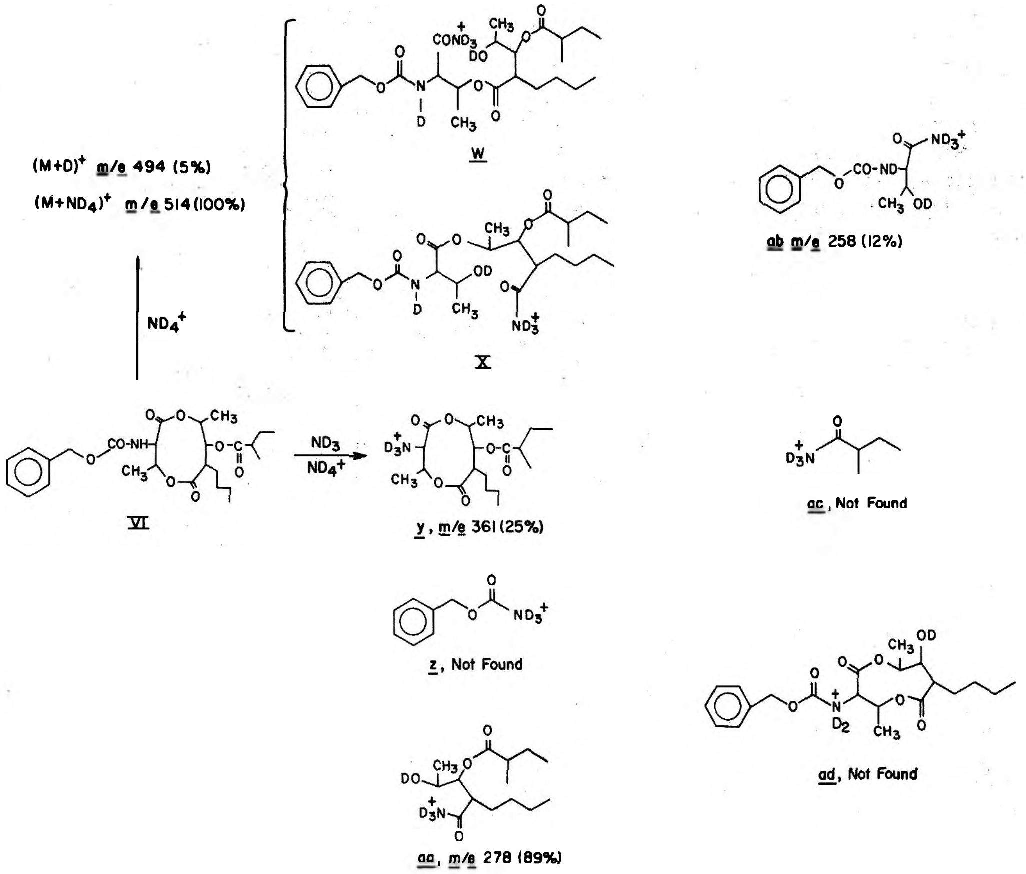
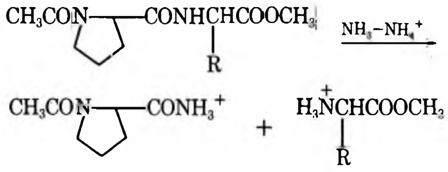


Figure 2. (a) EI mass spectrum of N-acetylated prolyltryptophan methyl ester (VII); (b) CI (ND_3) mass spectrum of N-acetylated prolyltryptophan methyl ester (VII).

Scheme III



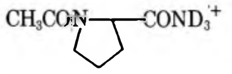


af, *m/e* 157

ag

(Two hydrogens exchange for deuterium atoms, most probably the hydrogens on the indole nitrogen and on the amide bond nitrogen. This exchange is followed by deuteration.) The adduct ion $[M + ND_4]^+$ occurs at *m/e* 381. The McLafferty rearrangement ion (ae) remains at *m/e* 201, with the satellite peak *m/e* 202 caused by deuterium scrambling of the indole hydrogen or by deamination of ag.

Under the low-energy conditions of CI, the ion at *m/e* 160 is persistently found as an abundant ion in all eight dipeptide spectra.



ah, *m/e* 160

Conclusions

The data presented above show that ammonolysis of a variety of chemical bonds occurs under CI mass spectrometry conditions. The chemical bonds affected are amide, ester, and lactone bonds. As these types of bonds are base sensitive in solution chemistry, it is not surprising that ammonolysis in the gas phase occurs. Indeed, in solution chemistry, dipeptide amides are synthesized by subjecting diketopiperazines to ammonolysis.[17]

A sufficient molar excess of NH_3 in the ion source of the mass spectrometer exists to ensure that reaction would proceed to the formation of the ammonolysis products. At a pressure of 1 Torr NH_3 in the source at 500°K, 50 μmol of NH_3 are present. By means of a heated direct introduction probe, a total amount of 10 μmol of the sample is introduced into the ion source over a period of 100–300 sec. Under normal operating conditions, a continual molar excess of several hundredfold of NH_3 over sample is assured.

Ammonolysis of base-sensitive bonds (a reaction which is standard in solution chemistry) has never been reported before to occur under the conditions of CI mass spectrometry. The conditions employed in this study are typical for CI mass spectrometry and have been utilized by others to study other classes of compounds.[10,11]

Experimental Section

The proline dipeptides were purchased from Fox Chemical Co., Los Angeles, Calif., or Sigma Chemical Co., St. Louis, Mo. They were acetylated in methanol–acetic anhydride (4:1) for 4 hr.[18] The esterification was completed by reaction with diazomethane.

The antimycin A complex was purchased from Nutritional Biochemicals Co., Cleveland, Ohio, and acetylated and methylated as above. Deformylation was done by treating a methanolic solution with concentrated HCl.[2] Compound VI was kindly provided by Dr. Mitsuhiro Kinoshita, Keio University, Yokahama, Japan.

CI mass spectra were obtained with a CEC 21-110 B (lot 9) instrument, modified for high-pressure work.[19] Ammonia and methane pressures were 0.1–0.9 Torr, as measured with a hollow probe connected to a capacitance manometer (MKS Instruments, Inc., Burlington, Mass.). Instrumental conditions follow: ionizing voltage, 200 eV; ionizing current, 200 μA (total, unregulated); accelerating voltage, −8.4 kV; magnetic scanning. The repeller voltage was set at 0 V/cm. Source temperature varied from 105 to 225°, depending upon the temperature necessary to vaporize each individual sample.

Ammonia and methane were of research grade and were purchased from Matheson LaPorte, Tex.

Low-resolution (EI) mass spectra were obtained on an LKB 9000. Samples were introduced on a direct introduction probe (ionizing voltage, 70 eV; ionizing current, 60 μA; accelerating voltage, −3.5 kV; source temperature 270°; probe temperature, 130–140°).

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Registry No.—I, 50858-98-5; VII, 50803-85-5.

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Micellar Catalysis of Ester Hydrolysis. The Influence of Chirality and Head Group Structure in "Simple" Surfactants

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d-, *l*-, and *dl*-*p*-nitrophenyl α-methoxyphenylacetates (I) were hydrolyzed at pH 7.0, 8.0, and 9.0 in aqueous micellar solutions of cetyltrimethylammonium bromide, *N*-benzyl-*N*-cetyldimethylammonium bromide, *d*-, *l*-, and *dl*-*N*-α-methylbenzyl-*N*,*N*-dimethylcetylammonium bromide, and *d*-, *l*-, and *dl*-*N*-α-methyl-*p*-methoxybenzyl-*N*,*N*-dimethylcetylammonium bromide. Rate constants for the pseudo-first-order hydrolyses reveal significant micellar catalysis, but limited dependence on head group structure, and no substantial stereoselectivity. Similar results were obtained in hydrolyses of I catalyzed by inverse (*n*-hexyl alcohol–water) micellar solutions of the same surfactants. The uv spectra of *N*-*n*-tetradecyl-2,4-dinitroaniline, solubilized in the various surfactant solutions, afforded a measure of the "polarity" of the micellar Stern layers.

The catalysis of organic reactions by surfactant micelles is an area of great endeavor.[3] Many organic reactions have now been examined, and attention is turning toward the influence of surfactant structure on catalytic efficiency. Particularly because of the often-cited enzyme–micelle analogy,[3,4] the question of chirality has become topical.

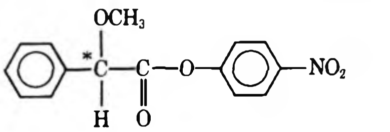
There has been little study of stereochemical effects in micelle-catalyzed reactions, and our demonstration of micellar control of stereochemistry in the nitrous acid deamination reaction appears to have been the first such report.[5,6] More recently, catalysis of the mutarotation of 2,3,4,6-tetramethyl-α-D-glucose by inverse micelles has been reported.[7]

Of very direct concern to us was the communication by Bunton, Robinson, and Stam of the stereoselective hydrolysis of *d*- or *l*-*p*-nitrophenyl α-methoxyphenylacetate catalyzed by surfactants derived from D-(−)-ephedrine.[8] This was the first report of catalytic interaction between chiral micellar reagents and chiral substrates,[9] and coincided with our own developing interests.[10]

Here, we present a full report of some micelle-catalyzed hydrolyses of optically active and racemic *p*-nitrophenyl α-methoxyphenylacetate. We employed rather simple surfactants in this initial study, and considered the effects of structural variation of the surfactant head group and of the introduction of a *single* center of chirality. The micellar catalysts were examined under normal (aqueous) conditions, and, briefly, under nonaqueous (inverse micelle) conditions.

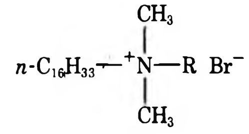
Results

Synthesis. The substrates were *d*-, *l*-, and *dl*-*p*-nitrophenyl α-methoxyphenylacetate (I). Racemic or optically active mandelic acids were O-methylated with dimethyl sulfate in aqueous sodium hydroxide solution; the methoxy acids were converted to the acid chlorides with oxalyl chloride, whereupon treatment with *p*-nitrophenol in toluene and pyridine afforded I. The *d*- and *l*-α-methoxyphenylacetic acids, from which the esters were obtained, were >99% optically pure, and subsequent hydrolysis of *d*-I, followed by reisolation of the *d*-α-methoxyphenylacetic acid, demonstrated that optical purity had been preserved to >96% in the acid → ester sequence.[11]



I

The surfactants were all of the general form II, and are described in Table I.



$$n\text{-}C_{16}H_{33}\text{—}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{\overset{|}{\underset{|}{{}^+N}}}}\text{—R}\ Br^-$$

II

Surfactant IIb was prepared from *N*,*N*-dimethylbenzylamine and cetyl bromide in refluxing acetone. The catalysts of the *N*-α-methylbenzyl-*N*,*N*-dimethylcetylammonium bromide series (IIc) were prepared from the appropriate *d*-, *l*-, or *dl*-α-methylbenzylamine by dimethylation,[12] followed by reaction with cetyl bromide in refluxing ethanol. The active amines were >97% optically pure, and it is assumed that this holds for the resulting surfactants. The catalysts of the MeO-16 (IId) series were prepared from cetyl bromide and *N*,*N*-dimethyl-α-methyl-*p*-methoxybenzylamine, which was obtained from *p*-methoxyacetophenone by a Leuckart reaction, followed by dimethylation.[12] *d*- or *l*-α-methyl-*p*-methoxybenzylamines were derived from the racemate by fractional crystallization (respectively) of the *d*- or *l*-tartrate salts. The amines, and hence *l*-IId and *d*-IId, were at least 85% optically pure.[11]

All of the surfactants were purified by repetitive crystallizations, and log [surfactant] *vs.* surface tension graphs did not display minima.

Table I
Surfactants and Their Critical Micelle Concentrations

Compd	R	Abbreviation	Cmc, $M \times 10^4$ [a]
IIa	CH_3	CTA-Br	8.6[b]
IIb	$CH_2C_6H_5$	CBzDA-Br	2.73 ± 0.15[c]
dl-IIc	$CH(CH_3)C_6H_5$	*dl*-16	2.73 ± 0.11
l-IIc	$CH(CH_3)C_6H_5$	*l*-16	2.08 ± 0.06
d-IIc	$CH(CH_3)C_6H_5$	*d*-16	2.29 ± 0.11
dl-IId	$CH(CH_3)$-*p*-$CH_3OC_6H_4$	*dl*-MeO-16	1.56 ± 0.07
l-IId	$CH(CH_3)$-*p*-$CH_3OC_6H_4$	*l*-MeO-16	1.43 ± 0.10
d-IId	$CH(CH_3)$-*p*-$CH_3OC_6H_4$	*d*-MeO-16	1.46 ± 0.09

[a] Determined in distilled water, resistivity >1.5 × 10^6 ohm cm from graphs of surface tension *vs.* log [surfactant]. Measurements were made with a Fisher automatic surface Tensiomat on solutions maintained at 31.0°. The results are mean values of three runs on separately prepared stock solutions, unless otherwise noted. Errors are average deviations from the means. Details of the experimental method appear in ref 5 (Moss, Talkowski, Reger, and Powell) and 10. [b] Single run. Literature values are 8 × 10^{-4} *M* [C. A. Bunton and L. Robinson, *J. Org. Chem.*, **34,** 773 (1969)] and 9.2 × 10^{-4} *M* (ref 3b). [c] Two determinations.

Table II
Maximum Pseudo-First-Order Rate Constants (sec^{-1}) for Micellar Hydrolysis of Ester I[a]

			$10^2 k_\psi^{max}$ at pH			
Case	Substrate	Surfactant[b]	9.0	8.0	7.0	8.0 − 7.0[c]
1	*dl*-I	CTA-Br	2.94[d]	0.332	0.147	0.185
2	*dl*-I	CBzDA-Br	2.92[e]	0.330[e]	0.152[e]	0.178
3	*dl*-I	*dl*-16	2.24	0.265	0.121	0.153
4	*dl*-I	*dl*-MeO-16	2.02	0.252	0.118	0.134
5	*dl*-I	*l*-16	*f*	0.271	0.133	0.138
6	*l*-I	*dl*-16	2.70	0.252	0.136	0.116
7	*l*-I	*l*-16	2.49	0.271	0.135	0.136
8	*l*-I[g]	*d*-16	2.47	0.267	0.139	0.128
9	*dl*-I	*l*-MeO-16	*h*	0.233	0.115	0.118
10	*l*-I	*dl*-MeO-16	2.10	0.221	0.113	0.108
11	*l*-I	*l*-MeO-16	2.04	0.223	0.108	0.115
12	*l*-I	*d*-MeO-16	2.07	0.236	0.109	0.127

[a] See the text and the Experimental Section for details of the measurements. From duplicate runs, and from the scatter of the k values in the plateau region, we estimate that the rate constants are reproducible to ±3%. [b] See Table I for surfactant abbreviations. [c] The difference in rate constants at pH 8.0 and 7.0 is recorded as a reflection of the *base-catalyzed* process at pH 8.0. [d] Reference 8 gives ~4.9×10^{-2} sec^{-1} in 0.01 M sodium borate buffer. The discrepancy may have to do with differing buffer concentration *and* quality; this is amplified in the Discussion. All of the rate constants of Table II were determined with a single lot of Fisher Certified buffer, and within several weeks. [e] The plateau rate constant could not be determined owing to limited surfactant solubility. The quoted value is therefore not necessarily a maximum. [f] See text. [g] The following additional k_ψ^{max} values were determined at pH 9: *d*-I in *d*-16, 0.0240 sec^{-1}; *d*-I in *l*-16, 0.0235 sec^{-1}. [h] Not determined.

Kinetic Results, Normal Micelles. Pseudo-first-order hydrolysis of I was followed spectrophotometrically by monitoring the appearance of *p*-nitrophenoxide at 400 nm. Runs were carried out at 25.0 ± 0.2°, in buffered aqueous solutions which contained 2.0×10^{-5} M substrate and 0.5% (volume) of purified dioxane. Hydrolysis studies were conducted at pH 9.0 (0.005 M borate buffer) and at pH 8.0 and 7.0 (0.01 M phosphate buffers).

At pH 8.0 and 9.0, runs were done at several surfactant concentrations, so as to derive a rate constant *vs.* [surfactant] profile. The profiles were of the expected form;[3b] *viz.*, the rate constant increased sharply as [surfactant] exceeded the cmc, and then reached a maximum at higher surfactant concentrations (~10 cmc). At still higher [surfactant], inhibition was observed. Plateau values of k_ψ were generally encountered at $1.5\text{-}3.0 \times 10^{-3}$ M surfactant, and are taken as ~k_m, the hydrolytic rate constants in the micellar phase. pH 7.0 rate constants were determined only at the [surfactant] corresponding to k_ψ^{max} at pH 8.0. Table II contains the data.

Base values for *noncatalyzed* hydrolyses of I (k_0) were determined from runs carried out in the appropriate buffer solution but *without* added surfactant. We found $k_0 = 2.76 \times 10^{-3}$ and 4.06×10^{-4} sec^{-1} for hydrolyses of *dl*-I at pH 9.0 and 8.0, respectively. The former value is to be compared with 4.8×10^{-3}, which can be measured from Figure 1 of ref 8. (See footnote *d*, Table II.) The catalytic effectiveness (k^{max}/k_0) of the various micellar systems is given in Table III.

Kinetic Results, Inverse Micelles. Friberg and coworkers reported that certain compositions of CTA-Br, *n*-hexyl alcohol, and water yielded inverse CTA-Br micelles which catalyzed the basic hydrolysis of *p*-nitrophenyl esters.[13] These ternary catalytic systems are complicated, and the microenvironment of the components strongly depends on their relative proportions.[14] For example, in 1:4.5 mixtures of CTA-Br:H_2O, in *n*-hexyl alcohol, the *n*-hexyl alcohol serves as an intermicellar liquid for inverse CTA-Br micelles with hydrated polar cores.

We carried out a brief study of the hydrolysis of I in several *n*-hexyl alcohol–water–surfactant systems. However, in the absence of a complete phase-diagram study of the new ternary systems, the exact state of the catalytic species present in our apparently homogeneous solutions (*i.e.*, inverse micelles, smaller hydrated ionic aggregates, or hydrated ion pairs) remains uncertain.

Table III
Effectiveness of the Micellar Catalysts. Hydrolysis of *dl*-I[a]

	k_ψ^{max}/k_0	
Surfactant	pH 9.0	pH 8.0
CTA-Br	10.7	8.17
CBzDA-Br	10.6[b]	8.12[b]
dl-16	8.11	6.52
dl-MeO-16	7.32	6.20

[a] k_ψ^{max} values are from Table II. For surfactant abbreviations, see Table I. [b] See footnote *e*, Table II.

Table IV
Hydrolysis of *dl*-I in Inverse Micelles[a]

Surfactant	$10^2 k_{obsd}$, sec^{-1}
CTA-Br	2.67
CBzDA-Br	2.59
l-16	1.78
l-MeO-16	1.92

[a] Results of single determinations; see the text for details. Surfactant abbreviations are defined in Table I.

For a comparison of micellar effectiveness as a function of head groups, arbitrary solutions of surfactant–*n*-hexyl alcohol–0.05 M pH 9 borate buffer were prepared in the mole ratios 0.04:0.71:0.25, respectively.[15] The substrate (*dl*-I) concentration was 2.0×10^{-5} M. The results appear in Table IV; note that with an alternative ternary catalyst composition, the effectiveness order could be different.

It was not possible to determine a meaningful k_0 value. Thus 10 ml of *n*-hexyl alcohol and 0.6 ml of 0.05 M pH 9 buffer were shaken for several hours and then centrifuged for 1 hr. Use of the resulting supernatant (*n*-hexyl alcohol saturated with buffer) as the hydrolytic medium led to very slow, non-first-order hydrolysis. Since this process was on the time scale of hours, whereas the inverse micelle catalyzed process was completed within several minutes, buffer *not* solubilized by the micelles makes a negligible contribution to the hydrolyses of Table IV. Alternatively, one might take k_0 as the rate constant for hydrolysis of *dl*-I in 0.05 M pH 9 buffer. This was found to be 0.0450 sec^{-1}.

Chirality studies were carried out with *dl*-, *d*-, and *l*-16, using approximately optimized catalytic systems. Solutions of 1, 2, 3, or 4 g of *d*-16 in 10 ml of *n*-hexyl alcohol

Table V
Hydrolysis of Ester I in Inverse Micelles of *dl*-, *d*-, and *l*-16[a]

Substrate	Surfactant	$10^2\ k_\psi$, sec^{-1}
dl-I	*dl*-16	4.16
dl-I	*d*-16	4.47
d-I	*d*-16	4.77[b]
l-I	*d*-16	5.06
l-I	*l*-16	6.00
d-I	*l*-16	4.44

[a] The substrate concentration was 2×10^{-5} *M*. These are mainly results for single runs. See the text for details and Table I for surfactant abbreviations. [b] Average of two runs, 4.44 and 5.10×10^{-2} sec^{-1}.

Table VI
Uv Maxima (Å) of the Long-Wavelength Absorption Band of III in Various Solvents[a]

Solvent	λ_{max}	$E_T(30)$[b]	Z[c]
Cyclohexane	3320	30.9[d]	
Benzene	3481	34.5	54
1,2-Dimethoxyethane	3497	38.2	62.1
Acetone	3522	42.2	65.7
Acetonitrile	3536	46.0	71.3
Dimethylformamide	3593	43.8	68.5
Water	3641[e]	63.1	94.6

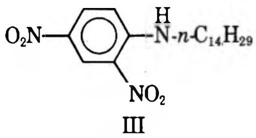
[a] The solutions were 3–6 $\times 10^{-5}$ *M* in III; ε for the band of interest was 1–2 $\times 10^4$. All organic solvents were of spectral grade, and were dried before use by distillation from Na, Na, $LiAlH_4$, K_2CO_3, CaH_2, and BaO, respectively. Water was distilled from $KMnO_4$. [b] A solvent polarity parameter based on the transition energy (kcal/mol) of the intramolecular charge-transfer band of a pyridinium phenol betaine; see ref 21. [c] Energy (kcal/mol) of the longest wavelength charge-transfer band of 1-ethyl-4-carbomethoxypyridinium iodide; see ref 22. [d] *n*-Hexane was used. [e] Probe III is insoluble (uv) in water. The cited λ_{max} is that of *N*-*n*-butyl-2,4-dinitroaniline, prepared by the procedure of ref 20.

were prepared. The rate constant for hydrolysis of *dl*-I was determined for each solution as a function of the amount of added 0.05 *M* pH 9 buffer (0.2–0.8 ml). Optimum catalysis was observed with *n*-hexyl alcohol–surfactant–buffer = 10 ml:3 g:0.4 ml (81:8:22 mmol ratio). Kinetic results with this catalytic system are collected in Table V.

Uv Studies. The uv spectra of micelle-solubilized molecules have provided details of the local environment of the solubilized species.[16-18] A broad summary of this work is that "molecules of appreciable polarity occupy the micellar surface, not the micellar interior."[19] Molecules of hydrolytic interest, such as esters, fall into this class.[3a]

We carried out two sets of uv experiments, the first to probe the nature of the Stern layers of our surfactant micelles, and the second to characterize the solubilization site of ester I.

The probe solubilizate *N*-*n*-tetradecyl-2,4-dinitroaniline (III) was readily prepared,[20] and its uv spectrum was



III

measured in several solvents; *cf*. Table VI. The behavior of the long-wavelength absorption band of III, as a function of solvent, is consistent with that of a π → π* transition. Note, especially, the bathochromic shift of λ_{max}, which accompanies increasing solvent polarity, as well as the general parallel of λ_{max} with $E_T(30)$[21] and Z[22] parameters.[23]

Table VII
Absorption Maxima (Å) for III in Micellar Environments[a]

Surfactant micelle[b]	λ_{max}
CTA-Br	3586
d-16[c]	3566
dl-MeO-16[d]	3560
CBzDA-Br[e]	3540

[a] 0.56 *M* surfactant and 3×10^{-4} *M* III in 99:1. water–dioxane (by volume). [b] See Table I for surfactant abbreviations. [c] An identical maximum was observed with *l*-16.[26] [d] We thank Mr. C. E. Powell for this experiment. [e] 0.0015 *M* surfactant was used. The concentration is limited by solubility.

Table VIII
Uv Maxima of Ester I

Solvent	λ_{max}, Å	ε
Cyclohexane	2668	9100
Aqueous *dl*-16	2705	5900[a]
Water	2707	7600

[a] This solution corresponds to the medium of a kinetic run which gave k_ψ^{max}: 2×10^{-3} *M* *dl*-16, 2×10^{-5} *M* *dl*-I, and 0.5 vol. % dioxane. Base was omitted. It is believed that I is completely solubilized by the micelles under these conditions.

Probe III appears to be a sensitive mirror of solvent polarity.[23] Moreover, its long hydrophobic tail and polar chromophore make it likely that, when solubilized by a micelle, the tail will anchor in the micelle's hydrocarbon core, while the chromophore will reside in the Stern layer or near the surface of the micelle.[17,24,25] Similarly, an "anchored" (spin label) micellar probe, *N*-4-(2,2,6,6-tetramethylpiperidine-1-oxyl)-*N*,*N*-dimethyl-*n*-dodecylammonium ion, has been used to study sodium dodecyl sulfate micelles.[18]

Table VII gathers the λ_{max} values observed for probe III solubilized in the various surfactant micelles.

Excepting the DMF results, which correlate very poorly, the data of Table VI afford a reasonable linear correlation of λ_{max} (III) and Z. According to the correlation, Z values of about 82, 77, and 70 can be determined for the average micellar environments scrutinized by the polar chromophore of probe III in CTA-Br, *d*-16, or CBzDA-Br, respectively. The first value compares reasonably well with Z = 85.5, derived from the fluorescence emission maximum of CTA-Br-solubilized 1-aminonaphthalene 7-sulfonate,[27] especially if it is granted that this probe, lacking a hydrophobic tail to anchor it, may observe a more aqueous region of the micelle's Stern layer (*i.e.*, may enjoy a time-averaged residence closer to the micelle surface).

The present results also agree with those of Gitler in suggesting that the polarity of the Stern layer of CTA-Br micelles is definitely lower than that of water.[27] The observed Z value is similar to that of ethanol (79.6). Note, too, the still lower Z values for *d*-16 and CBzDA-Br micelles, which may indicate a lower effective polarity in the Stern layers, owing to the increased hydrocarbon content of the aromatic head groups. The similarity of λ_{max} for III solubilized in either *d*-16 or *dl*-MeO-16 rules out important charge-transfer interactions between the *p*-methoxyphenyl micellar head groups and the 2,4-dinitroaniline chromophores of III.

The lower Z value of micellar CBzDA-Br, compared to those of micellar *d*-16 or *dl*-MeO-16, is somewhat puzzling. Perhaps the Stern layer of the former features tighter packing of head groups and closer average approach of head group and probe. Close packing and approach may be somewhat inhibited in the latter micelles because of steric problems associated with the α-methyl substituent at the benzylic carbon. This could lead to more "open" and aqueous Stern layers.[28]

Finally, we determined uv spectra of substrate *dl*-I under several conditions, in order to examine its solubilization environment (Table VIII). Unfortunately, λ_{max} is not very solvent sensitive. However, the near identity of λ_{max} for aqueous and micellar solutions suggest that I is solubilized at or close to the micelle–water interface (micellar surface). A similar conclusion was reached in a study of dimethyl phthalate solubilization in dodecylammonium chloride micelles.[17] We speculate that the *p*-nitrophenyl moiety of solubilized I is closer to the micellar surface than the 2,4-dinitrophenyl chromophore of probe III. Whether this is also true of the ester linkage of I is not known.

Discussion

In their important implications, the Results are clear, and this Discussion can be limited to a brief exposition followed by a prognosis of the future course of stereoselective micellar catalysis.

Table I reveals no significant differences between the cmc's of optically active and racemic MeO-16 surfactants. This is in accord with analogous comparisons of racemic and active *N*-methyl-*N*-*n*-dodecylephedrinium bromide,[8] 2-octylammonium and 2-octyltrimethylammonium ions,[10] and *N*-alkyl-*N*,*N*-dimethylalanine hydrobromides.[29] In contrast, the cmc's recorded for *d*-16 and *l*-16 are significantly lower than that of *dl*-16. However, the large Δcmc between the *d* and *l* surfactants suggests caution in accepting these results as an initial instance of stereochemical differentiation in micellization. Traces of homologous impurities can alter cmc's without being detected by microanalysis. Indeed, the analogous tetradecyl surfactants, *d*-14, *l*-14, and *dl*-14, exhibit no significant cmc differences.[30]

Table III reveals that surfactants IIb–d cause substantial catalysis of the basic hydrolysis of I. The magnitude of catalysis (k_ψ^{max}/k_0) is larger than that observed in studies of the basic hydrolyses of *p*-nitrophenyl hexanoate, octanoate, and dodecanoate in *n*-tetradecyl, *n*-dodecyl, and *n*-tetradecylammonium ion micelles, respectively.[31–33] Note, however, that *dl*-16 and *dl*-MeO-16 are rather less effective catalysts than CTA-Br toward the more complicated substrate, I.

The data of Table III are based on k_ψ^{max} (plateau) values and should reflect conditions in which the substrate is essentially all solubilized (*i.e.*, in which $k_\psi^{max} \cong k_m$, the rate constant for hydrolysis in the micellar phase). One can then note that the catalytic trend suggests poorer catalysis by the surfactants with the more highly *branched* head groups. Current attribution[3] of cationic micellar catalysis of basic ester hydrolysis, in part, to electrostatic stabilization of the anionic transition state, and to enhancement of hydroxide ion activity by its desolvation at the cationic micellar surface,[34] provides a simple rationalization of the trend: the more effective the hydrocarbon screening of the head group's cationic centers,[28] the lower the catalytic efficiency of the micelles.

Possibly, a similar argument can explain the decreasing catalytic efficiencies of isomeric hexadecyl sodium sulfates (in the acidic hydrolysis of methyl orthobenzoate) as the head group is moved in from the terminus of the alkyl chain.[35] Other explanations are possible, however,[35] and, lest ours be accepted too readily, we note that Bunton has reported an opposite structure *vs.* catalytic efficiency sequence: phenyl- and 2,4-dimethoxyphenylcetyldimethylammonium bromides are more effective than CTA-Br in catalyzing reactions of OH^- and F^- with *p*-nitrophenyl diphenyl phosphate, and of OH^- with 2,4-dinitrochlorobenzene.[36] The sequence was mainly due to better substrate *binding* by the aryl-substituted surfactants,[36] but a small catalytic advantage persisted, even at k_ψ^{max}, in the latter reaction. Further work is clearly required to elucidate the relation between head-group structure and catalytic efficacy.

Table IV indicates a similar catalytic order, CTA-Br ~ CBzDA-Br > *l*-MeO-16 ~ *l*-16, in the inverse micellar hydrolyses of ester I. However, as these k_ψ values were not necessarily maxima, the order may not truly reflect catalytic efficiency. In comparison to the hydrolysis of *dl*-I in 0.05 *M* pH 9 buffer ($k_0 = 4.50 \times 10^{-3}$ sec^{-1}), *optimal* catalysis by *dl*-16 inverse micelles (Table V), for which $k_\psi = 4.16 \times 10^{-2}$ sec^{-1}, leads to $k_\psi/k_0 \cong 9.3$. This is similar to the ratio for *normal dl*-16 micelles (8.11, Table III), and parallels the results of Friberg and Ahmad,[13] who found similar magnitudes of catalysis for the basic hydrolysis of *p*-nitrophenyl laurate in either normal (aqueous) or inverse (hexanol–water) CTA-Br micelles.

The main purpose of our study was to search for stereoselective hydrolysis of *active* ester I, solubilized by *active* surfactants IIc or IId. Cases 7 and 8[37] and 10–12 of Table II reveal no substantial stereoselectivity. Bunton[8] reported $10^2{}_\psi k_\psi^{max} = 7.86$ and 7.07[38] for the hydrolyses of *l*-I and *d*-I in *l*-*N*-*n*-dodecyl-*N*-methylephedrinium bromide micelles. Expressed as $100(k_d^{max} - k_l^{max})/k_l^{max}$, the maximum stereoselectivity was about 11.5%. The parallel experiments of Table II exhibit no such selectivity; *e.g.*, from case 7 and footnote *f*, a stereoselectivity of 6% can be calculated, but it is not significantly beyond the combined uncertainties of the determinations (±3%). The ephedrinium micelles[8] appear to be more stereoselective than our own (see below).

There is an additional complicating feature, however. Bunton[8] also noted that *dl*-I was less reactive ($k_\psi^{max} = 4.28 \times 10^{-2}$ sec^{-1})[38] than either enantiomer (see above) in *l*-ephedrinium micelles, and also that, in CTA-Br micelles, *dl*-I was slightly more reactive (factor of 1.2[38]) than either enantiomer. It was therefore suggested that "more than one ester molecule is incorporated into each micelle, and that an enantiomeric substrate molecule perturbs the micellar structure, in such a way that the perturbed micelle then exhibits different activities towards the two enantiomers."[8,39] The CTA-Br observations have been questioned by Hindman and Jacobus,[40] who report no significant rate differences for the CTA-Br- or CTA-Cl-catalyzed hydrolyses of active or racemic I.

We find $k_\psi^{max} = 0.0294$ and 0.0298 sec^{-1}, respectively, for hydrolysis of *dl*-I and *d*-I at pH 9, in CTA-Br micelles, and 0.005 *M* Fisher sodium borate buffer (H_3BO_3 and NaOH). With 0.01 *M* $Na_2B_4O_7$ buffer at pH 9, corresponding values of 0.0376 and 0.0384 sec^{-1} were measured. Although all of the values are lower than the 0.049–0.039 sec^{-1} reported in ref 8 (see Table II, footnote *d*), there is no indication of stereoselectivity.

Jacobus[40] indicates that, as 0.01 *M* pH 9 sodium borate buffer ages, it yields gradually decreasing rate constants for hydrolysis of I. We have also observed this effect. The data of Table II, repeated with older buffer, gave 20–30% lower rate constants. The rate data *within* Tables II, IV, and V were collected within a period of several weeks, and should be free of the "aging" effect. Comparison with data determined with other lots of buffer, and in *other* laboratories, however, is probably dangerous, especially when small rate differences are involved.

Another chance to investigate the effect in question arises in comparison of k_ψ^{max} for hydrolyses of *dl*-I and *l*-I in *l*-16 micelles. (We studied these cases with a new lot of buffer and found somewhat higher values than those of Table II, cases 7 and 8.) The *k* values were 3.08×10^{-2} and 3.22×10^{-2} sec^{-1}, respectively; again we found no significant rate differences for the hydrolysis of active or racemic I, catalyzed by a chiral surfactant micelle. The observational differences of Bunton,[8] Jacobus,[40] and those of our laboratory merit further study.

Table V reveals no experimentally significant stereoselectivity in basic hydrolyses of I catalyzed by *inverse d-* or *l*-16 micelles in aqueous *n*-hexyl alcohol. We hoped that the surfactant head groups might pack more tightly in the inverse mode, and that the solubilized substrate would be more sensitive to the chirality information carried by the head groups. However, consideration of the kinetic results for all "enantiomeric" and "diastereomeric" substrate-surfactant pairs indicates the absence of stereoselectivity in excess of the scatter in the data.

In these initial studies of stereoselectivity in micellar catalysis, we employed "simple" or nonfunctionalized surfactants. We questioned whether chirality in the head group could be translated into a kind of "net chirality" throughout the micelle's Stern layer, such that the activation energies for hydrolyses of solubilized enantiomeric substrates would be differentiated. The negative results show that simple chirality does not suffice; more profound interactions between substrate and micelle and, perhaps, between the micellar head groups themselves, are required to amplify the chirality differences to a chemically significant level. Such interactions could take the form of hydrogen bonding or other complexation. The weak charge-transfer interaction possible between the *p*-nitrophenylate leaving group of I and the *p*-anisyl group of the MeO-16 surfactants does not make the latter more stereoselective than the simple "16" surfactants. *Functionalized* chiral surfactants appear to be required for substantial stereoselectivity.

Whereas our (nonstereoselective) chiral surfactants are slightly poorer catalysts than CTA-Br for hydrolysis of I, the stereoselective *l*-ephedrinium surfactant is about twice as effective as CTA-Br.[8] Bunton has suggested that the hydroxyl function of the ephedrinium head group is responsible for the augmented catalysis.[8,39] It could assist ester hydrolysis either by H bonding to the ester's carbonyl oxygen, thus aiding the attack of hydroxide ion at the carbonyl carbon, or by itself acting as a nucleophile, especially if it were first deprotonated by the external base.

The latter mode of catalysis is apparently involved in the micellar hydrolysis of phosphates at high pH (~12).[39,41] The former mode is likely to be involved in the catalytic action of choline-type surfactants in the pH range 7-10. For the basic hydrolysis of simple esters, these surfactants are superior to CTA-Br by 1-2 orders of magnitude.[42]

It seems reasonable that the stereoselectivity elicited by chiral surfactant micelle catalysts will increase as the micelles become better catalysts. Thus the *l*-ephedrinium surfactant,[8] which is two to three times as effective as our own chiral surfactants, appears to exhibit some catalytic stereoselectivity. The implication is that chiral surfactants, functionalized with *β*-hydroxyethyl or 4-methylimidazole[43] substituents, may show greater stereoselectivity than the chiral surfactants studied thus far. We are exploring this possibility.

Experimental Section[44]

***dl-p*-Nitrophenyl *α*-Methoxyphenylacetate (*dl*-I).** *dl*-Mandelic acid (25 g, 164 mmol) was converted to sodium *α*-methoxyphenylacetate by treatment with 7.57 *M* aqueous sodium hydroxide and excess dimethyl sulfate. The precipitated sodium salt was neutralized with dilute HCl; the liberated acid was isolated as an oil by ethereal extraction, and then crystallized from benzene-petroleum ether (bp 90-120°).[45] The pure acid (7.65 g, 28%), mp 69-70° (lit.[45] mp 70.5-71°), had ir ($CHCl_3$) 5.81 (carbonyl) and 9.01 *μ* (ether); nmr ($CDCl_3$) 7.44 (5 H, phenyl), 4.78 (1 H, benzylic), and 3.43 ppm (3 H, methoxy), all singlets.

The purified acid was converted to *dl*-I by stirring 2 g (12 mmol) with 1.5 equiv of oxalyl chloride at ambient temperature. After 2 hr, excess oxalyl chloride was removed under reduced pressure, and 1 equiv of *p*-nitrophenol, 15 ml of toluene, and 1 ml of pyridine was added. The mixture was refluxed (1 hr), cooled, and extracted with 0.1 *N* aqueous NaOH, followed by saturated aqueous $NaHCO_3$, until the aqueous extract was no longer yellow.[31,32] The toluene solution was washed with 0.1 *N* HCl and with water, and dried over $MgSO_4$. Removal of the toluene afforded an oil which was crystallized from methanol.[46] Recrystallization from methanol gave 1.05 g (29%) of white flakes, mp 50-51° (lit.[8] mp 46-48°). The ir spectrum (CCl_4) had 5.60 *μ* (carbonyl); nmr (CCl_4) 8.34, 8.20, 7.28, 7.14 (4 H, q, *p*-nitrophenyl), 7.46 (5 H, narrow m, phenyl), 4.93 (1 H, s, benzylic), and 3.50 ppm (3 H, s, methoxy).

Anal. Calcd for $C_{15}H_{13}NO_5$: C, 62.71; H, 4.57; N, 4.88. Found: C, 62.55; H, 4.42; N, 4.71.[47]

***l*- or *d-p*-nitrophenyl *α*-methoxyphenylacetate (*l*- or *d*-I)** were prepared as above, starting with commercially available *l*- or *d*-mandelic acids (Aldrich). The intermediate *l*-*α*-methoxyphenylacetic acid had mp 65-66° (lit.[48] mp 65-66°) and $[\alpha]^{25}D$ −149.3° (*c* 0.574 g/dl, ethanol); the literature value, under the same conditions is $[\alpha]^{20}D$ −150.7°.[48,49] Similarly, *d*-*α*-methoxyphenylacetic acid had mp 64-65° (lit.[48] mp 65-66°) and $[\alpha]^{25}D$ +149.6° (*c* 0.494 g/dl, ethanol); the literature[48] value, under the same conditions, is $[\alpha]^{20}D$ +150.0°.

The *l*-methoxy acid was converted to white needles of *l*-I, which had mp 55-56° (lit.[8] mp 49-50°) and $[\alpha]^{25}D$ −112.56° (c 5 g/dl, methanol). Similarly, *d*-I was obtained as white needles, mp 53.5-54.5° (lit.[8] mp 48.5-49.5°), $[\alpha]^{25}D$ +109.64° (*c* 5 g/dl, methanol).

The following experiment was carried out to demonstrate that the enantiomers of I were of high optical purity. *d*-I (0.5 g) was hydrolyzed in 25 ml of 0.1 *N* NaOH (steam bath, 30 min). The resulting solution was acidified to pH 1 with 0.1 *N* HCl and extracted with 3 × 25 ml of ether. The ethereal extract was dried ($MgSO_4$) and stripped; the residue was chromatographed on Brinkmann, SilPlate P20F-22, 2-mm (F-254) silica gel plates. Elution with acetone afforded 0.12 g of *d*-*α*-methoxyphenylacetic acid (R_f ~0.1), which was recovered with ether, and had $[\alpha]^{28}D$ +0.720° (*c* 0.5 g/dl, ethanol) or $[\alpha]^{28}D$ +144°. The recovered acid had >96% of the rotation of the initial *α*-methoxyphenylacetic acid, which itself had been >99% optically pure (see above).

Cetyltrimethylammonium bromide (CTA-Br, IIa) was obtained from City Chemical Corp. and was purified by standard methods[50] to afford white crystals, mp 244-247° (lit.[50] mp 227-235° dec).

***N*-Benzyl-*N*-cetyldimethylammonium bromide (CBzDA-Br, IIb)** was prepared by refluxing 50 g (0.37 mol) of *N,N*-dimethylbenzylamine (MCB) and 113 g (1 equiv) of cetyl bromide in 50 ml of acetone for 24 hr. Cooling afforded 85 g (65%) of crystals which after three recrystallizations from acetone had mp 79-80°.

Anal. Calcd for $C_{25}H_{46}NBr$: C, 68.14; H, 10.54; N, 3.18; Br, 18.13. Found: C, 67.60; H, 10.67; N, 3.29; Br, 17.61.[51]

***dl-N-α*-Methylbenzyl-*N,N*-dimethylcetylammonium bromide (*dl*-16, *dl*-IIc)** was prepared from *α*-methylbenzylamine (MCB). Conversion of the latter to *N*-*α*-methylbenzyl-*N,N*-dimethylamine was accomplished by the procedure of Clarke.[12] The tertiary amine (bp 70-71°, 9.7 Torr) was produced in 73% yield and had ir, nmr, and mass (M^+) spectra in accord with expectations. Quaternization of 41.3 g (0.28 mol) of the amine was effected by refluxing with 107 g (1.25 equiv) of cetyl bromide (Eastman) in 50 ml of absolute ethanol for 48 hr. Ethanol was stripped and crystallization was induced with ether. Three recrystallizations from acetone gave 60 g (48%) of *dl*-16, mp 111-112.5°, as a white powder.

***l*-16 and *d*-16** were prepared similarly. *l*-*α*-Methylbenzylamine (Aldrich) was distilled from sodium (bp 68-69.5°, 9.5 Torr) and had $[\alpha]^{23}D$ −18.63° (neat, *l* 0.5),[52] ~97.5% optically pure. It gave *l*-*N*-*α*-methylbenzyl-*N,N*-dimethylamine, $[\alpha]^{21}D$ −31.52° (neat, *l* 0.5), from which *l*-16 was obtained by cetylation. Recrystallized *l*-16 had mp 111-113° and $[\alpha]^{21}D$ −19.34° (c 0.454 g/ml, methanol, *l* 0.5).

Anal. Calcd for $C_{26}H_{48}NBr$: C, 68.70; H, 10.64; N, 3.22; Br, 17.58. Found: C, 68.71; H, 10.64; N, 3.22; Br, 17.83.

From *d*-*α*-methylbenzylamine (Aldrich), $[\alpha]^{23}D$ +18.57° (neat, *l*

0.5), ~97% optically pure,[52] we obtained *d-N-α*-methylbenzyl-*N,N*-dimethylamine, $[\alpha]^{21}_{\mathrm{D}}$ +31.44° (neat, *l* 0.5). Quaternization afforded *d*-16 as white crystals, mp 111.5–113°, $[\alpha]^{21}_{\mathrm{D}}$ +19.82° (*c* 0.454 g/ml, methanol, *l* 0.5).

Anal. Found: C, 68.58; H, 10.74; N, 3.28; Br, 17.86.

***dl-N-α*-Methyl-*p*-methoxybenzyl-*N,N*-dimethylcetylammonium Bromide (*dl*-MeO-16, *dl*-IId).** *dl-α*-Methyl-*p*-methoxybenzylamine was prepared from *p*-methoxyacetophenone (Aldrich) in 50% overall yield by a modified Leuckart procedure.[53] The product was purified by distillation, bp 65.0–65.5° (0.22 Torr) [lit.[53] bp 126° (20 Torr)], and had nmr (CCl_4) 7.29, 7.13, 6.83, 6.68 (4 H, q, aryl), 4.03 (1 H, q, J = 7 Hz, benzylic), 3.77 (3 H, s, methoxy), 1.27 (3 H, d, J = 7 Hz, methyl), 1.15 ppm (2 H, s, amino).

The *N,N*-dimethyl derivative was prepared by Clarke's procedure,[12] and the product, *dl-α*-methyl-*p*-methoxybenzyl-*N,N*-dimethylamine, was distilled from sodium, bp 65–65.5° (0.15 Torr). Nmr (CCl_4) showed essentially unchanged aryl, methoxy, and *C*-methyl resonances. The benzylic proton appeared at 3.15 (1 H, q, J = 7 Hz)) and the *N*-methyl resonance appeared at 2.14 ppm (6 H, s). The tertiary amine (25 g, 0.14 mol) and 53.2 g (1.25 equiv) of cetyl bromide in 50 ml of acetone were refluxed for 24 hr. Cooling afforded a solid, which was recrystallized four times from acetone to give 38.8 g (57%) of *dl*-MeO-16 as a white powder, mp 112–114°. Ir showed the absence of $^+$N–H stretching. Nmr (CCl_4) showed 7.84 and 6.94 (4 H, A_2B_2 "doublets," aryl), 5.56 (1 H, m, benzylic), 3.80 (3 H, s, methoxy), 3.37 (6 H, broad s, *N*-methyls), 1.90 (5 H, m, *C*-methyl + NCH_2), 1.23 (broad s,), and 0.87 ppm (crude t, cetyl group, 31 H).

Anal. Calcd for $C_{27}H_{50}NOBr$: C, 66.92; H, 10.39; N, 2.89; Br, 16.49. Found: C, 67.23; H, 10.54; N, 2.90; Br, 16.51.

***d*-MeO-16 and *l*-MeO-16.** *d-α*-Methyl-*p*-methoxybenzylamine was obtained by repeated recrystallization of the *d*-tartrate salt of the *dl* amine in methanol,[54] until constant melting point (181–183°) and rotation {$[\alpha]^{25}_{\mathrm{D}}$ +2.384° (*c* 13.25 g/dl, H_2O, *l* 1)} were obtained. A final recrystallization from water[55] and cleavage[54] afforded *d-α*-methyl-*p*-methoxybenzylamine, $[\alpha]^{20}_{\mathrm{D}}$ +24.4° (*c* 2 g/dl, methanol, *l* 1), 85.1% optically pure.[56] A parallel resolution using *l*-tartraric acid gave a salt with mp 181.5–184° and $[\alpha]^{25}_{\mathrm{D}}$ −0.440° (*c* 2.65 g/dl, H_2O, *l* 1), from which the *l* amine was obtained with $[\alpha]^{20}_{\mathrm{D}}$ −24.3°, 84.9% optically pure.[55,56]

Dimethylation of the active amines was accomplished as above: *d-N-α*-methyl-*p*-methoxybenzyl-*N,N*-dimethylamine, $[\alpha]^{24}_{\mathrm{D}}$ +27.05° (neat, *l* 0.5); *l* enantiomer, −27.01° (neat, *l* 0.5). Ir and nmr spectra were identical with those of the racemic compound.

Cetylation as above afforded *d*-MeO-16, white flakes, mp 118–119°, $[\alpha]^{25}_{\mathrm{D}}$ +28.84° (*c* 5 g/dl, methanol, *l* 1), and *l*-MeO-16, white flakes, mp 116.5–118°, $[\alpha]^{25}_{\mathrm{D}}$ −28.76° (c 5 g/dl, methanol, *l* 1). Nmr and ir spectra were identical with those of *dl*-MeO-16.

***N-n*-Tetradecyl-2,4-dinitroaniline (III)** was prepared from 10.0 g (46.9 mmol) of *n*-tetradecylamine and 9.49 g (1 equiv) of 2,4-dinitrochlorobenzene by the procedure of Mustafa and Zahran.[20] Recrystallization from 98% ethanol, followed by two recrystallizations from petroleum ether (bp 37–49°), gave light yellow crystals, which were dried at 1 mm for 24 hr, mp 58–59° (lit.[20] mp 53°). Mass spectral analysis indicated M^+ at 379 and contamination by at least 4% of the C_{16} homolog (M^+ at 407). The nmr spectrum[57] appeared to integrate normally, however: nmr (CCl_4) 8.95 (1 H, d, J = 3 Hz), 8.20 (1 H, d of d, J = 3.9 Hz), and 6.88 (1 H, d, J = 9 Hz) (3, 5, and 6 aryl protons), 8.46 (1 H, NH), 3.38 (2 H, q, J = 6 Hz, NCH_2), 2.0–0.67 (27 H, other alkyl).

The uv behavior of III is, however, unaffected by the presence of the C_{16} impurity: $\lambda_{\max}$ 260 nm (ϵ 7.54 × 10^3), 349 (1.50 × 10^4), ~420 (shoulder). The *N*-ethyl analog of III has $\lambda_{\max}$ at 260 and 348 nm.[58]

Anal. Calcd for $C_{20}H_{33}N_3O_4$: C, 63.30; H, 8.76; N, 10.53. Found: C, 64.28; H, 8.93; N, 10.29.[59]

Cmc determinations are described in Table I and its footnotes. Full descriptions of the technique have appeared.[5,10]

Kinetic studies are described in the text and in Tables II–V. We used a Beckman DB spectrometer equipped with a Sargent Model SRL recorder to monitor the appearance of *p*-nitrophenoxide ion at 400 nm. A Haake constant-temperature circulating pump maintained the sample and reference solutions at 25.00 ± 0.02°. Aqueous samples were composed of 3.0 ml of a solution containing surfactant and buffer plus 15 μl of a purified[60] dioxane solution of I, introduced at zero time. The final [I] was 2.0 × 10^{-5} *M*. Buffers were Fisher Certified Ph 7.00 (phosphate), 8.00 (phosphate), and 9.00 (borate). The latter buffer was prepared from 50 ml of a mixture which was 0.1 *M* with respect to both KCl and H_3BO_3, to which was added 20.8 ml of 0.1 *M* NaOH; the whole was diluted to 100 ml.[61] This solution (0.05 *M*) was diluted 1:9 for use with aqueous micellar solutions, and not at all for use with inverse micellar solutions.

Rate constants were obtained from plots of ($A^{\infty} - A^t$) *vs.* time (t), refined by a least-squares program on a Wang Model 700 calculator. Correlation coefficients were >0.999, and first-order kinetics were observed over >95% of reaction. Infinity values were taken at approximately 120, 16, and 13 half-lives for pH 7, 8, and 9 runs, respectively. A separate control experiment showed that Beer's law held for *p*-nitrophenoxide ion in 0.002 *M* *dl*-16 and 0.01 *M* pH 8 buffer.

The details of the inverse micellar kinetic studies are given in the text and in Tables IV and V.

Uv studies are described in the text and in Tables VI–VIII.

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Registry No.—*dl*-I, 31528-02-6; *l*-I, 31528-00-4; *d*-I, 31528-01-5; IIb, 3529-04-2; *dl*-IIc, 50640-90-9; *l*-IIc, 50640-91-0; *d*-IIc, 50640-92-1; *dl*-IId, 50640-93-2; *l*-IId, 50640-94-3; *d*-IId, 50640-95-4; III, 50641-10-6; *dl*-mandelic acid, 611-72-3; *α*-methoxyphenylacetic acid, 1701-77-5; *l*-mandelic acid, 17199-29-0; *d*-mandelic acid, 611-71-2; *N,N*-dimethylbenzylamine, 103-83-3; cetyl bromide, 112-82-3; *dl-α*-methylbenzylamine, 618-36-0; *l-α*-methylbenzylamine, 2627-86-3; *d-α*-methylbenzylamine, 3886-69-9; *dl-α*-methyl-*p*-methoxybenzylamine, 35600-82-9; *dl-α*-methyl-*p*-methoxy-*N,N*-dimethylamine, 50640-96-5; *d-α*-methyl-*p*-methoxybenzylamine, 22038-86-4; *l-α*-methyl-*p*-methoxybenzylamine, 41851-59-6; *d-N-α*-methyl-*p*-methoxybenzyl-*N,N*-dimethylamine. 50640-97-6; *l-α*-methyl-*p*-methoxybenzyl-*N,N*-dimethylamine, 50640-98-7.

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The Question of Amide Group Participation in Carbamate Hydrolysis

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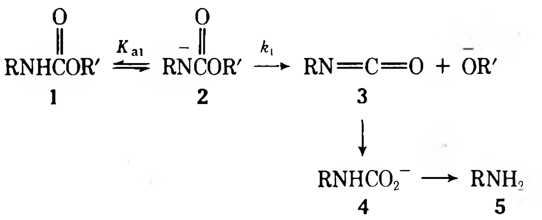
Phenyl *N*-(*o*-carbamoylphenyl)carbamate is cyclized to 2,4(1*H*,3*H*)-quinazolinedione in the presence of basic catalysis. A mechanism suggested involving rate-determining E1cB type elimination of phenoxide ion followed by trapping of the isocyanate intermediate by the amide group is consistent with data for model compounds. Phenyl *N*-methyl-*N*-(*o*-carbamoylphenyl)carbamate also cyclizes, but at a much slower rate (since the elimination–addition pathway is blocked); in this case the amide anion participates in the expulsion of phenoxide ion. When the amide group is attached to the leaving phenoxide ion as in salicylanilide carbamate, large rate enhancements are observed in hydroxide-catalyzed hydrolysis, but these may be explained in terms of the electronic effect of the substituent, rather than by participation. No evidence was found for appreciable carbamate group tautomerism.

Although simple carbamates, such as urethanes (**1**, R^1 = Et) are hydrolyzed only with difficulty even in highly alkaline solution,[1] carbamates with good leaving groups (such as phenyl carbamates, **1**, R^1 = Ph) may undergo rapid base-catalyzed cleavage. This has been interpreted in terms of the existence of a facile elimination–addition pathway for hydrolysis with the intermediate formation of the isocyanate **3** (Scheme I).[2,3] The isocyanate **3** has been shown to lie on the reaction pathway, since it can be trapped by both internal and external nucleophiles;[4] the addition of amine nucleophiles was shown to result in appreciable urea formation (by reaction of **3** with the amine after the rate-determining step) without changing the rate of disappearance of the starting carbamate **1**.

The elimination–addition pathway is so attractive that some nucleophilic groups, even when approximated to the reactive group (for example, **1**, R = *o*-$NH_2C_6H_4$), preferentially react *via* this mechanism, rather than directly attacking the carbamate center. In contrast, the ionized carboxy (**1**, R = o-carboxyphenyl)[5] and hydroxy (**1**, R = o-hydroxyphenyl)[6] groups have been shown to form cyclic products (isatoic anhydride and benzoxazinone, respectively) by direct nucleophilic attack on the carbamate. Because of the duality of behavior shown by these diverse

Scheme I



nucleophiles it is to be expected that certain groups will be borderline in this respect, participating in some instances in the rate-determining step, while in other cases merely trapping the isocyanate intermediate. We present evidence that the amide group acts in this way and show that the hydrolysis of salicylanilide carbamates may proceed through carbamate hydrolysis, contrary to a recent report.[7]

Results and Discussion

When phenyl *N*-(*o*-carbamoylphenyl)carbamate (**6**) is treated in dioxane–water at pH 9, smooth cyclization takes place and the quinazolinedione **8** may be isolated in near-quantitative yield. The cyclization is base catalyzed (see Table I), a plot of log k_{obsd} *vs.* pH being linear with unit slope. At lower pH, no pH-independent (or neutral) reaction becomes apparent, while, at the highest pH values amenable to study (where the cyclization was most rapid), the cyclization rate was still proportional to [HO⁻].

Two possible mechanisms of cyclization consistent with this kinetic behavior are outlined in Scheme II. The first involves the amide anion **7** as the nucleophilic group, displacing phenoxide ion to give the quinazolinedione **8** directly. Alternatively the carbamate could hydrolyze *via* the normal elimination–addition pathway (**6** → **9** → **10**), the quinazolinedione being formed after the rate-determining step. Since both the *N*-phenyl carbamate[4] and benzamide groups[8] are only weakly acidic (with pK_a values ≥ 14), the rate of cyclization (which is dependent on the concentration of the active species **7** or **9**) by the two pathways would be proportional to [HO⁻] in the pH range studied (as observed).

Scheme II

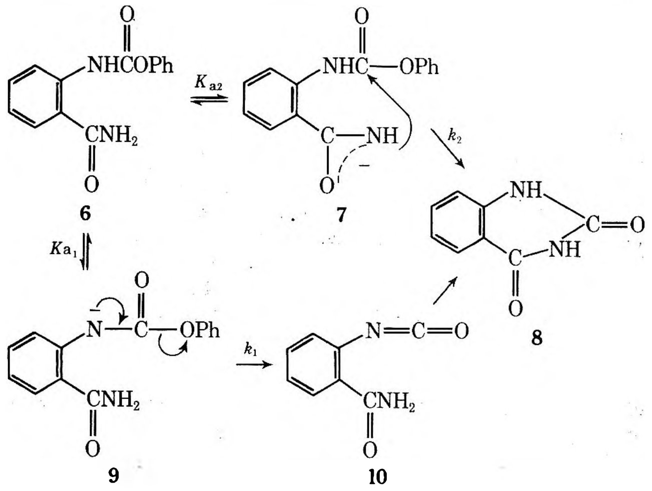


Table I
Observed First-Order Rate Constants for the Cyclization of Phenyl *N*-(*o*-Carbamoylphenyl)carbamate to 2,4(1*H*,3*H*)-Quinazolinedione[a]

pH	9.0	9.5	9.8	10.1	10.5
$10^2\ k_{obsd}$, sec⁻¹	0.23	0.63	1.09	3.75	6.85

[a] In 1:4 (v/v) dioxane–water at 25° (μ = 1.0, KCl).

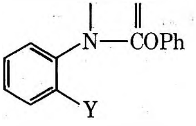
Table II
Summary of Rates of Hydrolysis and of Cyclization of Carbamates

Carbamate	k_1K_{a1} (or k_2K_{a2}), l. mol⁻¹ sec⁻¹	Carbamate	k_1K_{a1} (or k_2K_{a2}), l. mol⁻¹ sec⁻¹
1 (R = R' = Ph)	1.9×10^{-13}	**12d**	2.0×10^{-17}
6	2.4×10^{-12}	**13**	7.9×10^{-13}
11a	7.9×10^{-14}	**14a**	7.9×10^{-12}
11b	1.7×10^{-19}	**14b**	1.1×10^{-12}
12a	2.0×10^{-11}	**14c**	1.3×10^{-9}
12b	7.9×10^{-15}	**14d**	7.9×10^{-10}
12c	4.0×10^{-14}		

A distinction between the possible cyclization pathways can be made by comparing the reactivity of substrates in which participation by the *o*-carbamoyl group is not possible. Data for phenyl *N*-phenylcarbamate (**1**, R = R^1 = Ph), which hydrolyzes according to the mechanism of Scheme I, are summarized in Table II. The observed rate of hydrolysis of this carbamate is also specific base catalyzed, and the rate constants obtained are expressed in terms of the composite constant k_1K_{a1} (or k_2K_{a2}), which is obtained by dividing the observed rate constant at any pH by the hydrogen ion concentration. By comparing the values for **6** with the unsubstituted material (**1**, R = R^1 = Ph) it is clear that **6** cyclizes 12.6-fold more rapidly than **1** (R = R^1 = Ph) hydrolyzes at each pH.

A rate enhancement of this magnitude does not necessarily indicate that the amide group is acting as a nucleophile in the rate-determining step. It is expected that the electron-withdrawing amide group would enhance the reactivity of the carbamate (ρ is +0.64 for the effect of the variation of the N-aryl substituent on k_1K_{a1}).[4] Moreover, carbamates with substituents in the ortho position of the N-aryl ring have been shown to hydrolyze four- to tenfold more rapidly than the para-substituted analogs, attributable to the relief of some steric crowding in the conversion of **1** to **3**.[4] By combining the electronic and steric effect expected for the o-amido group, a rate enhancement of 10–20-fold relative to the unsubstituted material is predicted. The observed value of 12.6-fold is therefore well within these limits, and thus the amido group is not necessarily acting as a nucleophile in the rate-determining step.

Further support for the isocyanate pathway for **6** comes from data for the *N*-methyl carbamate **11a**. Because the nitrogen of the carbamate is disubstituted, the elimination–addition pathway (Scheme I) is blocked for this carbamate. The *N*-phenyl compound, **11b**, is hydrolyzed slowly by direct hydroxide ion attack on the carbamate linkage (with $k_{obsd} = 1.7 \times 10^{-5}$ l. mol⁻¹ sec⁻¹ at [HO⁻] = 1.0 *M*, 25°).[4] The reaction of **11a** is also base catalyzed but *ca.* 5×10^5-fold faster than that of **11b** (see Figure 1). Such a large rate enhancement can only be explicable in terms of rate-determining direct attack by the amide anion on the carbamate center in **11a**. The product formed, 2-(*N*-methyl)-4(1*H*,3*H*)-quinazolinedione, supports this interpretation since alternative kinetically



11a, Y = CONH$_2$
b, Y = H
c, Y = O$^-$
d, Y = CO$_2^-$

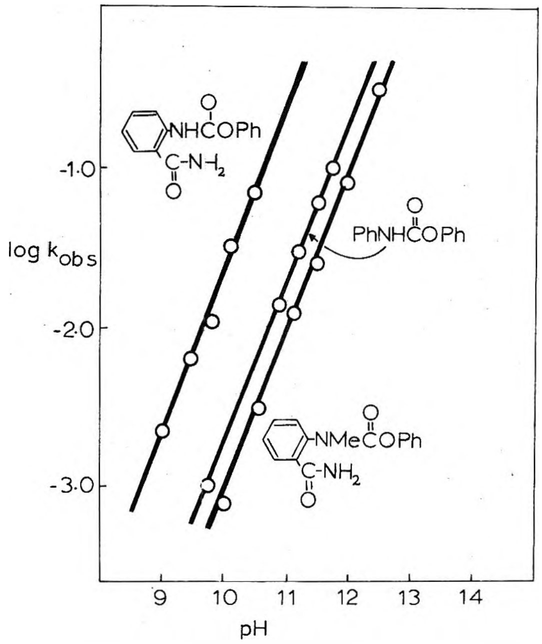


Figure 1. Plot of the logarithm of the observed rate constants (in reciprocal seconds) *vs.* pH for the cyclization of the carbamates **6** and **11** and for the hydrolysis of **1** (R = R^1 = Ph) at 25° in 4:1 water-dioxane at 25°.

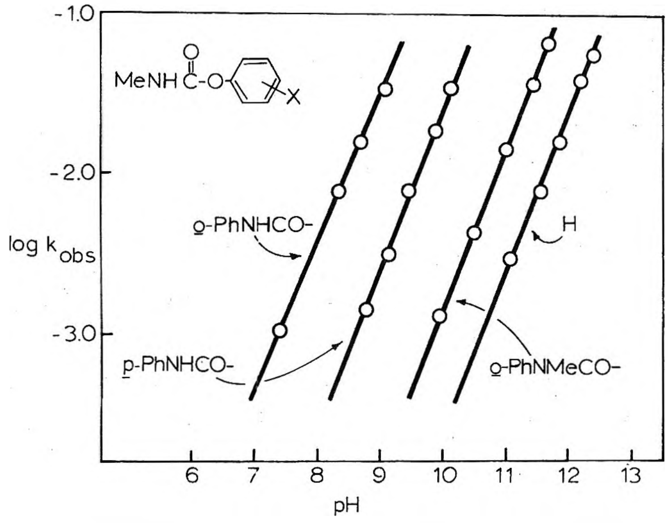


Figure 2. Plot of the logarithm of the observed rate constants (in reciprocal seconds) *vs.* pH for the hydrolysis of the aryl *N*-methylcarbamates **12a, 12b, 12c,** and **13** at 25° in 4:1 water-dioxane at 25°.

equivalent pathways (*e.g.*, assisted hydroxide ion attack at either the carbamate or amide centers) would be expected to give other products (*e.g.*, anthranilamide).

For compounds **11c** and **11d** (in which the nucleophile has been shown to participate also in the rate-determining step for cyclization of the unmethylated analogs), the presence of the *N*-methyl group actually *enhances* the rate of cyclization of the carbamate by 10-30-fold.[5,6] If this relationship also holds in the present instance, then **6** should cyclize (*via* **7**) at a rate less than one-tenth that observed for **11a.** Thus **6** actually cyclizes considerably more rapidly (at least 30 × tenfold) than expected on the basis of amide anion participation in the rate-determining step (**6** → **7** → **8**). The alternative E1cB mediated pathway (**6** → **9** → **10**) is therefore most likely operative, the o-amido group in **6** acting merely as an internal nucleophile to trap the isocyanate **10** which is formed in the rate-determining step. As shown above, the observed rate of cyclization of **6** is consistent with such a mechanism. However, the alternative mechanism involving amide anion attack on the carbamate becomes dominant when the isocyanate pathway is blocked by N,N disubstitution.

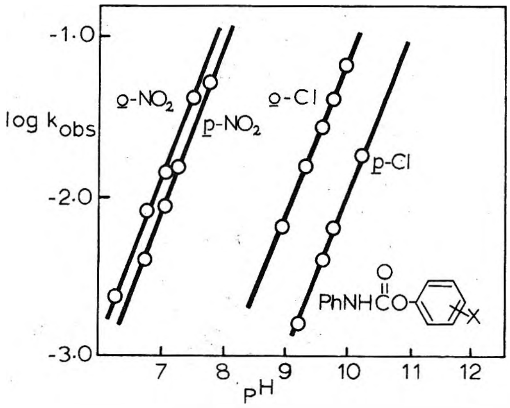
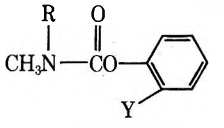
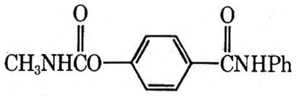


Figure 3. Plot of the logarithm of the observed rate constants (in reciprocal seconds) *vs.* pH for the hydrolysis of the o- and *p*-chlorophenyl and o- and *p*-nitrophenyl *N*-phenylcarbamates at 25° in 4:1 water-dioxane.

When an *N*-phenyl carbamoyl group is attached to the ortho position in the leaving phenoxide ion (as in **12a**), a large rate enhancement (relative to the unsubstituted material **12b**) is observed (Figure 2). The products in this case are not cyclic;[7] instead methylamine and salicylanilide are formed. This does not rule out participation by the neighboring amide group either acting as a general base or as a nucleophile to give a cyclic intermediate which is itself hydrolyzed rapidly to the observed products under the conditions of the experiment. Substituents in the leaving group have a very large effect ($\rho = -3.2$) on the rate of E1cB carbamate hydrolysis[2,3] and the rates of hydrolysis (expressed as k_1K_{a1} values) are correlated by σ^- for the substituents. Thus we have found that the para-substituted isomer **13** is hydrolyzed 100-fold more rapidly than the unsubstituted material **12b.** This is explicable in terms of the electron-withdrawing effect of the *p*-phenyl carbamoyl group (σ^- value for $CONH_2$ is +0.62,[9] giving a calculated rate difference also of *ca.* 100).

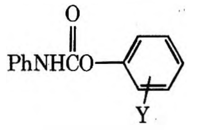


12a, R = H; Y = CONHPh
b, R = Y = H
c, R = H; Y = CON(Me)Ph
d, R = Me; Y = CONHPh

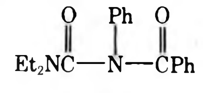


13

The ortho isomer **12a** is actually hydrolyzed 25-fold more rapidly than the para isomer **13** (to give methylamine and *p*-hydroxybenzanilide) (Table II). The more rapid hydrolysis of the ortho isomer appears to be general, since we have found that the o-nitro (**14c**) and o-chloro (**14a**) carbamates (Figure 3) hydrolyze more rapidly (sevenfold in the case of the o-chloro group) than the para-substituted analogs (see Table II). The rate enhancement is, however, small (60%) in the case of the o-nitro isomer. This most likely arises since the *p*-nitro group is strongly



14a, Y = *o*-Cl
b, Y = *p*-Cl
c, Y = *o*-NO$_2$
d, Y = *p*-NO$_2$



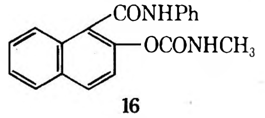
$Et_2NC(=O)-N(Ph)-C(=O)Ph$

15

electron withdrawing by resonance (as shown by the use of a σ^- value to correlate data for the *p*-nitro-substituted compound).[3] To achieve this, the nitro group must become coplanar with the aromatic ring. This coplanarity, essential for optimum reactivity, is not possible in the *o*-nitro isomer owing to the adjacent carbamate group. When the o-amide group is disubstituted (as in **12c**) the rate of hydrolysis is actually 25-fold slower than that of the para-substituted material **13** (see Table II). The slow reaction of the methylated compound **12c** can be attributed to steric inhibition of resonance stabilization during reaction; the presence of the *N*-methyl group forces the carbamoyl group out of the plane of the phenyl ring of the leaving group (this is clear from molecular models), thus reducing its electron-withdrawing ability.

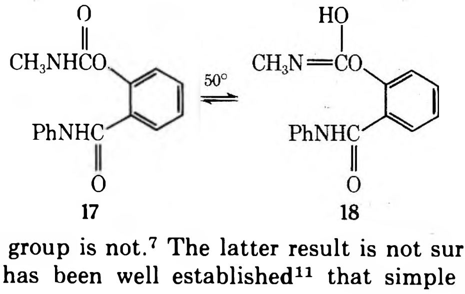
When the carbamate nitrogen is disubstituted, as in **12d,** then the E1cB pathway is blocked and the carbamate hydrolyzes very slowly (see Table II); the observed rate of hydrolysis is just that expected for direct HO^- attack on the carbamate linkage.[4,10] This contrasts with the behavior shown by compound **11a,** in which the amide group most likely participates. The possibility therefore arises that the slow rate of hydrolysis measured for **12d** at high pH was actually the subsequent reaction of a material formed rapidly by initial amide anion participation in **12d.** This is a viable possibility since the *N*-acylurea **15,** which is analogous to *N,N*-dimethyl-*N'*phenyl-*N'*-(*o*-hydroxybenzoyl)urea, is hydrolyzed at a rate ($k_{obsd} = 3.7 \times 10^{-4}$ sec^{-1} at $HO^- = 1.0\ M$) comparable to that observed for **12d.** To investigate this, we have carefully examined the ultraviolet spectrum of **12d** in the pH region 7–11 and have found no evidence for reaction. Moreover, when **12d** does react at pH >11, repetitive scans of the ultraviolet region show tight isosbestic points, showing the absence of relatively stable intermediates.

Several alternative modes of catalyzed hydrolysis of **12a** have previously been suggested,[7] with in each case the carbamate moiety being converted to a nucleophilic group. The reactivity of **12a,** like that of **6,** can, however, be explained without the intervention of neighboring-group participation. Because of the large sensitivity to substituent effects shown in the leaving group in the elimination–addition pathway, even a small change in the effective σ value of a substituent (by N-methylation of the amide group, for example) would bring about a marked change in reactivity. It is likely that a similar effect might explain the observed[7] low reactivity of the carbamate **16;** the interactions between the peri hydrogen and the neighboring phenylcarbamoyl group force the latter to adopt a conformation out of the plane of the aromatic rings.



16

Evidence has been put forward on the basis of nmr studies to suggest that the carbonyl group of the carbamate **17** is readily tautomerizable to **18** while the anilide carbonyl group is not.[7] The latter result is not surprising, since it has been well established[11] that simple amides exist almost exclusively (with tautomeric constants $<10^{-6}$) in that form. However, because of the structural similarities between the amide and carbamate groups (and their tautomers), it is unlikely that **18** would be sufficiently stabilized to allow nmr detection. We have therefore reexamined the nmr spectrum of **17.**



17 **18**

Thus the nmr spectrum of **17** in DMF-d_7 gives rise to a singlet at δ 10.00 attributable to the anilide proton and a doublet at δ 2.78 and 2.70 due to the *N*-methyl group. The aromatic ring protons and the proton on the carbamate nitrogen resonate as a multiplet between δ 7.0 and 8.0. In addition to these signals two other singlets at δ 10.50 and 3.03 have been observed by Hsi, *et al.*,[7] which were attributed to the hydroxyl proton and the *N*-methyl group of structure **18.** It was also reported that addition of D_2O to the sample removes the signal at δ 10.50 and also results in the collapse of the doublet at δ 2.78 and 2.70 to a singlet at δ 2.76, the other signals remaining unaffected. Heating the sample (to 50°) in DMF-d_7 resulted in an increase in the intensity of the peaks at δ 10.50 and 3.03 with a corresponding diminution of the *N*-methyl doublet at δ 2.78 and 2.70; this effect is reversed by cooling.

We have reexamined the nmr spectrum of **17** under the same conditions and found no trace of the peaks at δ 10.50 and 3.03 at 30° or at 50°. The doublet at δ 2.78 and 2.70 is not symmetrical at room temperature, the peak at δ 2.78 being more intense. At 50° both peaks have equal intensity and addition of D_2O results in the collapse of the doublet. A similar examination of the spectrum of phenyl *N*-methylcarbamate shows only the peaks corresponding to the expected structure (**12b**). Reports are also available of the nmr spectra of a group of *N*-methyl carbamates used as pesticides,[12] and these show no trace of substrate tautomerization. Studies on other carbamates point to partial double bond character occurring along the ethereal oxygen–carbon bond, rather than tautomerization.[13]

It is difficult, therefore, to reconcile the previously reported results for **17.** However, the anilide proton from salicylanilide, a possible hydrolysis product from **17,** does resonate at δ 10.5. Also the spectrum of neat dimethylformamide gives a doublet at δ 2.98 and 2.82 (at 34.5°). The relative intensity of the two peaks changes on heating to 50°, the peak at δ 2.98 increasing. The residual protons in DMF-d_7 give a similar effect.

Experimental Section

Materials. All inorganic compounds used were Analar grade. Dioxane was BDH Analar grade, used without further purification. Deionized water was twice distilled from alkaline potassium permanganate.

The solvent used for the kinetic experiments, 4:1 water–dioxane, was prepared by mixing four volumes of water with one volume of dioxane at 25°. The ionic strength was maintained at 1.0 by the addition of potassium chloride. The pH of the solution was maintained either by the presence of low (0.01 *M*) concentrations of pH-Stat–ultraviolet spectrophotometer, which has previously been described.[4]

Melting points were taken on a Hoover oil-bath capillary melting point apparatus and are uncorrected. Ir spectra were measured using a Perkin-Elmer Model PE257 spectrometer, the solids being examined as KBr disks. Nmr spectra were run on a Perkin-Elmer Model 20A spectrometer.

Substrates. Phenyl *N*-Methylcarbamate. Method A. To a stirred solution of phenol (0.94 g, 0.01 mol) in dry benzene (20 ml) was added a solution of methyl isocyanate (0.57 g, 0.01 mol) dissolved in benzene (5 ml). A drop of triethylamine was added and the mixture was stirred at room temperature for 20 min. On evaporation of the solvent *in vacuo,* the residue was recrystallized from diethyl ether–petroleum ether (bp 40–60°) to give the carbamate, mp 83–85°, nmr δ 7.7 (m, ArH and NH).

Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 5.96; N, 9.30. Found: C, 63.70; H, 5.40; N, 9.09.

***p*-Benzanilido *N*-Methylcarbamate.** To a solution of *p*-hydroxybenzoic acid (2.96 g, 0.02 mol) dissolved in anhydrous THF (15 ml) was added a solution of dicyclohexylcarbodiimide (4.12 g, 0.02 mol), dissolved in anhydrous THF (20 ml) and aniline (1.86 g, 0.02 mol). The mixture was allowed to stand at 0° for 4 hr and the precipitated urea was filtered off. Evaporation of the solvent *in vacuo* gave an oil, which solidified on dissolution in ether followed by addition of petroleum ether. The solid was recrystallized from ethanol–water to yield *p*-hydroxybenzanilide, mp 198–199° (lit.[14] mp 196–197°). The anilide was converted to the carbamate using method A above, and on recrystallization from chloroform–petroleum ether had mp 176–178°.

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.6; H, 5.2; N, 10.4. Found: C, 66.60; H, 5.35; N, 10.60.

Phenyl *N*-(*o*-Carbamoylphenyl)carbamate. To a stirred solution of anthranilamide (2.72 g, 0.02 mol) in ether (50 ml) at ambient temperature was added a solution of phenyl chloroformate (1.56 g, 0.01 mol) in ether (20 ml). The precipitated anthranilamide hydrochloride was filtered off and the filtrate was reduced to dryness *in vacuo*. The residue was recrystallized from chloroform–petroleum ether to give phenyl *N*-(*o*-carbamoylphenyl)carbamate, mp 159–160°.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: C, 65.60; H, 4.68; N, 10.91. Found: C, 65.61; H, 4.65; N, 11.02.

Phenyl *N*-Methyl-*N*-(*o*-carbamoylphenyl)carbamate. To a stirred solution of *N*-methylanthranilamide (3.0 g, 0.02 mol) in THF (50 ml) was added phenyl chloroformate (1.56 g, 0.01 mol) in 5 ml of the same solvent. A drop of pyridine was added and the mixture was refluxed for 30 min. The precipitated hydrochloride of *N*-methylanthranilamide was filtered off and the filtrate was evaporated to dryness. The residue was recrystallized from chloroform–petroleum ether to give phenyl *N*-methyl-*N*-(*o*-carbamoylphenyl)carbamate, mp 146–148°.

Anal. Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.18; N, 10.36. Found: C, 66.44; H, 5.11; N, 10.35.

***o*-Nitrophenyl *N*-Phenylcarbamate.** To a stirred solution of o-nitrophenol (2.58 g, 0.01 mol) dissolved in 20 ml of dry benzene was added phenyl isocyanate (1.19 g, 0.01 mol) dissolved in 10 ml of the same solvent. Pyridine (0.2 ml) was added as catalyst and the mixture was refluxed for 30 min. On cooling the carbamate was precipitated by reducing the solvent *in vacuo*. Recrystallization from chloroform–pentane gave *o*-nitrophenyl *N*-phenylcarbamate, mp 127–128°.

Anal. Calcd for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.87; N, 10.85. Found: C, 60.50; H, 4.08; N, 11.05.

Similarly prepared was *o*-chlorophenyl *N*-phenylcarbamate, mp 123–125°.

Anal. Calcd for $C_{13}H_{10}ClNO_2$: C, 63.02; H, 4.04; N, 5.65. Found: C, 63.47; H, 4.05; N, 5.95.

The preparation of *p*-chlorophenyl *N*-phenylcarbamate, mp 148–150°, and *p*-nitrophenyl *N*-phenylcarbamate, mp 150–152°, has previously been described.[4]

o-Benzanilido *N*-methylcarbamate, *o*-(*N'*-methyl)benzanilido *N*-methylcarbamate, and o-benzanilido *N,N*-dimethylcarbamate were prepared by the method of Hsi, *et al.*,[7] and had physical properties described.

2,4(1*H*,3*H*)-Quinazolinedione and 2-(*N*-methyl)-4(1*H*,3*H*)-quinazolinedione were prepared from methyl 2-ureidobenzoate and methyl 2-(*N*-methylureido)benzoate by the method of Hegarty and Bruice.[15]

***N,N*-Diethyl-*N'*-benzoyl-*N'*-phenylurea.** *N,N*-Diethyl-*N'*-phenylformamide chloride (1.0 g) was refluxed for 16 hr with an equimolar quantity of silver benzoate (1.15 g) in dry ether. The precipitated silver chloride was filtered off and evaporation of the solvent gave the urea, mp 74–75°.

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.75; N, 9.5. Found: C, 72.90; H, 7.10; N, 9.40.

Kinetic Measurements. The kinetics of hydrolysis or cyclization of the N-aryl and N-alkyl carbamates were studied in 1:4 dioxane–water at 25° by following the change in optical density at suitable wavelengths. For those experiments measured in the presence of buffer (or those which were self-buffered at high pH) 3-ml quartz cuvettes were used, the reaction being initiated by the addition of 1 drop of a concentrated (usually 10^{-2} *M*) solution of the substrate in dioxane to the buffer solution in the cuvette. Optical density *vs.* time plots were then obtained using a Unicam Model SP800B spectrophotometer equipped with multiple thermostattable cell compartment, scale expansion accessory, and external AR25 recorder. Preliminary repetitive scans of the ultraviolet region established the suitable wavelengths at which the optical density changed in the course of the reaction; it was established that the observed rate constants were independent of the wavelength chosen to study the reaction. Some measurements were also made in the absence of added buffer species. In this case, the course of the reaction was also followed spectrophotometrically using a Cary Model 14 spectrophotometer fitted with a special cell (which has previously been described)[4] whose contents can be maintained at constant pH using a radiometer pH-Stat assembly. In all cases good pseudo-first-order rate constants were obtained to >95% reaction. The individual constants were calculated either graphically or using a weighted least-squares program using an Olivetti Underwood Programma 101 calculator. In all cases the pH values quoted were the values directly measured in 4:1 water–dioxane using a Radiometer Model PHM 26 pH meter equipped with a Metrohm EA 125U combined glass electrode. The electrode was initially standardized using Radiometer aqueous buffer solutions. The pH of the reaction solutions was measured before and after a kinetic experiment; any run which showed an excessive pH drift (±0.05 pH unit) was discarded.

The products of hydrolysis were determined in all cases by comparing the ultraviolet spectrum obtained at the completion of a kinetic experiment with the spectrum of an authentic sample of the product (or mixture of products). In most cases the products were additionally identified by actual isolation by carrying out the reaction on a larger scale than that used for the spectrophotometrically measured runs; thin layer chromatography established the identity of the products formed in each case. When one of the products (*e.g.*, the quinazolinedione **8**) had a pK_a value within measurable range, additional confirmation of its presence as a reaction product could be obtained by recording the change in the uv spectrum of the product as the pH was changed; this gave an estimate of the pK_a of the product, which could be compared with the value for an authentic sample measured under the same conditions.

Registry No.—**1** (R = R' = Ph), 4930-03-4; **6**, 50585-30-3; **11a**, 50585-31-4; **11b**, 13599-69-4; **12a**, 5591-49-1; **12b**, 1943-79-9; **12c**, 35410-16-3; **12d**, 35410-18-5; **13**, 50585-32-5; **14a**, 16400-07-0; **14b**, 16323-15-2; **14c**, 21468-56-4; **14d**, 6320-72-5; **15**, 50585-33-6; 2,4-(1*H*,3*H*)-quinazolinedione, 86-96-4; phenol, 108-95-2; methyl isocyanate, 624-83-9; *p*-hydroxybenzoic acid, 99-96-7; aniline, 62-53-3; anthranilamide, 88-68-6; phenyl chloroformate, 1885-14-9; *N*-methylanthranilamide, 4141-08-6; *o*-nitrophenol, 88-75-5; phenyl isocyanate, 103-71-9.

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Acidities and Partition Coefficients of Fluoromethanesulfonamides

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The half-neutralization potentials (HNP) of a series of biologically active fluoromethanesulfonamides were determined in 67% *N,N*-dimethylformamide–water. A plot of aqueous pK_a *vs.* HNP for nine methanesulfonamides and fluoromethanesulfonamides in the series was used to calculate the pK_a's of the remaining water-insoluble sulfonamides. The pK_a's of eight aryl-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides correlated better with the Hammett substituent constant σ than with σ^- or σ_{phenol}. The Hammett reaction constant ρ was 2.15. The stepwise addition of fluorine atoms to the (methanesulfonyl)amino moiety in three related series of aryl-substituted fluoro-*N*-phenylalkanesulfonamides gave a linear acidity increase of 1.47 pK_a units per fluorine. Partition coefficients were measured in 1-octanol–water for 28 1,1,1-trifluoro-*N*-phenylmethanesulfonamides. The results demonstrated that this type of compound is considerably more lipophilic ($\log P = 3.05$ for 1,1,1-trifluoro-*N*-phenylmethanesulfonamide) than the corresponding carboxylic acids or phenols. The effect of the stepwise increase of α-fluorine content upon partition coefficient was not linear, but a second-order equation provided an excellent correlation.

It recently was reported that many fluoromethanesulfonamides have potent herbicidal[1] and anti-inflammatory[2] activity. These compounds are nitrogen acids of a unique structural type which exhibit novel chemical and biological properties. The presence of fluorine in the (fluoromethanesulfonyl)amino group of these nitrogen acids confers upon them high acidity and lipophilicity which contribute to their biological activity. This paper reports an investigation into the unusual acidic and lipophilic properties of these compounds. The general term fluoromethanesulfonamide is used to describe sulfonamides in which one to three atoms of fluorine are attached to the carbon of the (methanesulfonyl)amino moiety.

Methodology and Results

Acidity Measurements. Many of the fluoromethanesulfonamides in this study were insufficiently water soluble for direct measurement of hydrogen ion concentration. Therefore, aqueous pK_a's of nine water-soluble sulfonamides were determined by direct titration or by back-titration of the corresponding salt. The pK_a's of methanesulfonamide[3] and *N*-phenylmethanesulfonamide[4] were obtained by direct titration in water by other investigators. These pK_a values were plotted *vs.* half-neutralization potentials (HNP) determined in a 67% *N,N*-dimethylformamide (DMF)–water solvent system to give the calibration line of Figure 1. The pK_a and HNP values used in the plot are collected in Table I. The line shown in Figure 1 was obtained by the least-squares method and is described by the equation

$$pK_a = 5.58 - (0.0138 \pm 0.0005)\text{HNP} \qquad (1)$$
$$r,\ 0.999;\ \text{SE},\ 0.149;\ F,\ 2{,}754$$

where r is the correlation coefficient, SE is the standard error of the dependent variable, and F is the ratio of the mean sum of error squares removed by the regression to the mean sum of squares of the error residuals not removed by regression. The 95% confidence limits (± two standard deviations) are given for the independent variable.

Equation 1 was utilized to calculate pK_a's of 18 water-insoluble or sparingly soluble methanesulfonamides and fluoromethanesulfonamides from HNP measurements in the 67% DMF–water solvent system. The calculated pK_a's are collected in Table II. It should be emphasized that the pK_a values reported in this investigation are apparent pK_a values since the calculations do not include activity corrections. This method of obtaining pK_a's for water-insoluble acids has been utilized in the past when the acids were restricted to one class.[5-7]

Partition Coefficient Measurements. The partition coefficients of 28 methanesulfonamides and fluoromethanesulfonamides were measured by a modification of the standard technique of Hansch[8] using a 1-octanol–water solvent system. The partition coefficient P is defined as

$$P = C_o/C_w(1 - \alpha) \qquad (2)$$

where C_o is the equilibrium concentration of a compound in the octanol phase, C_w is the equilibrium concentration in the water phase, and α is the degree of dissociation in water.

The initial experimental measurements in this study were made under nonbuffered conditions and required correction for the degree of dissociation. However, during the course of the investigation it was observed that the metal and organic amine salts of these nitrogen acids were exceedingly soluble in organic solvents, raising the possibility that some of the ionized sulfonamide was also contributing to C_o. This problem was obviated by making the partition coefficient measurements in an acidic buffer system of pH 1 (0.1 *N* perchloric acid) in which the sulfonamide was nonionized. This procedure was verified by determining partition coefficients of benzoic, 4-chloro-, and 3-methoxybenzoic acids in the 0.1 *N* perchloric acid buffered system. These values agreed well with literature values reported by Hansch[8] in which the degree of dissociation was employed to calculate partition coefficients for these same three acids measured in a nonbuffered system. Table III lists the measured partition coefficients for a series of sulfonamides as a function of fluorine content, while Table IV contains substituent constant (π) values calculated[8] from partition coefficients (eq 7) determined for 21 substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides.

Discussion

Acidities. The well-known Hammett equation provides a means of studying the influence of 3- and 4-substituents on the side-chain reactions of benzene derivatives and was utilized to more fully characterize the acidity of the substituted fluoro-*N*-phenylmethanesulfonamides of this report. The Hammett equation is usually given in the form

$$\log K = \log K_o + \rho\sigma \qquad (3)$$

where K and K_o are equilibrium constants for the substituted and unsubstituted compounds respectively, σ is a measure of the polar effect of the substituent relative to

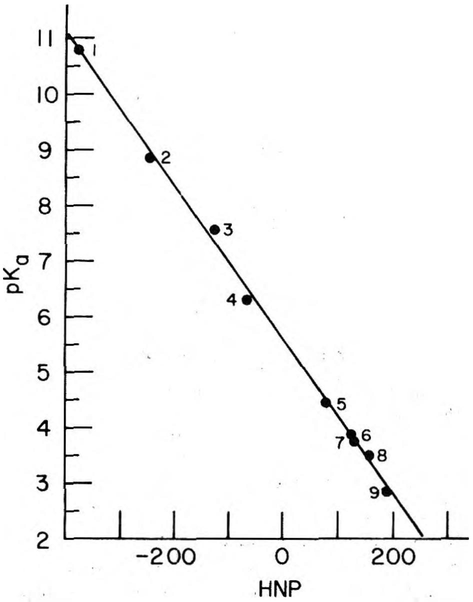

Figure 1. Calibration plot of pK_a in water *vs.* HNP in 67% DMF-water for a series of nine methanesulfonamides and fluoromethanesulfonamides. Data from Table I.

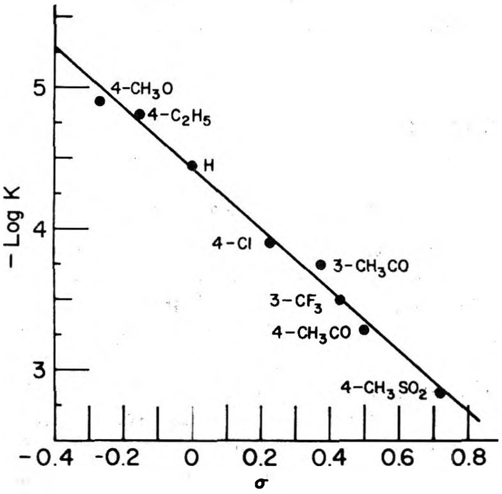

Figure 2. Linear free energy relationship for the ionization of substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides in water at 25°.

Table I
Experimentally Determined pK_a and HNP Values

No.	Compd	HNP,[a] mV	pK_a[b]
1	$NH_2SO_2CH_3$	−377	10.8[3]
2	$C_6H_5NHSO_2CH_3$	−245	8.85[4]
3	$CH_3NHSO_2CF_3$	−124	7.56
4	$NH_2SO_2CF_3$	−68	6.33
5	$C_6H_5NHSO_2CF_3$	78	4.45
6	$4\text{-}ClC_6H_4NHSO_2CF_3$	125	3.90
7	$3\text{-}CH_3COC_6H_4NHSO_2CF_3$	132	3.75
8	$3\text{-}CF_3C_6H_4NHSO_2CF_3$	160	3.50
9	$4\text{-}CH_3SO_2C_6H_4NHSO_2CF_3$	190	2.84

[a] 67% DMF–water. [b] Water.

Table II
Experimentally Determined HNP and Calculated pK_a Values for a Series of 18 Methanesulfonamides and Fluoromethanesulfonamides

No.	Compd	HNP,[a] mV	Calcd pK_a
10	$NH_2SO_2CFH_2$	−271	9.32
11	$3\text{-}C_6H_5COC_6H_4NHSO_2CH_3$	−189	8.19
12	$NH_2SO_2CF_2H$	−180	8.06
13	$C_6H_5NHSO_2CFH_2$	−144	7.57
14	$C_6H_5CH_2NHSO_2CF_3$	−90	6.82
15	$3\text{-}C_6H_5COC_6H_4NHSO_2CFH_2$	−86	6.77
16	$C_6H_5NHSO_2CF_2H$	−44	6.19
17	$3\text{-}C_6H_5COC_6H_4NHSO_2CF_2H$	10	5.44
18	$4\text{-}CH_3OC_6H_4NHSO_2CF_3$	49	4.90
19	$4\text{-}C_2H_5C_6H_4NHSO_2CF_3$	55	4.82
20	$2\text{-}CH_3,4\text{-}ClC_6H_3NHSO_2CF_3$	122	3.90
21	$3\text{-}C_6H_5COC_6H_4NHSO_2CF_3$	136	3.70
22	$2,4\text{-}diFC_6H_3NHSO_2CF_3$	155	3.44
23	$4\text{-}CH_3COC_6H_4NHSO_2CF_3$	166	3.29
24	$4\text{-}C_6H_5COC_6H_4NHSO_2CF_3$	171	3.22
25	$2,4\text{-}diClC_6H_3NHSO_2CF_3$	190	2.96
26	$2,4,6\text{-}triClC_6H_2NHSO_2CF_3$	209	2.70
27	$2\text{-}CF_3,4\text{-}ClC_6H_3NHSO_2CF_3$	217	2.59

[a] 67% DMF–water.

hydrogen, and ρ, the reaction constant, is a measure of the susceptibility of the reaction to polar effects.

From the pK_a values of Tables I and II and using the least-squares method, a plot (Figure 2) of pK_a (*i.e.*, $-\log K$) *vs.* Hammett σ values was prepared for a series of eight 1,1,1-trifluoro-*N*-phenylmethanesulfonamides. The σ values were from ref 9, Table 4-1, and are based on the ionization of substituted benzoic acids. This straight line had a ρ of 2.15, $\log K_0$ of −4.42, and r of 0.994. The value for the reaction constant is more similar to the ρ of 2.21 obtained[10] for the ionization of substituted phenols in water at 25° than it is to the ρ of 1.00 for benzoic acid ionization under the same conditions.

Because of the possibility of direct resonance interaction between the substituent group and the reaction center, additional correlations were attempted. The second correlation utilized σ^- values[9] for the 4-CH_3CO and 4-CH_3SO_2 substituents. However, Van Bekkum, Verkade, and Wepster[10] have proposed that a multiplicity of σ values should be used, depending upon reaction type, rather than one σ^- value for all such reactions. Accordingly, the third correlation utilized σ_{phenol} values[10] for the 4-CH_3O, 4-Cl, 4-CH_3CO, and 4-CH_3SO_2 substituents while the remaining substituents retained their original σ values. All of these fits are compared in Table V.

Thus, the pK_a's of these eight aryl-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides correlated better with the Hammett substituent constant σ than with σ^- or σ_{phenol}.[11] These results contrast with those obtained previously by Willi[12] for the ionization of substituted benzenesulfonamides, $XC_6H_4NHSO_2C_6H_5$. The best fit of the Willi data with a substituent constant requires use of σ^- with a resulting ρ of 1.74 (r, 1.00).

Another interesting aspect of this work concerns the effects on pK_a of fluorine accumulation in methanesulfonamides. The equations for the calculated fits (least-square methods) of pK_a to the number (n = 0–3) of α-fluorine atoms for three series of nitrogen acids are as follows.

$$NH_2SO_2CH_{3-n}F_n \qquad pK_a = 10.82 - 1.47n \qquad (4)$$
$$r,\ 0.998;\ \text{SE},\ 0.14;\ F,\ 546$$

$$C_6H_5NHSO_2CH_{3-n}F_n \qquad pK_a = 8.95 - 1.46n \qquad (5)$$
$$r,\ 0.997;\ \text{SE},\ 0.17;\ F,\ 387$$

$$3\text{-}C_6H_5COC_6H_4NHSO_2CH_{3-n}F_n \qquad pK_a = 8.25 - 1.48n \qquad (6)$$
$$r,\ 0.998;\ \text{SE},\ 0.14;\ F,\ 575$$

These exceptionally good fits indicate that the effect of accumulation of fluorine in these acids is linear with each additional fluorine atom increasing the acidity by about 1.47 pK_a units. This additivity is probably due to the small steric change in replacing hydrogen by fluorine and also to the fact that fluorine addition is occurring two atoms away from the acidic site. When these conditions

Table III
Variation of Partition Coefficient as a Function of Fluorine Content

No.	n	Log P
	$C_6H_5NHSO_2CH_{3-n}F_n$	
2	0	0.95
13	1	1.35
16	2	1.95
5	3	3.05
	$4\text{-}ClC_6H_4NHSO_2CH_{3-n}F_n$	
28	0	1.85
29	1	2.25
30	2	2.84
6	3	3.96

Table IV
Calculated Substituent Constant π for a Series of Substituted 1,1,1-Trifluoro-*N*-phenylmethanesulfonamides

Phenyl substituent	Substituent constant, π 3-Substituted[a]	4-Substituted[a]	2,4-Disubstituted
H	0	0	0
F	0.37 (23384-01-2)	0.20 (23384-00-1)	0.01
Cl	0.95 (23384-03-4)	0.91	0.83
Br	0.77 (23384-08-9)		
I		1.34 (23384-10-3)	
CF_3	1.45	1.42 (23384-12-5)	
HO	−0.54 (23375-12-4)		
CH_3		0.55 (37595-73-6)	
C_6H_5		1.92 (50585-77-8)	
CH_3S		0.69 (23375-06-6)	
CH_3CO	−0.27	−0.22	
C_6H_5CO		1.23	
CH_3O	0.08 (23384-33-0)	−0.05	
CH_3SO_2	−1.20 (23375-08-8)	−1.06	

[a] Registry numbers are in parentheses.

Table V
Comparison of Fits of Log K to Different Substituent Constants for Eight 1,1,1-Trifluoro-*N*-phenylmethanesulfonamides

Substituent constant	Ref	ρ	r	SE	F
σ	9	2.15	0.994	0.08	575
σ^-	9	1.54	0.975	0.18	118
σ_{phenol}	10	1.27	0.969	0.20	92

are not met, acidifying substituent effects are not linear, as shown by Pearson and Dillon with carbon acids.[13]

Partition Coefficients. Hansch and coworkers[8,14-16] have developed a method of correlating biological activity with the free energy related parameters of π and Hammett σ value. The substituent constant π is defined in eq 7

$$\pi = \log P_x - \log P_H \quad (7)$$

where P_H is the partition coefficient of the parent compound, in this case $C_6H_5NHSO_2CF_3$, and P_x is the partition coefficient for a derivative. The π values were calculated for 21 1,1,1-trifluoro-*N*-phenylmethanesulfonamides from experimentally determined partition coefficients. Comparison of these π values (Table IV) with those given by Hansch[8] for phenoxyacetic acids, phenylacetic acids, benzoic acids, and phenols gave no clear correlation with any of these systems, although the π values are of similar magnitude. For instance, the CH_3SO_2 substituent is hydrophilic while halide substituents are lipophilic when compared to the parent compounds. However, the 1,1,1-trifluoro-*N*-phenylmethanesulfonamide series is distinctly more lipophilic overall than the four series of compounds in the Hansch study,[8] with the following log P values for the parents in each series listed as follows.

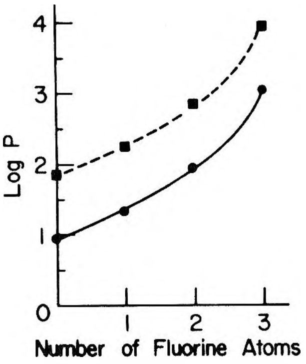

Figure 3. Variation of log P as a function of fluorine content: ■, $4\text{-}ClC_6H_4NHSO_2CH_{3-n}F_n$; ●, $C_6H_5NHSO_2CH_{3-n}F_n$. Data from Table III.

Compd	Log P
Phenoxyacetic acids	1.28
Phenylacetic acids	1.41
Benzoic acids	1.88
Phenols	1.46
1,1,1-Trifluoro-*N*-phenylmethanesulfonamides	3.05

The π values determined in this study have been correlated with preemergence herbicidal activity in a paper by Yapel[17] of these laboratories. The Yapel study found that the 3- and 4-substituted 1,1,1-trifluoro-*N*-phenylmethanesulfonamides behave as two separate classes and large positive Hammett σ values enhance herbicidal activity in either class. In addition, surfactants used in greenhouse herbicidal tests were found to affect biological activity by virtue of enhanced penetration into the plant in some cases. This complication required measurement of π values in the presence of surfactant for better correlations.[17,18]

As a further aspect of the present study, the partition coefficients in Table III were plotted against number of fluorine atoms as in the acidity study. In these plots (Figure 3), linear relationships were not observed, but good second-order fits were obtained[19] with eq 8 and 9.

$C_6H_5NHSO_2CH_{3-n}F_n$

$$\log P = 0.97 + 0.17n + 0.18n^2 \quad (8)$$

r, 0.999; SE, 0.07; F, 278

$4\text{-}ClC_6H_4NHSO_2CH_{3-n}F_n$

$$\log P = 1.87 + 0.15n + 0.18n^2 \quad (9)$$

r, 0.999; SE, 0.08; F, 218

The reason for this extra enhancement of lipophilicity with increase of fluorine content is not readily apparent. Obviously, structural and electronic variations are occurring with variation of the number of fluorine atoms. These changes are in the hybridization at the carbon atom attached to the fluorine atoms, in d-orbital interaction of the sulfur with the adjacent pair of electrons on the nitrogen atom, as well as in the steric change which occurs when hydrogen is replaced by fluorine. How each of these changes quantitatively affect lipophilicity is not known.

Experimental Section

Acidity Measurements. Experimental pK_a values in Table I were obtained by potentiometric titration as outlined by Albert and Serjeant[20] and calculated by eq 10. The measurement of pH

$$\text{p}K_a = \text{pH} + \log\,[\text{HA}]/[\text{A}^-] \qquad (10)$$

during the stepwise titration of a known sample weight with standard titrant permits calculation of pK_a, since the mole ratio of the acid-base conjugated pair is determined from the amount of titrant added. The experimental procedure consisted of dissolving 0.33 mmol of sulfonamide in water (40 ml) and titrating with standard base. For compounds of limited solubility (sulfonamides **7**, **8**, and **9**) the corresponding potassium salt was titrated with standard acid and the data up to the point of precipitation were utilized for calculation of pK_a.

Half-neutralization potentials, *i.e.*, the potential in millivolts at 50% neutralization, were determined in 67% DMF-water. Note that in eq 10 pK_a is equal to the pH of the solution at 50% neutralization. This relationship gives validity to the usage of half-neutralization potentials as a measure of intrinsic acidity. The potentiometric procedure consisted of dissolving 0.33 mmol of sulfonamide in DMF (26.8 ml) followed by the addition of water (12.6 ml). The solution was titrated with tetrabutylammonium hydroxide (Eastman 7744, 25% in methanol, diluted with water to 0.25 *N*) using a Sargent Model D recording titrator employing a Beckman glass combination electrode (39142). Using this system, pH 4 and 9 buffers read 165 and −132 mV, respectively.

Partition Coefficient Measurements. For purification, the 1-octanol was washed three times with 1 *N* NaOH and six times with distilled water. The purified 1-octanol was then saturated with 0.1 *N* aqueous perchloric acid. The sulfonamide (0.12–0.15 g) was dissolved in the prepared 1-octanol, an equal volume of 0.1 *N* aqueous perchloric acid (1-octanol saturated) was added, and the mixture was agitated on a mechanical shaker for 1 hr. After separation, the aqueous layer was centrifuged and analyzed for sulfonamide by uv spectrophotometry (Cary Model 14). The concentration of sulfonamide remaining in 1-octanol was determined by difference. Log *P* values so obtained were estimated to have uncertainties of ±2%.

Nonfluorinated Sulfonamides. Methanesulfonamide (**1**) is commercially available. *N*-Phenylmethanesulfonamide (**2**) and *N*-(4-chlorophenyl)methanesulfonamide (**28**) were prepared according to the published procedure.[21]

***N*-(3-Benzoylphenyl)methanesulfonamide (11).** To a stirred solution of 3-aminobenzophenone (19.7 g, 0.1 mol) and 300 ml of dry benzene, methanesulfonyl chloride (11.5 g, 0.1 mol) was added dropwise at 50–55°. After stirring for 48 hr at 50–55°, the reaction mixture was cooled and 250 ml of 10% sodium hydroxide was added. The alkaline layer was removed, washed with benzene (100 ml) and chloroform (100 ml), and then made acidic with concentrated HCl. The yellow solid was filtered and recrystallized from ethanol-water to afford 20.8 g (75.5%) of **11**, mp 99.0–101°.

Anal. Calcd for $C_{14}H_{13}NO_3S$: C, 61.1; H, 4.8. Found: C, 61.2; H, 4.8.

1-Fluoromethanesulfonamides. 1-Fluoromethanesulfonyl chloride and 1-fluoro-*N*-phenylmethanesulfonamide (**13**) were prepared according to Farrar.[22]

1-Fluoromethanesulfonamide (10). Ammonia was slowly bubbled into a stirred solution of 1-fluoromethanesulfonyl chloride (13.2 g, 0.1 mol) in dichloromethane (100 ml) at room temperature. After 3 hr, the solvent was evaporated and the residue was extracted with ether. The ether was evaporated to give a white solid, which was recrystallized from hexane-ether to afford 5.3 g (46.9%) of **10**, mp 80.5–82.5°.

Anal. Calcd for CH_4FNO_2S: C, 10.6; H, 3.6; N, 12.4. Found: C, 10.8; H, 3.6; N, 12.5.

***N*-(3-Benzoylphenyl)-1-fluoromethanesulfonamide (15).** To a stirred solution of 3-aminobenzophenone (86.5 g, 0.44 mol) and *N*,*N*-dimethylaniline (53.0 g, 0.44 mol) in dichloromethane (800 ml), 1-fluoromethanesulfonyl chloride (54.3 g, 0.41 mol) in dichloromethane (100 ml) was added dropwise in 15 min. The resulting solution was heated at reflux temperature for 27 hr. The solution was cooled, washed two times with 500 ml of 10% HCl, and extracted twice with 500 ml of 10% sodium hydroxide. The alkaline layer was separated, washed with dichloromethane, decolorized with charcoal, cooled with ice, and made acidic. The crystalline product was filtered and recrystallized from ethanol to yield 87.2 g (67.6%) of **15**, mp 117–119°.

Anal. Calcd for $C_{14}H_{12}FNO_3S$: C, 57.3; H, 4.1; N, 4.9. Found: C, 57.2; H, 4.2; N, 4.7.

***N*-(4-Chlorophenyl)-1-fluoromethanesulfonamide (29).** In a manner analogous to the preparation of sulfonamide **15**, *N*-(4-chlorophenyl)-1-fluoromethanesulfonamide (**29**) was obtained in an 88.0% yield, mp 86.5–88°.

Anal. Calcd for $C_7H_7ClFNO_2S$: C, 37.6; H, 3.2; N, 6.3. Found: C, 37.8; H, 3.1; N, 6.3.

1,1-Difluoromethanesulfonamides. 1,1-Difluoromethanesulfonyl chloride, *1,1-difluoro-N-phenylmethanesulfonamide* (**16**), and *N*-(4-chlorophenyl)-1,1-difluoromethanesulfonamide (**30**) were prepared according to Farrar.[22] The synthesis of *N*-(3-benzoylphenyl)-1,1-difluoromethanesulfonamide (**17**) has been described.[2]

1,1-Difluoromethanesulfonamide (12). Ammonia was bubbled for 2 hr into a stirred solution of 1,1-difluoromethanesulfonyl chloride (15.1 g, 0.1 mol) in dichloromethane (100 ml) at 0°. The solvent was evaporated and the residue was sublimed under vacuum to give 4.0 g (30.5%) of **12**, mp 64.0–65.5°.

Anal. Calcd for $CH_3F_2NO_2S$: C, 9.2; H, 2.3; N, 10.7. Found: C, 9.5; H, 2.4; N, 10.6.

1,1,1-Trifluoromethanesulfonamides. The preparation of 1,1,1-trifluoromethanesulfonamide (**4**) and of 1,1,1-trifluoro-*N*-phenylmethanesulfonamide (**5**) was reported by Brice and Trott.[23] The synthesis of *N*-(3-benzoylphenyl)-1,1,1-trifluoromethansesulfonamide (**21**) has also been reported.[2] The preparation of most of the remaining 1,1,1-trifluoro-*N*-phenylmethanesulfonamides is the subject of a forthcoming paper from these laboratories. The syntheses of the remaining sulfonamides not described in the forthcoming paper are given as follows.

1,1,1-Trifluoro-*N*-methylmethanesulfonamide (3). To a stirred solution of methylamine (676 g, 21.8 mol) in diethyl ether (1 l.) at −60°, 1,1,1-trifluoromethanesulfonyl fluoride (1035 g, 6.81 mol) was added over a period of 1.5 hr. After stirring at −60° for an additional 2 hr, the mixture was allowed to warm to 0° and washed with 3 *N* hydrochloric acid. The aqueous phase was washed with three 200-ml portions of dichloromethane. The dichloromethane and ether phases were combined, dried, and evaporated. The residue was distilled to afford 877 g (78.9%) of pure **3**, bp 86–94° (20 mm).

Anal. Calcd for $C_2H_4F_3NO_2S$: C, 14.7; H, 2.5. Found: C, 14.9, H, 2.4.

1,1,1-Trifluoro-*N*-phenylmethylmethanesulfonamide (14). Trifluoromethanesulfonic acid anhydride (70.5 g, 0.25 mol) was added dropwise to a stirred and cooled (ice bath) solution of benzylamine (27.0 g, 0.25 mol) and triethylamine (25.3 g, 0.25 mol) in chloroform (200 ml). The reaction mixture was then allowed to warm to room temperature and stirred with excess 10% sodium hydroxide. The alkaline layer was separated, washed with chloroform, cooled, and made acidic. The crystals were filtered and recrystallization from ligroin afforded 20.2 g (33.8%) of **14**, mp 42.5–45°.

Anal. Calcd for $C_8H_3F_3NO_2S$: C, 40.2; H, 3.4. Found: C, 40.2; H, 3.5.

***N*-(4-Benzoylphenyl)-1,1,1-trifluoromethanesulfonamide (24).** Sulfonamide **24** was prepared in 52.6% yield in the same manner as sulfonamide **14** and was recrystallized from ethanol-water to afford pure **24**, mp 136–137°.

Anal. Calcd for $C_{14}H_{10}F_3NO_3S$: C, 51.1; H, 3.1. Found: C, 50.7; H, 3.2.

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Registry No.—**1**, 3144-09-0; **2**, 1197-22-4; **3**, 34310-29-7; **4**, 421-85-2; **5**, 456-64-4; **6**, 23384-04-5; **7**, 23375-11-3; **8**, 23384-11-4; **9**, 23375-10-2; **10**, 50585-72-3; **11**, 50585-73-4; **12**, 50585-74-5; **13**, 2070-61-3; **14**, 36457-58-6; **15**, 22736-84-1; **16**, 658-43-5; **17**, 22736-85-2; 18, 23384-34-1; **19**, 50585-75-6; **20**, 23375-23-7; **21**, 22731-26-6; **22**, 23384-22-7; **23**, 23383-94-0; **24**, 22731-28-8; **25**, 23383-96-2; **26**, 23383-97-3; **27**, 23375-24-8; **28**, 4284-51-9; **29**, 50585-76-7; **30**, 1513-31-1.

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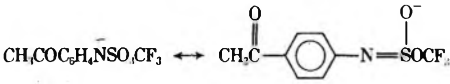

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Behavior of the Sulfoxide Group on the Nitration of Some Aryl Derivatives

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The product composition and the dependence of the reaction rates on acidity for the nitration of methyl phenyl sulfoxide in 83–100% sulfuric acid have been determined. The observed behavior compared with that of diphenyl sulfoxide and the dimethylphenylsulfonium ion shows that the species B and BH$^+$ present at equilibrium are involved in the nitration of sulfoxide compounds. Relative reactivities and partial rate factors of the conjugate acid form of the substrates are calculated at high acid concentrations.

The substituent effect of the sulfoxide group in an aromatic system can be expected to derive from polar and conjugative interactions. For methyl phenyl and diphenyl sulfoxide, the study of the nature of the interactions with the phenyl ring and the relative importance of their effects on the nitration reaction present some difficulties, in part because of the unreactivity of these substrates in such solvents as nitroethane and acetic acid, and in part because of the oxidation reaction ($>SO \rightarrow >SO_2$) occurring in acetic anhydride or aqueous sulfuric acid below the range of 80%.[1]

Working at high concentrations of sulfuric acid, a substitution reaction has been observed and the isomeric composition of nitro compounds formed is dependent on medium acidity.[1,2]

There is evidence that sulfoxides in acid solution are protonated at the oxygen atom.[3,4] Thus the interpretation of substituent effects for nitrations in concentrated sulfuric acid needs a preliminary investigation concerning the nature of the reactive species involved in the reaction.

We now consider the kinetics of the nitration of methyl phenyl sulfoxide over the range 83–100% sulfuric acid and the acidity dependence of the substitution reaction compared to that observed for diphenyl sulfoxide[2] and dimethylphenylsulfonium ion.[5]

Results and Discussion

In the range 83–100% sulfuric acid, methyl phenyl sulfoxide reacts with nitric acid to give products whose nature and composition are a function of acid concentration (Table I). At lower acidities oxidation (sulfoxide → sulfone) and nitration reactions are observed; at higher acidities only nitration occurs and the isomeric composition of nitro derivatives in the whole range studied shows predominant meta substitution which increases with the acidity of the medium.

The values of second-order rate coefficients (k_2) for the nitration reaction are reported in Table II together with the calculated rate coefficients for attack at one ortho (k_o), meta (k_m), and para (k_p) position.

Comparison of the results in Tables I and II with those obtained for diphenyl sulfoxide[2] shows that the stoichiometric rate coefficients for the –SOMe group are less than those for the –SOPh group by a factor of *ca.* 10; however, both substrates are very similar in the dependence of the product composition on acidity. Thus the meta/para ratio increases for PhSOMe and Ph_2SO respectively by a factor of 5.7 and 5 as the medium acidity increases.

The shape and slopes of the rate profile of methyl phenyl sulfoxide in the range 83–100% are reported in Figure 1 together with those of diphenyl sulfoxide and dimethylphenylsulfonium ion. The values of the slopes for methyl phenyl sulfoxide (+0.265 and −0.0507) below and above 90% sulfuric acid are close to the value observed for diaryl sulfoxide[2] at the lower acidities and to that for the dimethylphenylsulfonium ion[5] at the higher acidities.

To aid in the identification of the reacting species, the experimental rate profile for the nitration of methyl phenyl sulfoxide is compared in Figure 2 with that calculated for reaction of the free base.

The calculated curve has been obtained using that of the dimethylsulfonium ion as a model and by applying a correction for the variation of the conjugated acid corrected for the free base concentration with acidities. Since the sulfoxides cannot be regarded as Hammett bases,[3,4] the [BH$^+$]/[B] ratios have been calculated by the method of

Table I
Oxidation and Nitration Products of Methyl Phenyl Sulfoxide in Aqueous Sulfuric Acid at 25°

H_2SO_4, %	Oxidation, %[a]	Nitration, %[b]	Nitromethyl phenyl sulfoxide, % *o*-	% *m*-	% *p*-	*m*-/*p*-
82.5	56	44	10.1	63.7	26.2	2.43
83.2	47	53	9.7	65.0	25.3	2.57
83.9	42	58	9.3	66.3	24.4	2.70
85.0	26	74	8.8	68.2	23.0	2.96
85.2	23	77	8.7	68.6	22.7	3.02
87.6		100	7.5	73.0	19.5	3.74
88.4		100	7.1	74.5	18.4	4.05
90.3		100	6.2	77.7	16.1	4.83
91.4		100	5.7	79.6	14.7	5.41
93.3		100	4.8	82.9	12.3	6.75
93.4		100	4.7	83.2	12.1	6.87
94.7		100	4.1	85.4	10.5	8.17
96.1		100	3.4	88.0	8.6	10.27
98.4		100	3.3	90.2	6.5	13.88

[a] Methyl phenyl sulfone. [b] *o*-, *m*-, *p*-nitrophenyl methyl sulfoxides.

Table II
Second-Order Rate Coefficients (l. mol^{-1} sec^{-1}) for Nitration of Methyl Phenyl Sulfoxide in Aqueous Sulfuric Acid at 25°[a]

H_2SO_4, %	10^4k_2	10^6k_o	10^5k_m	10^6k_p	k_p/k_m
82.5	1.10	0.55	3.49	2.88	0.82
83.9	2.83	1.33	9.39	6.91	0.73
85.2	5.69	2.48	19.51	12.91	0.66
87.6	24.58	9.28	89.66	47.90	0.53
88.4	32.33	11.56	120.40	59.50	0.49
90.3	36.90	11.44	143.40	59.41	0.41
91.4	32.16	9.20	128.00	47.80	0.37
93.4	28.01	6.62	116.50	33.90	0.29
94.7	23.32	4.79	99.60	24.39	0.24
96.1	19.06	3.25	83.86	16.33	0.19
98.4	14.13	2.34	63.69	9.18	0.14

[a] k_o, k_m, and k_p have been calculated from the isomeric distribution given in Table I. The Arrhenius parameters calculated at 98.4% sulfuric acid are E_a = 12.4 kcal mol^{-1}, log A = 6.22 l. mol^{-1} sec^{-1}, and ΔS^* = −30.1 cal mol^{-1} $°K^{-1}$.

Yates.[6] Comparison of the experimental rate profile for methyl phenyl sulfoxide with that of sulfonium ion (Figure 1) and that for the hypothetical free base (Figure 2) shows that experimental results accord well with reaction through the conjugate acid. However there is one difficulty in the assumption that reaction occurs entirely through the conjugate acid. This arises from the variation of the isomer distribution with acidity; variation is observed also in the nitration of diphenyl sulfoxide. In the nitration of methyl phenyl sulfoxide, the values of the slopes for nitration below and above 90% sulfuric acid are +0.275 and −0.041 for meta substitution and +0.240 and −0.103 for para substitution; the corresponding values for the nitration of diphenyl sulfoxide are +0.267 and −0.057 for meta substitution and +0.237 and −0.101 for para substitution. The greater slope of para substitution compared to meta at high acidities suggests that part of the reaction still involves the free base, but the rate profiles in Figures 1 and 2 suggest that this is not a *major part*.

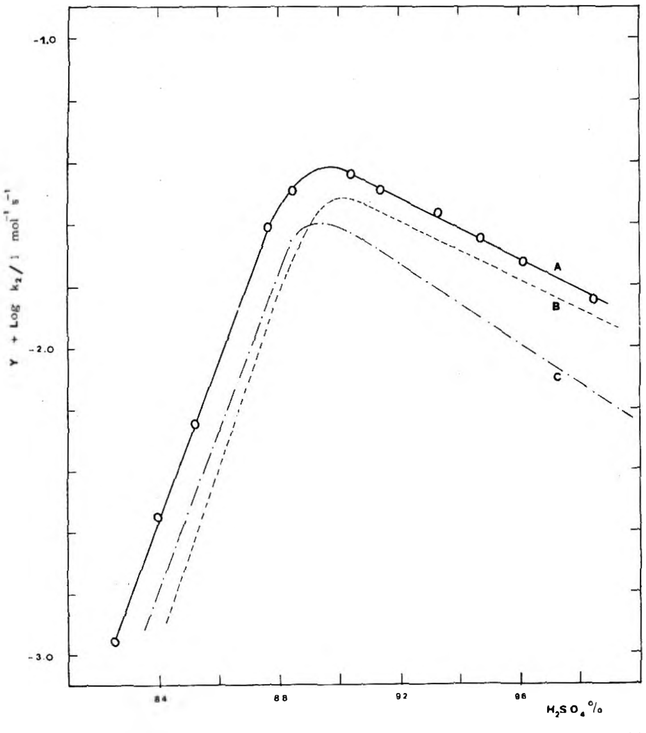

Figure 1. Rate profiles and slope values for the nitration of (A) methyl phenyl sulfoxide (+0.265, −0.0507); (B) dimethylphenylsulfonium methylsulfate (+0.284, −0.047); (C) diphenyl sulfoxide (+0.260, −0.064). Values of the constant Y are A = 0; B = 0; C = +1.

A mechanistic encounter rate criterion[7] for methyl phenyl sulfoxide in 98% sulfuric acid was also adopted and log k_2 (encounter) (4.90) was compared with the observed value (−2.81). At the same acidity the corresponding values for the diphenyl sulfoxide are 6.03 and −2.12. These results for the compounds examined indicate that nitration can occur *via* the free base. Indeed, for the arylmethyl relative to diaryl derivative, one can expect that the higher basicity constant[3] should decrease the proportion of reaction through the free base, and this is consistent with the smaller proportion of para substitution observed.

We assume therefore that, for both substrates, reaction occurs mainly through the conjugate acid but with a small contribution, which decreases with acidity, from reaction through the free base. The rate profiles suggest that this contribution should be very small at high acidities, and,

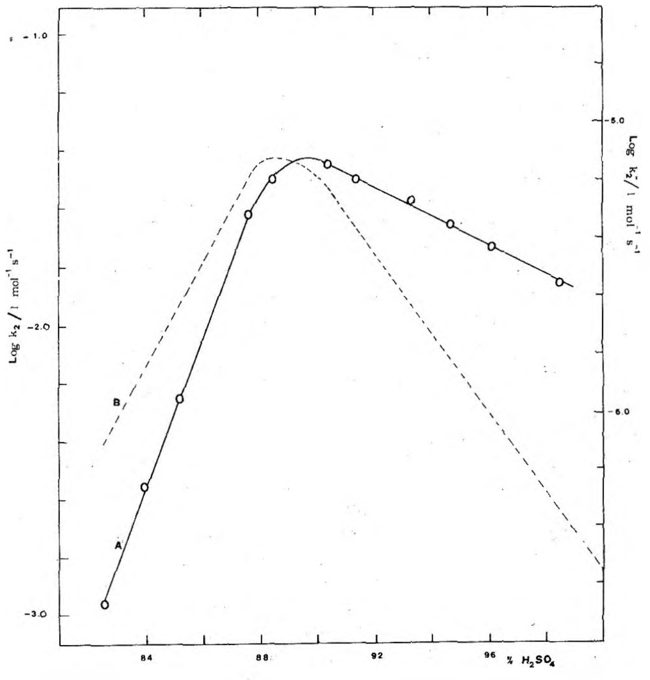

Figure 2. A, the experimental rate profile [log k_2 (obsd)] for the nitration of PhSOMe; B, expected rate profile [log k_2'' (calcd)] for the free base, calculated following $k_2'' = C\,(k_2/h_0)$.

for the purpose of calculating relative reactivities and partial rate factors for the reaction in *ca.* 98% sulfuric acid, the free base component has been ignored. The results are given in Table III. The comparison between the $PhSMe_2^+$ ion and the conjugate acids of sulfoxides shows small differences on the reactivity compared to overall deactivating influence of the positive pole.

However, on the cation of sulfoxides the change from $-S(OH)Me^+$ group to $-S(OH)Ph^+$ increases the reactivity by a factor of *ca.* 10, and in these compounds the amount of para increases more than the amount of meta nitration. This behavior suggest a progressively decreasing influence of π(d–p) overlap relative to the electrostatic deactivating effect in the sequence $PhSMe_2^+$, $PhS(OH)Me^+$, $PhS(OH)Ph^+$.

Experimental Section

Materials. *m*-Nitrophenyl methyl sulfoxide was prepared by nitration of methyl phenyl sulfoxide (0.1 *M*) with nitric acid (0.15 *M*) in 98% sulfuric acid at 25°. After 3 hr the reaction mixture was quenched in cold water, neutralized with sodium hydroxide, and extracted with chloroform. Drying and evaporation of the solvent gave the *m*-nitro derivative as the larger product of the reaction (*cf.* Table I). The compound was purified by crystallization from 95% ethanol, mp 117–118° (lit. mp 117–118° obtained by oxidation of *m*-nitrophenyl methyl sulfide[8]).

All the other compounds were prepared and purified as described in the literature and shown to be pure by glc and tlc. Sulfuric and nitric acid were Analar reagents. For all nitrations 16.2 *M* nitric acid was used. Solutions of sulfuric acid required as reaction media for kinetic or isomeric runs were obtained by diluting concentrated sulfuric acid and were standardized by titration with 0.1 *N* sodium hydroxide (normex) using an automatic titrator (Amel-235).

Kinetics. In order to avoid decomposition,[9,10] a concentration range of sulfuric acid up to 99% was used; also methyl phenyl sulfoxide was dissolved in thermostated solvent immediately before the start of the nitrations. The general procedure was followed as described previously[2] for the nitration of diphenyl sulfoxide. The extent of reaction was determined in a Hitachi Perkin-Elmer EPS 3T sepctrometer from the variation in the optical density at 300 nm in samples of the reaction mixture, quenched at suitable times in cold aqueous 0.1 *M* sodium hydroxide.

At this wavelength and at concentrations used, absorptions of other compounds are negligible; appropriate corrections were made when methyl phenyl sulfone was present. Nitro derivatives are proportional to optical densities; the latter do not vary with the base concentration (0.2–0.02 *N*) or with the time (up to 2 hr).

In all cases good second-order kinetics during individual kinetic runs have been observed and the second-order rate coefficient at a given acidity was shown to be independent of the initial concentrations of the reactants when varied over the range 0.0454–0.0986 *M*. Details of the integrated rate coefficients through a typical kinetic run are given in Table IV.

Total amount of nitro derivatives was calculated as described previously for the nitration of diphenyl sulfoxide.[2] The values of extinction coefficients of *o*-, *m*-, and *p*-nitrophenyl methyl sulfoxides at 300 mm derived from measurements on 0.1 *N* sodium hydroxide solutions of the pure isomers were as follows: ortho, 3302; meta, 1398; para, 5305.

Product Analysis. Nitration mixtures, some of these residual solutions from the kinetic runs, were poured into cold water, neutralized with aqueous sodium hydroxide at low temperature, and rapidly extracted with chloroform. In this way, possible alkaline cleavage of nitrophenyl methyl sulfoxides to nitrophenols can be avoided. The presence of *o*-, *m*-, and *p*-nitrophenyl methyl sulfoxides was ascertained by glc and tlc analysis together with methyl phenyl sulfone on the range 82–87% sulfuric acid. Samples of solutions were analyzed by glc analysis in a Hewlett-Packard 5700 A instrument and the oxidation–nitration composition was determined with a 120-cm column packed as reported previously.[2] Tests with mixtures of known composition showed partial separation of the three mononitro compounds by glc analysis; the separation was complete for the corresponding amino sulfides. The isomeric compositions of nitro compounds were then evaluated after quantitative reduction of the nitration solutions with stannous chloride and gaseous hydrogen chloride as reported elsewhere.[2]

Table III

Reaction Rates Relative to Benzene and Partial Factors for Nitration of Methyl Phenyl and Diphenyl Sulfoxides in Aqueous Sulfuric Acid at 25°

Compd	Expected reactive specie	Relative rate	$10^9 f_o$	$10^9 f_m$	$10^9 f_p$	$\frac{\log f_p}{\log f_m}$	$\frac{\log f_o}{\log f_m}$
$PhSMe_2^+$		3.98×10^{-9} [a]	0.26	11.2	0.94	1.13	1.21
PhSOMe	*c*	4.57×10^{-9} [b]	0.45	12.4	1.78	1.11	1.18
Ph_2SO	*c*	2.19×10^{-8} [b]	1.15	27.4	8.53	1.06	1.18

[a] Calculated at 98.7% H_2SO_4 from the relative rate with respect to $PhNMe_3^+$: N. C. Marziano, E. Maccarone, and R. C. Passerini, *Tetrahedron Lett.*, 17 (1972). [b] Calculated at 98.7% H_2SO_4 from the relative rate with respect to $PhSMe_2^+$ using observed rate constants. [c] Conjugate acid.

Table IV

Nitration of Methyl Phenyl Sulfoxide in 91.4% Sulfuric Acid at 25° [a]

Time, sec	300	420	540	660	780	900	1080	1200	1320	1560	1800	2100	2280	2700	3060	3600
OD (300 nm)[b]	0.200	0.298	0.380	0.432	0.488	0.551	0.644	0.689	0.737	0.841	0.917	1.028	1.082	1.200	1.269	1.395
10^2 *M*[c]	0.479	0.714	0.910	1.034	1.168	1.319	1.542	1.650	1.765	2.014	2.196	2.462	2.591	2.874	3.039	3.341
$10^4 k_2$, l. mol^{-1} sec^{-1} [d]	30.66	33.81	34.45	32.88	32.05	32.11	32.59	32.00	31.74	32.18	31.56	32.29	32.02	32.07	31.14	31.58

[a] [PhSOMe] = 5.67×10^{-2} *M*; [HNO_3] = 9.86×10^{-2} *M*. [b] Dilution factor before measurement of OD = 50. [c] Total concentration of *o*-, *m*-, and *p*-nitro derivative calculated as reported: N. C. Marziano, E. Maccarone, and R. Passerini, *J. Chem. Soc. B*, 745 (1971). [d] Average $k_2 = 32.16 \times 10^{-4}$ l. mol^{-1} sec^{-1}.

o-, *m*-, and *p*-aminophenyl methyl sulfides were determined by glc analysis carried out using the same column described above and reported before.[2]

The reduction process, as the glc analysis, was shown to be satisfactory (±2%) by the use of synthetic mixtures of pure isomers. Oxidation-nitration composition as isomeric compounds values are an average of three gas chromatographic analysis and the areas are corrected by calculated correction factors.

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Registry No.—Methyl phenyl sulfoxide, 1193-82-4; diphenyl sulfoxide, 945-51-7.

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Reaction of Aromatic Substrates with Sulfonyl Nitrenes[1a]

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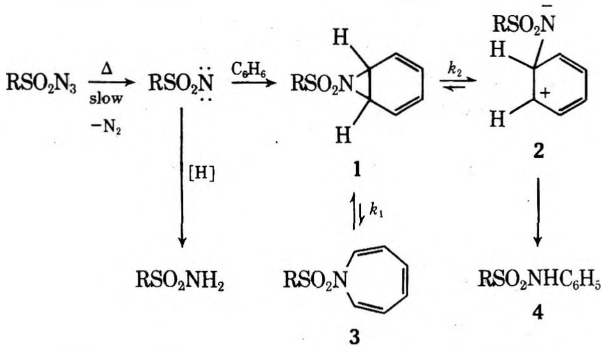
The thermolysis of methanesulfonyl azide in aromatic solvents bearing electron-withdrawing substituents has been studied quantitatively in the presence and absence of compounds known to catalyze singlet → triplet interconversions. The results show that the singlet sulfonyl nitrene formed initially drops to the triplet to a certain extent: the singlet adds to the aromatic nucleus to give a benzaziridine intermediate that ring opens to yield the meta-substituted anilide predominantly. The triplet attacks the nucleus as expected of a highly electrophilic diradical and leads mainly to the ortho isomer. In nitrobenzene, the nitrene behaves only as the electrophilic triplet and, in addition to nitroanilides, yields products in which the nitro group has been displaced.

The thermal decomposition of sulfonyl azides in aromatic solvents, which was first studied by Bertho, Curtius, and Schmidt,[1b] occurs slowly at 120°, is unimolecular,[2] and leads to singlet nitrenes.[3] This is followed by an addition to the aromatic nucleus to give a benzaziridine intermediate (**1**), with ring opening of the latter to form the observed *N*-sulfonanilides (**4**)[3] *via* **2** being a relatively fast, thermodynamically controlled process, and ring opening to form the azepine (**3**) being an even faster kinetically controlled reaction.[4] The unsubstituted primary sulfonamides, products of hydrogen abstraction by the nitrene, are also formed in these reactions.



The isomer ratios and relative reactivities[3] in the reactions of methanesulfonyl nitrene with toluene, anisole, and chlorobenzene could be explained readily on the basis of the above mechanism. Electron-donating substituents facilitate addition to the aromatic nucleus while electron-withdrawing ones slow the addition down. The substituent determines the direction of ring opening **1** → **2** by whether or not it can stabilize the developing positive charge in the aromatic nucleus in the product-, but not rate-, determining step. Since formation of a σ complex is not rate determining, partial rate factors have no physical significance in this reaction[3] and are not considered here.

It would then be predicted that an electron-withdrawing substituent would not only deactivate the nucleus but would also direct the ring opening of the aziridine ring to favor formation of the meta isomer. Confirmation of this appeared to be forthcoming from studies of the benzenesulfonamidation of methyl benzoate and benzoyl chloride using benzenesulfonyl azide, when the isomer ratios were reported to be ortho, 43%; meta, 54%; para, 3%; and meta, 100%, for these two substrates, respectively, and the total rate ratio $^{CO_2Me}{}_{H}K = 0.38$.[5] Since these latter data were obtained from fractional distillation experiments and we had found in earlier work[3] that these led to poor quantitative results, it was felt that the reaction of sulfonyl nitrenes with aromatic nuclei bearing electron-withdrawing substituents should be reinvestigated quantitatively using gas-liquid chromatography (glc). Once

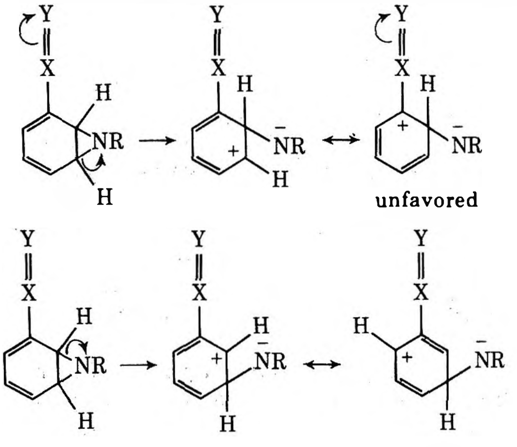


Table I
Methanesulfonamidation of Aromatic Substrates

Registry no.	X in C_6H_5X	Overall yield, %	Yield of $CH_3SO_2NH_2$,[a] %	Yield of CH_3SO_2-NHC_6H_4X,[a] %	Isomer ratio for $CH_3SO_2NHC_6H_4X$, % Ortho	Meta	Para	Total rate ratio ${}^{X}_{H}K$
	CH_3[b]	99.5	22.7	76.8	65.4	2.4	32.2	1.86
	OCH_3[b]	70.7	3.8	66.9	55.5	1.2	43.3	2.54
108-90-7	Cl	78.2	13.1	65.1	57.4	0.9	41.7	0.44
93-58-3	CO_2CH_3[b]	26.0	4.6	21.4	64.3	34.4	1.3	0.30
98-95-3	NO_2	17.0	11.7	5.3	55.4	13.4	31.2	c
100-47-0	CN	11.2	5.8	5.4	68.9	31.1	0.0	c
98-08-8	CF_3	51.0	25.8	25.2	53.0	46.1	0.9	0.07

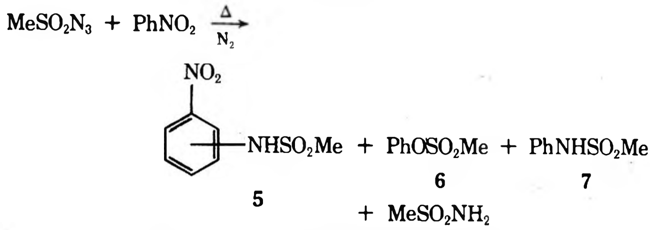
[a] Based on sulfonyl azide. [b] Reference 3. [c] Not determined.

again, in order to facilitate the elution of the reaction products from the column, it was decided to use methanesulfonyl azide instead of benzenesulfonyl azide as the source of the nitrene intermediate. We now report the reaction of methanesulfonyl nitrene with methyl benzoate, benzonitrile, benzotrifluoride, and nitrobenzene.

Decomposition of methanesulfonyl azide in degassed methyl benzoate under nitrogen gave the methyl *N*-methanesulfonylaminobenzoates in an ortho:meta:para ratio of 64.3:34.4:1.3. The corresponding ratio in nitration[6] is 28.3:68.4:3.3, and in free-radical phenylation it is 57:17:25.[7] A polar free radical would be expected to yield a higher proportion of ortho isomer than does the phenyl radical.[8] Methanesulfonamide was isolated as well (4.6%) but no product of addition to the substituent. The total rate ratio (measured by competition experiments) was ${}^{CO_2Me}_{H}K = 0.3$. In agreement with the prediction made above the methoxycarbonyl substituent deactivates the ring toward attack by the electrophilic nitrene but, contrary to what was expected for the singlet species, the ortho and not the meta isomer was the main product of attack, though the proportion of meta isomer increased markedly as compared with toluene as substrate (2.4%). This would be consistent with a substitution by the electrophilic triplet sulfonyl nitrene radical. The yield of anilides was much lower than those obtained (65–77%) when an electron-donating substituent was present.[3] Methanesulfonamidation of ethyl benzoate took place similarly but the peaks tailed badly on gas chromatographic analysis and quantitative analysis was not attempted.

Similar results were obtained with benzonitrile and benzotrifluoride (Table I), the yield of sulfonamidation products being quite low (5.4 and 25.2%, respectively) and the ortho isomer being the main product. The proportion of meta isomer was again much higher than when an electron-donating substituent was present and, in the case of benzonitrile, no para-substituted product could be detected.

On going to a substrate bearing an even more electron-withdrawing substituent a dramatic change took place. Using scrupulously degassed reagents a maximum 5.3% yield of nitro-*N*-methanesulfonanilides (5) was obtained in the ratio of ortho:meta:para of 55.4:13.4:31.2. This is strikingly similar to the isomer ratio obtained in the homolytic arylation of nitrobenzene using the electrophilic *p*-nitrophenyl radical (ortho:meta:para = 58.15:27).[9] Just as interesting were the other products formed in this reaction in addition to methanesulfonamide, namely phenyl methanesulfonate (6) and methanesulfonanilide (7). Much tar was also formed.



These results are entirely consistent with an attack of the nitrobenzene ring by triplet electrophilic methanesulfonylnitrene. Displacement of a nitro group by electrophilic free radicals is known. Thus, hydroxyl radicals react with nitrobenzene to give phenol,[10] and displacement of an NO_2 group has been observed in a Pschorr cyclization.[11] Evolution of nitric oxide in the decomposition of sulfonyl azides has been observed[5,12] but not accounted for.

When the reaction was carried out in the presence of air the amount of nitro-*N*-methanesulfonanilide dropped, eventually to zero, with increasing oxygen concentration, and only the ortho isomer could be detected. The yield of 6 was unaffected by the presence of O_2 but that of 7 dropped drastically. Only a small change in the yield of methanesulfonamide was observed (see Experimental Section).

A possible explanation for these observations is as follows. Thermolysis of the sulfonyl azide leads to the singlet electrophilic sulfonyl nitrene, which may add to surrounding aromatic molecules, if the latter are sufficiently reactive, to give aziridine intermediates. If the substrate is unreactive toward attack by an electrophilic singlet the latter has time to drop to the triplet ground state[13] [alternatively, the substituent (or NO in the nitrobenzene reaction) could perhaps catalyze the singlet → triplet conversion (as ethyl acetate may do in the case of cyanonitrene)] which would then attack (not very efficiently) the aromatic nucleus as do other electrophilic free radicals, and the isomer ratio observed would reflect this. The effect of O_2 upon the yields of 5 and 7 is consistent with the interception of a radical before it can react with nitrobenzene. In the presence of radicals, sulfonyl azides can undergo S–N bond cleavage.[14] The formation of 6 may then be rationalized as follows.

$$MeSO_2N_3 + R\cdot \longrightarrow MeSO_2\cdot + RN_3$$

$$MeSO_2\cdot \xrightarrow{[O]} MeSO_3\cdot \longrightarrow \underset{6}{MeSO_3Ph} + [NO_2\cdot]$$

Oxygen abstraction by $MeSO_2\cdot$ either from nitrobenzene or possibly by disproportionation (but not by reaction with atmospheric oxygen in view of the lack of effect of the latter upon the yield of 6) finds a parallel in the decomposition of $PhSO_2CHN_2$ in benzene when one of the products is $PhSO_3CH_2SO_2Ph$.[15] The formation of 7 probably involves either displacement of $NO_2\cdot$ by $MeSO_2NH\cdot$ (formed by hydrogen abstraction), or by $MeSO_2N\cdot$ to give $C_6H_5\dot{N}SO_2Me$ which undergoes hydrogen abstraction.

To explain the greatly increased proportion of meta isomer from the reactions with methyl benzoate, benzoni-

Table II
Methanesulfonamidation of Methyl Benzoate and Benzotrifluoride in the Presence of Various Additives

Conditions	Products, %				
	Ortho	Meta	Para	$MeSO_2NHC_6H_4X$	$MeSO_2NH_2$
	A. $PhCO_2Me$				
Sealed tubes under N_2	64.3	34.4	1.3	21.4	4.6
Sealed tubes under air	59.8	38.1	2.0	16.3	5.9
With oxygen bubbled through	55.1	42.6	2.3	20.5	5.3
CCl_4 (20 molar excess)	62.4	35.2	2.4	16.0	*a*
CCl_4 (40 molar excess)	62.9	35.0	2.1	12.9	*a*
CH_2Br_2 (20 molar excess)	56.4	34.9	8.7	2.0	28.3
CH_2Br_2 (40 molar excess)	29.9	57.5	12.6	1.1	44.2
Cobalt (III) acetylacetonate	32.3	63.3	4.4	2.2	*a*
Manganese (II) acetylacetonate	27.3	68.2	4.5	1.3	*a*
Manganese (II) acetylacetonate (trace)	61.4	37.1	1.5	16.6	*a*
$MnCl_2 \cdot 4H_2O$	61.6	36.7	1.67	13.6	*a*
Gattermann copper	56.2	40.5	3.3	5.8	*a*
Iron powder	60.7	37.9	1.4	19.1	*a*
	B. $PhCF_3$				
Degassed under N_2	53.4	45.6	1.0	20.4	21.9
With oxygen	48.0	47.5	4.5	24.4	16.0
CH_2Br_2 (20 molar excess)	34.3	50.0	15.7	0.94	46.5
Copper (II) acetylacetonate	38.2	58.1	3.7	4.3	29.5
Manganese (II) acetylacetonate	43.9	54.1	2.0	4.1	29.0
$Co_2(CO)_8$	31.2	66.8	2.0	2.9	16.1
$Fe_3(CO)_{12}$	30.7	64.0	5.3	0.75	61.5
$Fe(CO)_5$	23.8	69.7	6.5	0.55	53.2

[a] Not determined.

trile, and benzotrifluoride, it is tempting to suggest that two competing processes are operating: (1) the addition of singlet nitrene to give an *N*-sulfonylaziridine intermediate which, on ring opening, gives mainly the meta isomer σ complex as discussed above, and (2) a direct free-radical substitution by triplet electrophilic sulfonyl nitrene, which would lead mainly to the ortho isomer. As the aromatic nucleus becomes more deactivated toward attack by an electrophilic singlet species [$\sigma_p(CO_2Me) = 0.45$; $\sigma_p(CF_3) = 0.54$][16] the latter has time to undergo spin inversion to the triplet to some extent. With nitrobenzene [$\sigma_p(NO_2) = 0.78$][16] this process appears to be complete. The isomer ratios observed for methyl benzoate, benzonitrile, and benzotrifluoride do not conform to either "pure" electrophilic substitution or "pure" radical substitution but rather to a dual mechanism.[17] The total rate ratios (Table I) confirm that these nuclei are deactivated toward electrophilic attack. These ${}^{X}{}_{H}K$ values must, therefore, be composites of two different mechanistic processes. This receives support as follows.

A good linear relationship is observed for the plot of log ${}^{X}{}_{H}K$ *vs.* σ_p when X = OCH_3, CH_3, H, and Cl. Much more scatter is observed when log ${}^{X}{}_{H}K$ is plotted against $\sigma_p{}^+$. The better fit with σ_p than with $\sigma_p{}^+$ is consistent with a transition state resulting from the attack of the aromatic nucleus by a highly reactive species. If σ_p is taken only as a measure of the overall electron-donating or slightly withdrawing ability of the substituent this correlation is understandable. The total rate ratio is, however, a measure of the rate of attack at all the ring positions, and the above linearity with σ_p is not altogether meaningful. On the other hand, the points for methoxycarbonyl and trifluoromethyl are well off this plot (Figure 1). This is understandable not only because of the above duality of mechanisms but also because the relative amount of para isomer in these cases is very low (the main products are the ortho and meta isomers) and σ_p will be a poor measure of the overall reactivity of the nucleus.

In order to obtain more data on this dual mechanism, the methanesulfonamidations of methyl benzoate and benzotrifluoride were carried out in the presence of compounds which are known to facilitate singlet → triplet nitrene conversion.[20] The results of this study are given in Table II.

Methylene bromide is known to be an efficient heavy atom solvent for catalyzing singlet → triplet intersystem crossing of cyanonitrene.[20] Methylene chloride is reported to do the same to carbethoxynitrene.[21] Addition of a large excess of methylene bromide to methyl benzoate and benzotrifluoride before decomposition of the $MeSO_2N_3$ had a dramatic effect both on the relative yields of products and the isomer ratios. The yield of methanesulfonamide increased sharply; that of the *N*-mesylanilines dropped very markedly. The main product of methanesulfonamidation

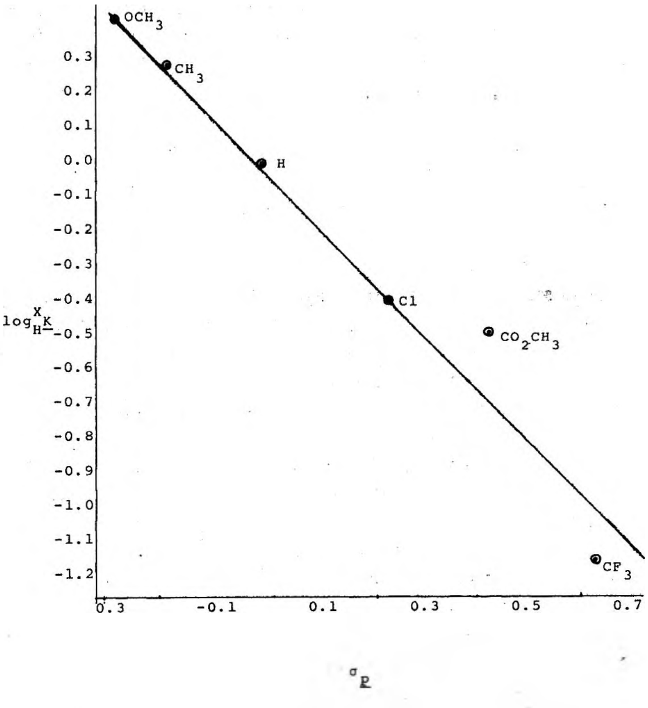


Figure 1. Plot of total rate ratio log ${}^{X}{}_{H}K$ *vs.* σ_p for the methanesulfonamidation of aromatic substrates.

Table III
Authentic N-Mesylanilides $XC_6H_4NHSO_2Me$

Registry no.	X	Yield, %	Mp, °C	Molecular formula	Found, %		Calcd, %	
					C	H	C	H
716-41-6	o-CO_2Me	53	90.5–91	$C_9H_{11}NO_4S$	46.83	4.64	47.15	4.84
32087-05-1	m-CO_2Me	73	125.5–126	$C_9H_{11}NO_4S$	47.39	5.20	47.15	4.84
50790-28-8	p-CO_2Me	63	149.5–150	$C_9H_{11}NO_4S$	47.01	4.82	47.15	4.84
50790-29-9	o-CN	50	103	$C_8H_8N_2O_2S$	49.36	4.21	48.98	4.11
50790-30-2	m-CN	65	154.5–155	$C_8H_8N_2O_2S$	48.99	4.36	48.98	4.11
36268-67-4	p-CN	75	197.5	$C_8H_8N_2O_2S$	49.22	4.22	48.98	4.11
50790-31-3	o-CF_3	68	79–80	$C_8H_8F_3NO_2S$	40.55	3.41	40.17	3.37
50790-32-4	p-CF_3	65	127–128	$C_8H_8F_3NO_2S$	40.22	3.54	40.17	3.37

is now the meta isomer, as predicted on the basis of an attack of the nucleus by a singlet species. That CH_2Br_2 was a very efficient hydrogen donor was shown by carrying out the decomposition of the azide in this solvent alone. A very clean reaction (unlike the ones in aromatic solvents) occurred to give a 93% yield of methanesulfonamide. These results can be readily interpreted as follows. Methylene bromide catalyzes some intersystem crossing of singlet to triplet, and triplet sulfonyl nitrene hydrogen-abstracts very efficiently from CH_2Br_2 to give $MeSO_2NH_2$. Remaining singlet nitrene does not and adds to the aromatic solvent as predicted above to give mainly the meta-substituted anilide.

When the decompositions were carried out in the presence of copper(II), manganese(II), and cobalt(III) acetylacetonates instead of methylene bromide again the yields of "substitution" products decreased enormously and the relative amount of meta isomer increased at the expense of ortho isomer as the amount of added complex was increased. The transition metal complexes appear to catalyze the singlet → triplet conversion and to trap the triplet in the form of intractable materials (the amorphous products and tars were found to contain transition metal). What is left of the singlet adds to the aromatic substrate as before. When the decompositions in benzotrifluoride were carried out in the presence of $Fe(CO)_5$, $Fe_3(CO)_{12}$, or $Co_2(CO)_8$ an even greater increase in the proportion of meta relative to ortho isomer was observed and, in these cases, when azide was present in excess over transition metal carbonyl, novel nitrene-metal complexes were isolated as amorphous solids. These will form the subject of a forthcoming publication. Manganous chloride, copper, and iron, all of which were insoluble in the reaction medium, had little effect upon the product ratio, as did carbon tetrachloride in 40-molar excess. These results are, therefore, consistent with the intermediacy of both singlet and triplet sulfonyl nitrenes in these unreactive aromatic solvents.

As discussed above, triplet sulfonyl nitrene abstracts hydrogen efficiently from aliphatic solvents, and it appears that metal-complexed sulfonyl nitrenes can do likewise from both aliphatic and aromatic solvents (see above, ref 22). It has been argued, however, that free triplet sulfonyl nitrenes do not abstract hydrogen efficiently from aromatic solvents.[3,22] Breslow and Edwards found that m-dinitrobenzene caused the amount of insertion of n-octadecyloxycarbonyl nitrene into cyclohexane to increase at the expense of hydrogen-abstraction product and this was attributed to trapping by m-dinitrobenzene of the radicals catalyzing singlet → triplet transitions.[23] Addition of excess m-dinitrobenzene to methanesulfonyl azide in benzene before thermolysis led to a decrease in the yields of *both* methanesulfonamide *and* N-mesylaniline and, indeed, the ratio of amide to anilide *increased* slightly (from 1:4.7 to 1:3.8) upon addition of m-dinitrobenzene. This supports our belief that both products in benzene arise from the singlet species; the lower yields obtained in the presence of m-dinitrobenzene must reflect a reaction of the nitrene with the nitro compound which is present in large excess.

Experimental Section

Melting points are uncorrected. Nmr spectra were recorded on a 100-MHz instrument.

Reagents. Reagent-grade solvents were purified by standard techniques and kept over drying agent. They were distilled just prior to use. Methanesulfonyl azide was fractionally distilled behind a safety shield and stored in a desiccator at 0°.

Authentic Mesylanilides. These were prepared from the appropriate aniline, methanesulfonyl chloride, and dry pyridine with or without benzene as solvent. The properties of the new mesylanilides so obtained are given in Table III. The other anilides had the properties described in the literature.

General Procedure for the Decomposition of Methanesulfonyl Azide in Aromatic Solvents. All thermolyses were carried out in glass bombs which were stirred and immersed in a thermostated bath at 120°. The initial reaction solution was degassed by evacuating the frozen solution and thawing and repeating this procedure a number of times. The decompositions were allowed to proceed for 48–72 hr, the mixture was cooled to room temperature and filtered, and the insoluble black material was washed with hot acetone, benzene, or acetonitrile. The combined washings and filtrates were fractionally distilled through a Vigreux column and the solvent distillates were checked by gas chromatography to ensure that none of the products codistilled. The concentrated reaction mixtures were analyzed directly by glc after the addition of the appropriate internal standard. A number of synthetic mixtures were analyzed, under the same conditions to check the accuracy of the method.

Methanesulfonamidation of Degassed Methyl Benzoate. The only products detected by glc were methanesulfonamide and the methyl o-, m-, and p-methanesulfonamidobenzoates. These were collected and identified by comparing their ir spectra and melting points with those of authentic samples.

For the quantitative analyses, methanesulfonyl azide (0.15 g) was decomposed as described above in a 50-molar excess of methyl benzoate. The isomerides could be analyzed either on an 8.5 ft × 0.25 in. column packed with Apiezon N (25%) on Chromosorb W (60–80 mesh) and a column temperature of 250° and a He flow rate of 60 ml/min, or on an 8.25 ft × 0.25 in. column of Apiezon L (25%) on Gas-Chrom P (100–120 mesh) at 230° and a flow rate of 100 ml/min. p-Methanesulfonyltoluidide was used as the internal standard. Methanesulfonamide was separately analyzed on a 6 ft × 0.25 in. column packed with precipitated asphalt (25%) on Chromosorb W at 180° and a He flow rate of 85 ml/min (p-chloronitrobenzene as internal standard). The mean of three runs gave the following results: methanesulfonamide, 4.62 ± 0.6%; methyl N-methanesulfonamidobenzoate, 21.4 ± 0.6% (isomer ratios ortho, 64.3 ± 0.7%; meta, 34.4 ± 0.5%; para, 1.3 ± 0.2%); overall yield based on azide, 26.0 ± 1.0%.

Competitive runs between benzene and methyl benzoate were carried out by decomposing the azide in the mixed solvents in the molar ratio azide:benzene:methyl benzoate of 1:50:50. The products were analyzed on the above Apiezon N on Chromosorb W column. Analysis of two synthetic mixtures confirmed the accuracy of the method. The total rate ratio ${}^{CO_2Me}{}_{H}K$ thus obtained (average of three runs) was 0.30 ± 0.01.

Methanesulfonamidation of Methyl Benzoate in the Presence of Oxygen. The above reaction was repeated under two different sets of conditions: (a) in a sealed bomb under air and (b) under reflux with oxygen being bubbled through the solution at 120°. The results are given in Table II.

Methanesulfonamidation of Benzonitrile. Only methanesulfonamide and o- and *m*-cyano-*N*-methanesulfonanilides were formed and isolated. No *p*-cyano-*N*-methanesulfonanilide could be detected, so that if any is formed it must be present to the extent of less than 3% of the isomerides.

Quantitative analysis for methanesulfonamide was carried out as above while the o- and *m*-cyano derivatives were analyzed on the Apiezon L on Gas-Chrom P column described above using 1,2-diphenoxyethane as the internal standard. Synthetic mixtures were also analyzed as before. The yields of products were follow: methanesulfonanilides, 5.7 ± 0.5%; cyano-*N*-methanesulfonanilides, 5.4 ± 0.18% (isomer ratio ortho, 68.9 ± 0.25%; meta, 31.1 ± 0.22%); overall yield based on azide, 11.1 ± 0.75%.

Methanesulfonamidation of Benzotrifluoride. Methanesulfonamide and the three isomeric mesylaminobenzotrifluorides were isolated and characterized. Isomer ratios were determined on a 10 ft × 0.25 in. Apiezon L (25%) on Anakchrom ABS (60–70 mesh) column at 212° and a 60 ml/min He flow rate using benzophenone as the internal standard. The averages of five runs follow: methanesulfonamide, 25.8 ± 3.6%; mesylaminobenzotrifluorides, 25.2 ± 1.3% (isomer ratio ortho, 53.0%, meta, 46.1%; para, 0.9%); overall yield, 51.0 ± 1.7%.

A competitive reaction was carried out using a methanesulfonyl azide:benzene:benzotrifluoride molar ratio of 1:20:20. The products were analyzed on a 10 ft × 3/16 in. Apiezon L (25%) on Chromosorb W (60–200 mesh) column at 225° using benzophenone as the internal standard. The total rate ratio $[{}^{\mathrm{CF_3}}{}_{\mathrm{H}}K]$ thus obtained was 0.06 (average of four runs).

Methanesulfonamidation of Degassed Nitrobenzene. Qualitative Analysis. The thoroughly degassed solution was thermolyzed and the products were analyzed by glc. Methanesulfonamide and the nitro-*N*-methanesulfonanilides were characterized but, in addition, two more peaks were observed. These were collected and their infrared spectra and melting points were compared with those of authentic *N*-methanesulfonanilide, mp 101°, and phenyl methanesulfonate, mp 59–59.5°, and were found to be identical with these.

Quantitative Analysis. Methanesulfonyl azide (0.06 g) in a 50-molar excess of nitrobenzene was thoroughly degassed and decomposed under dry, oxygen-free nitrogen. Methanesulfonamide, methanesulfonanilide, and phenyl methanesulfonate were estimated using the 8.5 ft × 0.25 in. Apiezon N (25%) on Chromosorb W (60–80 mesh) column at 190°, while the isomeric nitro-*N*-methanesulfonanilides were estimated using a 3 ft × 0.25 in. column packed with Apiezon L (20%) on Gas-Chrom P (100–200 mesh) at 195° and a He flow rate of 68 ml/min. Biphenyl was used as the internal standard in both cases. Synthetic mixtures were also analyzed in this way. The results of three runs are as follows: methanesulfonamide, 11.7 ± 1.0%; phenyl methanesulfonate, 2.5 ± 0.5%; methanesulfonanilide, 18.6 ± 0.4; nitro-*N*-methanesulfonanilides, 5.3 ± 1.4% (isomer ratio ortho, 55.4%; meta, 13.4%; para, 31.2%); overall yield based on azide, 38.15 ± 3.0%.

Methanesulfonamidation of Nitrobenzene in the Presence of Oxygen. The above reaction was repeated under three different sets of conditions: (a) in undegassed nitrobenzene in a tube sealed under an air atmosphere; (b) under reflux open to the air at 120°; and (c) under reflux with oxygen being bubbled through the solution at 120°. The yields of products are summarized below. No *m*- or *p*-nitro-*N*-mesylanilide could be detected by glc under these conditions.

Conditions	Yield, % $MeSO_2NH_2$	$PhOSO_2Me$	$PhNHSO_2Me$	o-$NO_2C_6H_4NHSO_2Me$	Σ, %
a	10.9 ± 0.6	2.1 ± 0.2	15.2 ± 0.7	3.0 ± 0.2	31.2
b	9.9 ± 0.7	2.6 ± 0.6	4.5 ± 0.25	2.0	19.0
c	7.5 ± 0.25	2.5 ± 0.07	0.3 ± 0.02	0.0	10.3

Methanesulfonamidation of Benzene in Methylene Bromide. A solution of methanesulfonyl azide (0.3 g, 0.0025 mol) in a 4-molar (1 ml) or a 20-molar (5 ml) excess of benzene was diluted with a 100-molar excess of methylene bromide (17 ml) and the solutions were thermolyzed at 120° under N_2 in a sealed bomb. The products were methanesulfonamide and methanesulfonanilide; no biphenyl was detected. The quantitative analysis were carried out as described earlier.[3]

Molar ratio of azide: benzene: CH_2Br_2	$MeSO_2NH_2$, %	$MeSO_2NHPh$, %	Σ, %
1:4:100	90.95 ± 0.5	1.1 ± 0.3	92
1:20:100	69.8 ± 2.0	2.8 ± 0.03	72.6

Decomposition of Methanesulfonyl Azide in Methylene Bromide. Methanesulfonyl azide (0.3 g) was decomposed in methylene bromide (17 ml) at 120° to give methanesulfonamide (93%) in a very clean reaction.

Methanesulfonamidation of Benzene in the Presence of *m*-Dinitrobenzene. Methanesulfonyl azide (0.3 g) was decomposed in benzene (12.5 ml) containing *m*-dinitrobenzene (0.4 g, 0.003 mol). Methanesulfonamide (7.4 ± 0.1%) and *N*-methanesulfonanilide (34.8 ± 0.6%) were obtained. No biphenyl was detected.

Effect of Diluent and Additives upon Reaction of Methanesulfonyl Azide with Methyl Benzoate. Methylene Bromide. Methanesulfonyl azide (0.3 g) in methyl benzoate (6.8 g) was diluted with 20-molar (3.45 ml) or 40-molar (6.9 ml) excesses of methylene bromide and the thermolyses were carried out as usual. Since the isomeric methane sulfonamidobenzoates were formed in such small amounts, a large percentage error (estimated ±10%) may be introduced in the peak area measurements and was allowed for.

Carbon Tetrachloride. The reaction was repeated but using CCl_4 as the diluent. Methanesulfonamide was the main product but its yield was not determined.

In the Presence of Cobalt(III) Acetylacetonate. Methanesulfonyl azide (0.6 g) was decomposed in a 50-molar excess of methyl benzoate in the presence of cobalt(III) acetylacetonate (0.13–0.18 g) at 120°. A blank run in the absence of azide indicated that the metal complex did not give any isolable products with the benzoate. The overall yield of methyl *N*-methanesulfonamidobenzoates was 2.2% and the isomer ratio was ortho, 32.3; meta, 63.3; para, 4.4. The decompositions in the presence of other transition-metal compounds were carried out and analyzed similarly. The results of these reactions and of the ones of the similar decomposition of $MeSO_2N_3$ in benzotrifluoride in the presence of transition-metal compounds are collected and summarized in Table II.

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Registry No.—Methanesulfonyl azide, 1516-70-7; benzene, 71-43-2.

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Reaction of 3-[2′-Tetrahydropyranyl(furanyl)thio]indole with Silver Ion

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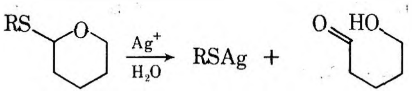
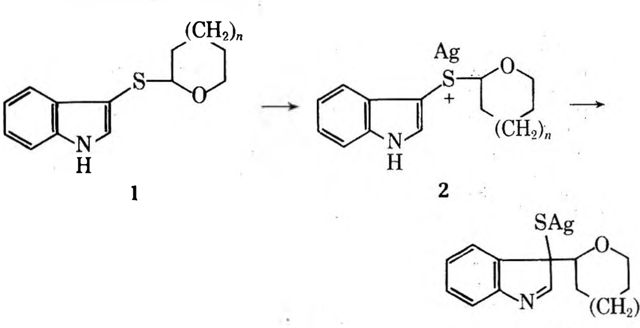
When 3-(2′-tetrahydropyranylthio)indole is treated with 1 equiv of silver ion in aqueous methanol, the silver salt of 3-thioindole and 5-hydroxyvaleraldehyde are produced quantitatively. If the reaction is carried out in an aprotic solvent (toluene, tetrahydrofuran), rearrangements occur to produce low yields of products in which the cyclic ether moiety is bonded to N-1 or C-2 of the indole nucleus. The reactions are envisaged as involving collapse of an initially formed adduct, in which silver ion is bound to sulfur, to release a cyclic ether oxonium ion which undergoes further reaction. Formation of the 1-tetrahydropyranyl(furanyl) compound is envisaged as involving intermolecular formation of 1-tetrahydropyranyl(furanyl)-3-tetrahydropyranyl(furanyl)thioindole which, *via* a silver ion adduct, loses the cyclic ether moiety from sulfur. It is suggested that the C-2-substituted compound may arise by a process in which the cyclic ether moiety is first bonded to C-3 of the indole nucleus followed by migration to C-2.

Reaction of 3-[2′-Tetrahydropyranyl(furanyl)thio]indole with Silver Ion. In connection with studies directed toward achieving new C-nucleoside (*e.g.*, formycin, pseudouridine, pyrazomycin)[1] syntheses, an investigation of the reactions of silver ion with 3-(2′-tetrahydropyranylthio)indole (**1a**) and 3-(2′-tetrahydrofuranylthio)indole (**1b**) was undertaken. Holland and Cohen[2] discovered that the sulfur–hemiacetal linkage is cleaved readily by silver ion in aqueous solution to yield quantitatively a silver mercaptide and a hydroxy aldehyde.



The present study was undertaken in anticipation that, in the absence of a protic solvent, a 1,2 shift from sulfur to carbon[3] might occur.



a, $n = 1$
b, $n = 0$

In accordance with the results of Holland and Cohen,[2] treatment of 3-(2′-tetrahydropyranylthio)indole (**1a**) with aqueous silver nitrate at room temperature resulted in the immediate precipitation of a quantitative yield of the silver salt of 3-thioindole[4] and 5-hydroxyvaleraldehyde, isolated as the corresponding 2,4-dinitrophenylhydrazone.[5] When equimolar amounts of **1a** and silver perchlorate (chosen because of its availability in anhydrous form, its solubility in organic solvents, and the low nucleophilicity of the perchlorate ion) were combined in benzene at room temperature a precipitate was formed which darkened (decomposed) quickly. Evidence consistent with the formulation of this precipitate as the coordination compound **2a** was obtained from two additional experiments. When **1a** and silver perchlorate were mixed in pyridine at room temperature no reaction occurred, indicating that the affinity of pyridine for silver ion prevents its coordination with the sulfur of **1a**. When the reactants were combined in toluene at −78° a colorless precipitate accounting for two-thirds of added reactants formed immediately. Addition of pyridine to the reaction mixture at this point caused the precipitate to dissolve with quantitative regeneration of the starting material, **1a**, indicating that the precipitate was not a product involving cleavage or rearrangement of the organic reactant. However, if the reaction mixture in toluene was allowed to warm in the absence of added pyridine, the original precipitate decomposed and pyridine was no longer capable of removing the silver, indicating that the silver ion was present as a mercaptide.

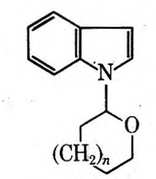
In addition to providing evidence consistent with the formation of coordination compound **2**, these experiments illustrate the extent to which the activity of silver ion is influenced by its interaction with solvent. After evaluation of a number of solvents, tetrahydrofuran was selected for use in the remainder of this study.

At −78° in tetrahydrofuran, no evidence for the reaction of **1a** with silver perchlorate was obtained. At higher temperatures (−15 to 25°) **1a** underwent reaction presumably *via* the intermediacy of complex **2a**, which, unlike its behavior in benzene and toluene, appears to be soluble in tetrahydrofuran. In contrast, 3-(2′-tetrahydrofuranylthio)-indole (**1b**) reacted in the presence of silver ion even at −78°. Except for these differences in affinity for coordination and reaction rate (which parallel the behavior of 2-*O*-alkyl acetals of tetrahydropyran and tetrahydrofuran toward acid-catalyzed hydrolysis),[6,7] the reactions of **1a** and **1b** with silver perchlorate in tetrahydrofuran were similar.

Silver ion mediated decomposition of **1a** or **1b** in tetrahydrofuran produced heterogeneous precipitates which, in favorable instances, accounted for essentially all of the added reactants (**1a** or **1b** and silver perchlorate). Removal of silver ion from a crude reaction product mixture (suspended in either the original tetrahydrofuran solution or in methanol) was accomplished by treatment with hydrogen sulfide, hydrogen chloride, or methyl iodide. The resulting product mixture was then subjected to chromatographic separation, either directly or following desulfurization with Raney nickel. In all instances, yields of characterized products were low, accompanied by highly colored, polar material[8] which was not characterized.

The precipitate obtained by reaction of **1b** with silver perchlorate in tetrahydrofuran at −15° was treated with hydrogen sulfide to remove silver followed by Raney nickel desulfurization. From the resulting product mixture, 1- and 2-(2′-tetrahydrofuranyl)indoles (**4b** and **5b**) were isolated. When **1a** was treated similarly and the reaction mixture was fractionated following removal of silver but without desulfurization, the disulfide (**6a**) of 1-(2′-tetrahydropyranyl)-3-thioindole and 1-(2′-tetrahydropyranyl)-3-(2′-tetrahydropyranylthio)indole (**8a**) were isolated.

In a reaction of **1a** with silver ion, when silver was removed after 30 min at 25° (during which time 25% of the reactants had formed a precipitate), **1a** was recovered unchanged from the solution. When the filtrate, formed in the same manner, was treated with excess methyl iodide (to methylate all silver coordination sites), 3-methylthioindole (**7**)[9] and 3-methylthio-1-(2′-tetrahydropyranyl)indole (**9a**) were produced.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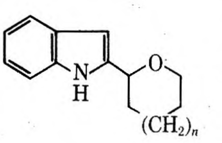
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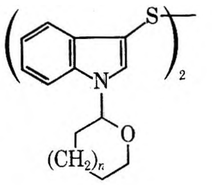
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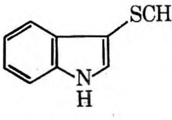
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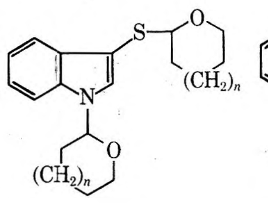
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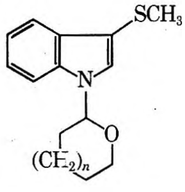
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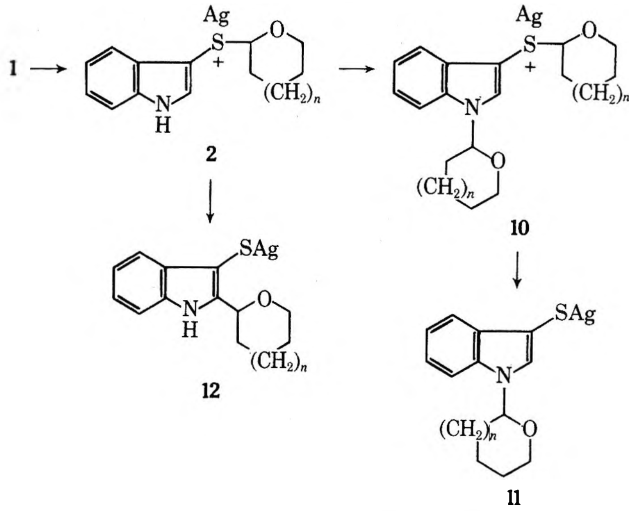
The results of this study allow the construction of Scheme I, which indicates the general features of the silver ion catalyzed reactions of **1**. The products isolated, irrespective of reaction conditions (*i.e.*, **4**, **6**, **8**, **9**), all possess a 2′-tetrahydropyranyl(furanyl) substituent on the indole nitrogen. The formation of such "rearrangement" products clearly must occur *via* an intermolecular pathway. The probable presence in solution of the secondary coordination compound **10**, as evidenced by the isolation of **8a** (and of **9a** from reactions in which methyl iodide was used), and the insolubility of 3-thioindole silver salt indicate that this "migration" of a cyclic ether moiety from sulfur to nitrogen is likely to occur exclusively *via* the path **2** → **10** → **11**. Interestingly, this sequence does not require formation of significant amounts of 3-thioindole silver salt, since, once some **10** is available, the reaction **2** + **10** → **11** + **10** → etc. is possible.

While the pathway to the 1-substituted compound **11** is clearly intermolecular, the origin of the 2-substituted product **12** is less certain. It is possible that a 2-substituted coordination compound analogous to **10** is an intermediate; however, as no evidence for such was found, the possibility that **12** arises *via* an intramolecular process must be considered. It is well known[10] that electrophilic substitution of 3-substituted indoles occurs readily at carbon 2, probably *via* a mechanism involving rearrangement of the adduct formed by initial attack at C-3.[11,12] In this light, although no direct evidence for the reaction process **1** → **3** was found, the possibility that **12** is formed *via* the pathway **1** → **2** → **3** → **12** is an attractive one.

Scheme I



The spectral properties of the variously substituted indoles comprising this study are highly characteristic and facilitated structural assignments. Among the isolated products from reactions of **1** with silver ion are compounds in which cyclic ether moieties are bonded variously to carbon, sulfur, or nitrogen in the 3-thioindole nucleus. The nuclear magnetic resonance (nmr) chemical shift exhibited by the proton on C-2′ of the cyclic ether moiety was, in every case, clearly identifiable and led readily to the correct assignment of the indole bonding site. Thus, the C-2′ proton of **1b** (C-2′ bonded to S) appears at δ 5.34, the corresponding resonance for 1-(2′-tetrahydrofuranyl)indole (**4b**, C-2′ bonded to N) appears at δ 5.92, and the signal in the spectrum of **5b** (C-2′ bonded to C) appears at δ 5.12. The compounds in the 2′-tetrahydropyranyl series exhibited analogous resonances, although shifted toward higher field; *e.g.*, for **1a** (C-2′ bonded to S) the signal appears at δ 4.84 and for **4a** (C-2′ bonded to N) the signal is at δ 5.35.

Definitive assignment of structure **5b** [as opposed to the isomeric structure 3-(2′-tetrahydrofuranyl)indole] was made by consideration of the nmr chemical shifts observed for the 2 and 3 protons of various indole derivatives. Thus, in the nmr spectrum[13] of 3-methylindole, the hydrogen at C-2 gives rise to a signal at δ 6.78 whereas the C-3 hydrogen in 2,5-dimethylindole appears at δ 6.10.[13,14] In the spectrum of 1-(2′-tetrahydrofuranyl)indole (**4b**) the C-2 hydrogen is observed at δ 6.9 and the C-3 hydrogen appears at δ 6.30. The resonance at δ 6.27 in the spectrum of **5b** clearly is that of the C-3 hydrogen and establishes the attachment of the tetrahydrofuranyl moiety as occurring at C-2.

These assignments are corroborated by examination of the mass spectra of the variously substituted compounds. The fragmentation of 1-(2′-tetrahydrofuranyl)indole (**4b**; see Figure 1A) is dominated by cleavage of the tetrahydrofuranyl moiety from the indole nucleus (*i.e.*, *m/e* 71 and 117). The fragmentations of the various *S*-tetrahydrofuranyl and *S*-tetrahydropyranyl compounds are similar in this respect (see Experimental Section). In contrast, the electron bombardment induced fragmentation of 2-(2′-tetrahydrofuranyl)indole (**5b**, see Figure 1B), in which the cyclic ether is linked to the indole nucleus *via* a carbon-carbon bond, is considerably more complex. Whereas the

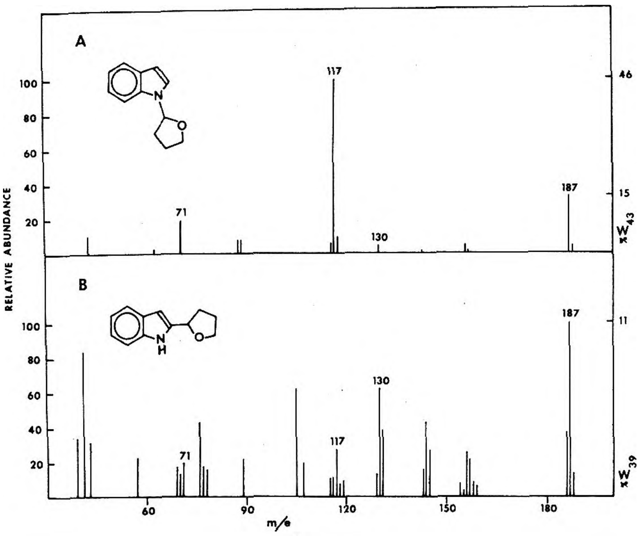


Figure 1. Mass spectra of 1-(2′-tetrahydrofuranyl)indole (**4b**), A, and 2-(2′-tetrahydrofuranyl)indole (**5b**), B.

indole·$^+$ rearrangement ion (*m/e* 117), formed by loss of dihydrofuran, is the most abundant ion (Σ_{43} = 46%) in the spectrum of **4b** (Figure 1A), this is a low-abundance ion (Σ_{39} = 3%) in the spectrum of **5b** (Figure 1B). Although the molecular ions represent comparable percentages of total ionization (*i.e.*, 15% for **4b** and 11% for **5b**), this ion is the base peak in the spectrum of **5b** (Figure 1B). These differences are strikingly similar to those observed in the spectra of N and C nucleosides.[15]

To facilitate structural assignments, authentic 1-(2′-tetrahydropyranyl)indole (**4a**) was synthesized by treatment of indolyllithium[16] with 2-chlorotetrahydropyran.[17] An attempt was made to prepare 3-(2′-tetrahydropyranyl)indole from the indole Grignard reagent[16,18] and 2-chlorotetrahydropyran[17] in ether; however, the only product formed in greater than trace amounts was again the N-substituted compound **4a**. This result is surprising in view of the absence of reports of such exclusive N-alkylation of an indole Grignard reagent in ether.[16,18,19]

Experimental Section

Infrared spectra were determined on a Perkin-Elmer 337 grating spectrophotometer. Nmr spectra were determined with a Varian HA-100 spectrometer using CCl_4 solutions; chemical shifts are expressed as parts per million (δ) downfield from an internal standard of tetramethylsilane. Mass spectra were obtained with a CEC Du Pont Model 21-110B spectrometer operated at 70 eV. Thin layer chromatography (tlc) was done on silica gel G. Melting points were determined on a microscope hot stage and are uncorrected. Elemental analyses were by Heterocyclic Chemical Corp., Harrisonville, Mo.

3-(2′-Tetrahydropyranylthio)indole (1a). To 250 ml of dimethylformamide, freshly distilled from calcium hydride and maintained under nitrogen, was added 0.5 g of an oil dispersion of sodium hydride, followed by 1.5 g (0.01 mol) of 3-thioindole.[4] After 2 hr, 1.2 g (0.01 mol) of 2-chlorotetrahydropyran[17] was added to the stirred solution. After several additional hours the reaction mixture was poured into ether and was extracted with brine and water. The ether solution was dried, decolorized with charcoal, and evaporated. The resulting crude product was crystallized from a mixture of hexane and ether to yield 0.56 g (24%) of 3-(2′-tetrahydropyranylthio)indole (**1a**) as cream-colored crystals: mp 84-85°; nmr δ 1.4-2.0 (m, 3′,5′-H), 3.45 (m, 6′-H), 4.16 (m, 6′-H), 4.84 (dd, J_1 = 6, J_2 = 3 Hz, 2′-H), 6.84 (d, J = 3 Hz, 2-H), 7.05-7.14 (m, 5-7-H), 7.64 (m, 4-H), 8.39 (br, NH).

Anal. Calcd for $C_{13}H_{15}NOS$: C, 66.9; H, 6.49; N, 6.0. Found: C, 67.0; H, 6.34; N, 5.82.

3-(2′-Tetrahydrofuranylthio)indole (1b). Employing 2-chlorotetrahydrofuran,[20] **1b** was synthesized in the same manner as **1a** in a yield of 28%. Recrystallization from 95% ethanol afforded colorless crystals: mp 98-100°; nmr δ 1.8-2.4 (m, 3′,4′-H), 3.8-4.15 (m, 5′-H), 5.3-5.42 (m, 2′-H), 7.02 (d, J = 2 Hz, 2-H), 7.1-7.2 (m, 5-7-H), 7.7-7.86 (m, 4-H), 8.48 (br, NH).

Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.8; H, 5.94; N, 6.39. Found: C, 65.8; H, 6.16; N, 6.18.

1-(2′-Tetrahydropyranyl)indole (4a). Method A. To a stirred solution of 2 g (0.017 mol) of indole in 50 ml of tetrahydrofuran was added 7.7 ml (0.017 mol) of a hexane solution of *n*-butyllithium. After 5 min, 2.04 g (0.017 mol) of 2-chlorotetrahydropyran[17] was added. After 30 min the solvent was evaporated and was replaced with 50 ml of methylene chloride. The methylene chloride solution was washed with water (2 × 50 ml), dried, and removed. The residue was chromatographed on a column of silicic acid (3 × 30 cm). 1-(2′-Tetrahydropyranyl)indole (**4a**), 1.44 g (42%), was eluted with 25% petroleum ether (bp 30-60°) in benzene as a colorless oil: bp 118° (0.2 mm); nmr δ 1.4-2.1 (m, 3′,5′-H), 4.58 (m, 6′-H), 4.96 (m, 6′-H), 5.35 (dd, J_1 = 8, J_2 = 4 Hz, 2′-H), 6.36 (d, J = 3.5 Hz, 3-H), 6.9-7.5 (m, 2,4-7-H); mass spectrum *m/e* (rel intensity), 201 (44), 144 (7), 130 (13), 117 (110), 85 (16).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.6; H, 7.46; N, 6.96. Found: C, 77.3; H, 7.44; N, 6.87.

Method B. To a solution of methylmagnesium iodide [prepared from 0.23 g (0.01 mol) of magnesium and 1.4 g (0.01 mol) of methyl iodide] in anhydrous ether was added 0.7 g (0.006 mol) of indole, and, after stirring for 3 hr, 0.72 g (0.006 mol) of 2-chlorotetrahydropyran[17] was added. After an additional 1 hr. water was added, and the ether phase was separated, washed several times with brine and water, and then dried. Removal of the solvent yielded crude 1-(2′-tetrahydropyranyl)indole (**4a**), which was separated from unreacted indole by preparative tlc. This material, 0.21 g (17%), was identical in all respects with the product prepared by method A.

Reaction of 3-(2′-Tetrahydropyranylthio)indole (1a) with Aqueous Silver Nitrate. Solutions of 23.3 mg (0.1 mmol) of 3-(2′-tetrahydropyranylthio)indole (**1a**) in 5 ml of 50% aqueous methanol and of 17 mg (0.1 mmol) of silver nitrate in 5 ml of water were cooled to 0° and combined. Immediately the silver salt of 3-thioindole precipitated, and was filtered and dried to yield 23 mg (90%) as an amorphous powder. Removal of the silver was accomplished by suspending the precipitate in methanolic hydrogen chloride. Tlc of the filtrate after removal of the silver chloride indicated the presence of 3-thioindole[4] and the corresponding disulfide. Treatment of the original filtrate with 2,4-dinitrophenylhydrazine reagent[21] yielded 15.8 mg (56%) of red crystals of the 2,4-dinitrophenylhydrazone of 5-hydroxyvaleraldehyde, mp 110-112° (lit.[5] mp 109°, 113-114°).

Reaction of 3-(2′-Tetrahydrofuranylthio)indole (1b) with Silver Perchlorate in Tetrahydrofuran. To a stirred, cooled (−15°) solution of 2.19 g (0.01 mol) of 3-(2′-tetrahydrofuranylthio)indole (**1b**) in 75 ml of dry tetrahydrofuran was added a cooled (−15°) solution of 2.07 g (0.01 mol) of silver perchlorate in 10 ml of dry tetrahydrofuran, whereupon the solution immediately became yellow. After 30 min the precipitate which had formed was collected, resuspended in 50 ml of methanol, and treated with hydrogen sulfide, the excess hydrogen sulfide being discharged with a nitrogen jet. The precipitated silver sulfide was removed with the filtrate passing directly into a suspension of *ca.* 10 g of Raney nickel in 150 ml of 7 *N* ammonium hydroxide. This mixture was heated under reflux on a steam bath for 2 hr. The hot mixture was then filtered to remove the Raney nickel, which was washed with 95% ethanol. The combined filtrate was evaporated and the resulting residue was triturated with methylene chloride (3 × 25 ml). The methylene chloride soluble portion was subjected to preparative chromatography to yield two products: 1-(2′-tetrahydrofuranyl)indole (**4b**, 50 mg) and 2-(2′-tetrahydrofuranyl)indole (**5b**, 5 mg). 1-(2′-Tetrahydrofuranyl)indole (**4b**) had nmr δ 1.62-2.16 (m, 3′,4′-H), 3.6-4.0 (m, 5′-H), 5.92 (t, J = 4 Hz, 2′-H), 6.30 (d, J = 3.5 Hz, 3-H), 6.8-7.3 (m, 2,5-7-H), 7.4 (m, 4-H); mass spectrum *m/e* (rel intensity), 187 (33), 130 (5), 117 (100), 71 (20); ir no NH. 2-(2′-Tetrahydrofuranyl)indole (**5b**) had nmr δ 1.86-2.44 (m, 3′,4′-H), 3.84-4.02 (m, 5′-H), 5.12 (dd, J_1 = 8, J_2 ≅ 1 Hz, 2′-H), 6.2 (m, 3′-H), 6.9-7.3 (m, 5-7-H), 7.44 (m, 4-H), 8.36 (br, NH); mass spectrum *m/e* (rel intensity) 187 (100), 154 (80), 144 (43), 130 (63), 117 (28), 71 (20); ir 3420 and 3310 cm^{-1} (NH).

Reaction of 3-(2′-Tetrahydropyranylthio)indole (1a) with Silver Perchlorate in Tetrahydrofuran. To a solution of 233 mg (1 mmol) of 3-(2′-tetrahydropyranylthio)indole (**1a**) in anhydrous tetrahydrofuran was added a solution of 207 mg (1 mmol) of silver perchlorate in anhydrous tetrahydrofuran. Concentrations in various reactions ranged from 0.01 to 0.002 *M* with no discernible difference in results. When the two solutions were combined at −78° a colorless solution resulted. The analysis of the solution (tlc) showed the presence of uncomplexed starting material, **1a**. No change was observed after several hours at −78°. When warmed (−15 to 25°), the solution turned yellow and an orange precipitate was formed; no uncomplexed starting material was evident in the solution by tlc analysis. The collected, dried precipitate, which appeared during 30 min at 25°, weighed 100 mg and accounted for approximately 25% of the combined weight of the thioketal **1a** and the silver perchlorate. The precipitate (fraction A), resuspended in tetrahydrofuran, and the filtrate (fraction B) were treated separately with hydrogen sulfide in ether and the resulting silver sulfide was removed. Water was added to each of the filtrates, followed by extraction with ether. The solvents were removed from the ether-soluble portions and the residues were separated by tlc (chloroform–acetone 95:5). From the original filtrate (fraction B) unreacted starting material **1a** was obtained; no **1a** was present in the precipitate (fraction A).

The components isolated from the precipitate (fraction A) were 3-thioindole,[4] 3-thioindolyl disulfide,[4] and 1-(2′-tetrahydropyranyl)-3-thioindolyl disulfide (**6a**): mp 136–140°; nmr δ 1.5–2.1 (m, 3′–5′-H), 3.68 (m, 6′-H), 4.0 (m, 6′-H), 5.39 (m, 2′-H), 6.9–7.6 (m, 2,4–7-H); mass spectrum *m/e* (rel intensity) 464 (3), 432 (4), 348 (4), 264 (19), 149 (100), 148 (20), 117 (20), 85 (60).

Reaction of Silver Complex 2a with Methyl Iodide. To a solution of silver complex **2a** (methyl iodide was unreactive toward **1a** in the absence of silver ion) prepared in tetrahydrofuran as described above was added an excess of methyl iodide. After several hours at room temperature (at lower temperatures, no reaction occurred) a yellow precipitate of silver iodide had formed. The mixture was filtered, water was added to the filtrate, and the solution was extracted with ether. By preparative chromatography the starting thioketal (**1a**). 3-methylthioindole[9] (**7**), 1-(2′-tetrahydropyranyl)-3-(2′-tetrahydropyranylthio)indole (**8a**), and 1-(2′-tetrahydropyranyl)-3-methylthioindole (**9a**) were isolated. 3-Methylthioindole[9] (**7**) had nmr δ 2.32 (s, SMe), 7.05–7.24 (m, 2,5–7-H), 7.68 (m, 4-H), 7.9 (br, NH). 1-(2′-Tetrahydropyranyl)-3-(2′-tetrahydropyranylthio)indole (**8a**) had nmr δ 1.5–2.1 (m, 3′–5′, 3″–5″-H), 3.4–3.8 (m, 6′,6″-H), 3.9–4.2 (m, 6′,6″-H), 4.80 (m, 2′-H), 5.38 (m, 2″-H), 6.9–7.7 (m, 2,4–7-H); mass spectrum *m/e* (rel intensity) 317 (11), 233 (43), 149 (100), 117 (6), 85 (63). 1-(2′-Tetrahydropyranyl)-3-methylthioindole (**9a**) had nmr δ 1.5–2.1 (m, 3′–5′-H), 2.29 (s, SMe), 3.60 (m, 6′-H), 4.0 (m, 6′-H), 5.32 (dd, $J_1 = 8$, $J_2 = 4$ Hz, 2′-H), 7.0–7.4 (m, 2,5–7-H), 7.62 (m, 4-H); mass spectrum *m/e* (rel intensity) 247 (51), 163 (100), 148 (32), 117 (6), 85 (50).

Reactions of Raney Nickel with 3-(2′-Tetrahydropyranylthio)indole (1a), 3-Methylthioindole[9] (7), and 1-(2′-Tetrahydropyranyl)-3-methylthioindole (9a). A few milligrams of **1a**, **7**, or **9a** in methanol was treated with a large excess (*ca.* tenfold by weight) of Raney nickel. After standing at room temperature for 0.5 hr, the suspension was filtered and the filtrate was evaporated. In the case of **1a** or **7**, the resulting product was identified as indole by tlc and comparison of spectra. In the case of **9a** the product was indistinguishable from 1-(2′-tetrahydropyranyl)indole (**4a**), prepared as described.

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Registry No.—**1a**, 50639,97-9; **1b**, 50639-98-0; **4a**, 50639-99-1; **4b**, 50640-00-1; **5b**, 50640-01-2; **6a**, 50640-02-3; **7**, 40015-10-9; **8a**, 50640-03-4; **9a**, 50640-04-5; Ag^+, 14701-21-4; silver nitrate, 7761-88-8; silver perchlorate, 7783-93-9; 3-thioindole, 480-94-4; 2-chlorotetrahydropyran, 3136-02-5; 2-chlorotetrahydrofuran, 13369-70-5.

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Stereoselective Formation of Some Thietane 1,1-Dioxides

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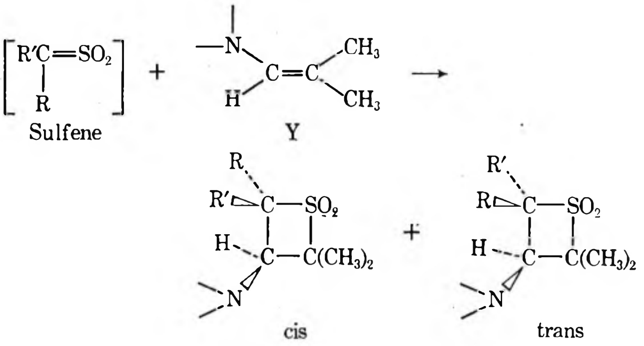
The reaction of substituted methanesulfonyl chlorides and ethanesulfonyl chlorides with triethylamine in the presence of 2-methyl-1-propenylamines is discussed. The observed stereoselectivity in the formation of products can be explained on the basis of a zwitterionic intermediate or a concerted $[{}_{\pi}2_s + {}_{\pi}2_s]$ process.

The chemistry of sulfenes has received considerable attention in the past decade and several reviews have appeared.[1] The reaction of sulfenes with enamines is probably the most extensively investigated reaction of these chemical intermediates, but data concerning the stereochemistry of the products derived from the reaction of substituted sulfenes with enamines is meager and inconclusive.[2] The present study deals with the stereochemistry of the products obtained in the reaction of a number of substituted methanesulfonyl and ethanesulfonyl chlorides with triethylamine in the presence of N,N-disubstituted 2-methyl-1-propenylamines.

Table I



Compd	R′	R	Y	% cis	% yield[a]
1	p-$C_6H_4CH_3$	H	I	82	50[b]
2	C_6H_5	H	I	74	94
3	C_6H_5	H	II	77	100
4	C_6H_5	H	III	73	100
5	p-C_6H_4Cl	H	I	62	75[b]
6	p-$C_6H_4NO_2$	H	I	0	69
7	Cl	H	I	65	34[b]
8	Cl	CH_3	I	72	77
9	Cl	CH_3	II	77	100
10	Cl	CH_3	III	85	98
11	Cl	CH_3	IV	72	100
12	Br	H	I	59	43[b]
13	Br	H	II	67	100
14	Br	H	III	73	100
15	I	H	I	63	82
16	CN	H	I	0	42
17	CN	CH_3	I	84	49[b]
18	CN	CH_3	II	83	83
19	CN	CH_3	III	74	81
20	CN	CH_3	IV	72	63
21	CH_3	H	I	42	24[c]
22	n-C_3H_7	H	I	39	32[c]
23	$CH_2C_6H_5$	H	I	45	98
24	O=CC_6H_5	H	I	0	*d*
25	O=CC_6H_5	H	II	0	64
26	O=CC_6H_5	H	III	0	88
27	O=COEt	CH_3	II	0	93
28	O=COEt	CH_3	III	27	89

[a] Crude yield. [b] Yield after recrystallization. [c] Yield after distillation; extensive decomposition occurred with the formation of polymeric tars. [d] Decomposed on standing.

Results

The reaction of mono- and disubstituted sulfenes with the following enamines, *N,N*-dimethyl-2-methyl-1-propenylamine (I), 2-methyl-1-propenylpyrrolidine (II), 4-(2-methyl-1-propenyl)morpholine (III), and *N,N*-diisopropyl-2-methyl-1-propenylamine (IV), led almost exclusively to a mixture of cis- and trans-substituted thietane 1,1-dioxides.[3] Surprisingly, in a large number of examples (see Table I, **1-5**, **7-15**, **17-20**), the preferred orientation in these cyclic sulfones was one in which the amino moiety and the sulfene substituent (other than alkyl) were in the less thermodynamically stable cis arrangement. A summary of the results of these experiments is presented in Table I.

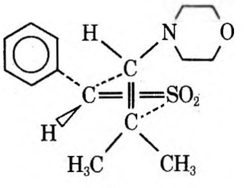
The cis percentages were determined by nmr analysis of crude reaction products obtained as explained in the Experimental Section. To avoid erroneous results due to possible differing solubilities of isomeric cycloadducts in the nmr solvent, samples for analysis were obtained by dissolving the entire crude residue in the solvent and analyzing an aliquot of this. In the experiments employing substituted methanesulfonyl chlorides, pure trans cycloadducts could be obtained quantitatively by equilibrating the isomeric mixtures with potassium *tert*-butoxide in *tert*-butyl alcohol for a period of from 1 day to 2 weeks. Further evidence for the stereochemical assignments to the products will be presented later.

Discussion

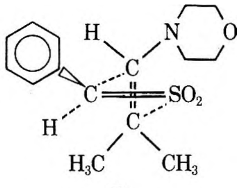
An investigation of the current literature on the addition of sulfenes to enamines suggests that this reaction may proceed *via* a two-step process.[4,5] Scheme I illustrates this stepwise process for the reaction of α-toluenesulfonyl chloride with triethylamine in the presence of *N,N*-dimethyl-2-methyl-1-propenylamine.

A rationale for the formation of the less stable cis isomer can be postulated based on the above reaction scheme in that electrostatic attractions between the positive and negative charges of the 1,4-dipolar intermediate, which can be delocalized by the amino and phenyl moieties, respectively, should favor cis geometry.[6] Even in those cases where the electronegative group stabilizing the carbanion moiety of the postulated intermediate is limited in its ability to delocalize the charge *via* resonance (*i.e.*, halides)[7] cis preference was still observed. The data in Table I, demonstrating that cis preference was not observed for substrates incapable of appreciable negative character β to the sulfonyl group in the zwitterionic intermediate, offers support for this theory (*e.g.*, Table I, **21-23**).

A concerted process $[_\pi2_s + {}_\pi2_a]$ could conceivably account for cis preference in the geometry of these products if steric considerations are taken into account along with a secondary orbital interaction between the amine lone pair and the π framework of the sulfene. Current theory requires that for this concerted process one unsaturated system must approach the other with an orthogonal orientation.[8] A cursory analysis of these interactions gives the following orientations as the most probable in the transition state for the reaction of phenylsulfene and III.


A

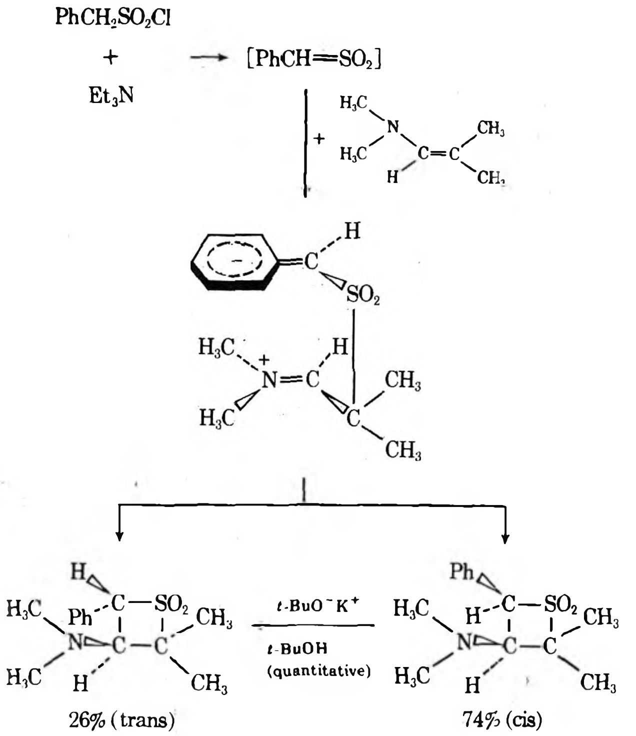
or


B

Either frontal or rear attack by sulfene on this enamine should yield the cis cycloadduct. If the reaction, however, were indeed proceeding *via* this mechanistic scheme, cis preference should not be limited to those cases involving electronegative substituents. As already indicated, aliphatic sulfonyl chlorides react under these conditions to give predominantly trans cycloadducts (Table I, **21-23**). If only conventional steric factors are considered, the alternate geometry would be expected from a concerted $[_\pi2_s + {}_\pi2_a]$ process.

A third alternative explanation which should not be overlooked is the concerted $[_\pi2_s + {}_\pi2_s]$ process. Although this process is thermally disallowed by Woodward-Hoffmann rules, recent theoretical considerations indicate that this would be the favored mode of addition in the case of cycloaddends of substantially different electron-accepting and -donating abilities and has been invoked to explain the results of the cycloaddition reactions of ketenes.[9a] In the reaction of sulfenes, a concerted process of this type coupled with the secondary electronic effects possible between the electron-donating amine moiety and the electron-attracting substituents of the sulfene moiety would sufficiently explain the results obtained in the course of this investigation. In the absence of the electron-attracting substituents trans products would predominate.

Scheme I



Preliminary results of semiempirical SCF-MO calculations do not support the idea of a stereochemistry-maintaining cisoid dipolar intermediate and thus lends further support to the pericyclic $[_\pi 2_s + {}_\pi 2_s]$ process.[9b] It is of interest to note that the difference between the $[_\pi 2_s + {}_\pi 2_s]$ process and the cisoid dipolar intermediate may be merely one of semantics and that the $[_\pi 2_s + {}_\pi 2_s]$ complex and the so-called dipolar intermediate are in fact one and the same species.

In the reaction of para-substituted phenylsulfenes a noticeable decrease in cis preference is observed in going from electron-donating to electron-withdrawing substituents. Whether this is due largely to substituent effects in the postulated intermediates or to differing rates of postisomerization in the products is still unclear. The effect of electron-withdrawing substituents on the aromatic ring on the intermediate zwitterion would be twofold: first, the intermediate carbanion moiety would be stabilized to a greater extent and perhaps permit an increased production of the more thermodynamically stable trans product; and second, the substituent would disperse the negative charge to a greater degree and reduce the "effective" electrostatic attractions. However, once the product has been formed, it is itself capable of postisomerization *via* carbanion formation at the 4 position. During the early stages of the reaction, triethylamine is in excess and the cycloadducts themselves contain a tertiary amine, either of which should be capable of catalyzing the isomerization. This isomerization was demonstrated to occur in the presence of Et_3N for the product mixture from the reaction of phenylsulfene and I but only slowly (see Experimental Section). This indicated that the substituents do play a role in the stereochemical course of the reaction but in order to assess the relative contribution of postisomerization in products **1-6** the substituted α-phenylethanesulfonyl chlorides[10] would need to be employed. Attempts to prepare these compounds, however, were not successful.

Postisomerization in the case of the less acidic halocycloadducts does not appear to be a problem, since pure *cis*-2,2-dimethyl-3-(*N,N*-dimethylamino)-4-chlorothietane 1,1-dioxide remained unchanged when treated with an equimolar amount of triethylamine in anhydrous diethyl ether for 3 days or acetonitrile for 1 day. The apparent "anomalies" associated with the products derived from benzoyl and cyanosulfenes are easily understood on the basis of this postisomerization phenomena due to the enhanced acidity of the 4 hydrogen in these cycloadducts.[11]

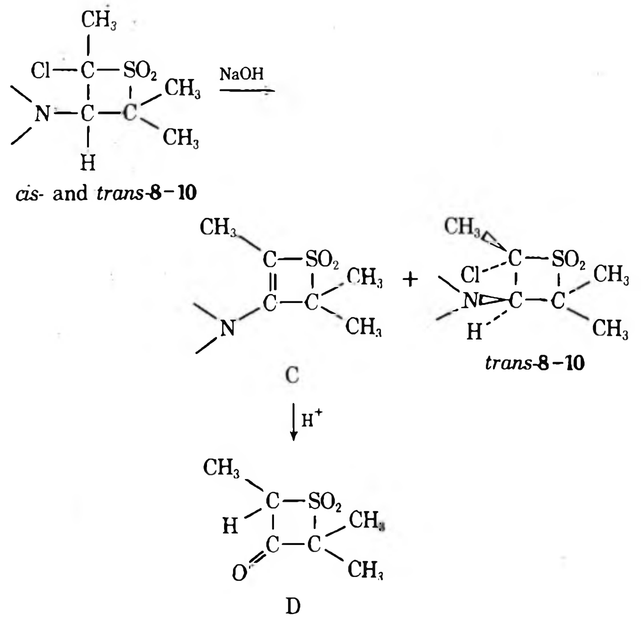
The results obtained with the substituted ethanesulfonyl chlorides are more significant on the basis that carbanion formation at the 4 position and subsequent isomerization is no longer possible. For the reactions of both α-cyanoethanesulfonyl chloride and α-chloroethanesulfonyl chloride, cis cycloaddition products predominated (Table I, **8-11** and **17-20**). With the former reaction, the results indicated that postisomerization was probably operative (Table I, **16**). The products derived from α-chloroethanesulfonyl chloride had a higher cis/trans ratio than was true for the chlorosulfene cycloadducts (see Table I, **7-11**), but this may simply reflect the decreased thermodynamic differences between the two isomers. Equilibration attempts, under reaction conditions, of pure *cis*-**7** afforded only cis isomer on work-up, demonstrating that postisomerization for this system was not occuring.

The results with α-carbethoxyethanesulfonyl chloride (Table I, **27** and **28**) were, however, puzzling at first in view of the postulated reaction scheme. This substrate was reported to react with triethylamine in the presence of 2-methyl-1-propenylpiperidine to give exclusively the trans cycloadduct in an 83% yield.[2b] The fact that ethyl chlorosulfonylacetate ($EtO_2CCH_2SO_2Cl$) gave only trans products was understandable owing to the ease of isomerization expected for this product, but, as in the case of the cyanosulfenes (Table I, **17-20**), a predominance of cis product was expected in the former reaction. Our own experiments confirmed the earlier report in that trans products predominated. A closer inspection of molecular framework models then revealed that for a zwitterionic intermediate of this type, with extensive delocalization of charges, electrostatic forces could effectively stabilize both cis and trans zwitterionic precursor forms. If this is the case, then the more thermodynamically stable product would be expected to predominate and steric factors would dictate product distribution. Several attempts were made to prepare and isolate the interesting α-benzoylethanesulfonyl chloride to further test this hypothesis, but they were unsuccessful.[12]

There has been some speculation in the literature[2a,b,13] that the Karplus correlation[14] is reliable for the thietane 1,1-dioxide ring system and hence applicable for assigning the cis-trans geometry of this ring system. The coupling constants observed in the cis and trans cycloadducts obtained during this investigation did not bear this out (see Experimental Section). A recent application of shift reagent, $Eu(fod)_3$, to this problem has allowed for an unambiguous designation of the stereochemistry of the products derived from bromosulfene and 1-(morpholino)cyclohexene.[2d] The results of this investigation confirmed earlier structural assignments based on equilibration data. An extension of these nmr data to the data obtained from the cycloadducts prepared in this investigation, coupled with the equilibration studies, allows their stereochemical assignments to be unambiguously made.

Another method, which has proved most helpful with products derived from disubstituted sulfenes, was reported recently for α-halothietane 1,1-dioxides.[2c] When a mixture of cis and trans isomers, *e.g.*, **9**, was subjected to treatment by aqueous alkali followed by acidic work-up, the keto sulfone 2,4,4-trimethylthietan-3-one 1,1-dioxide (D) and the pure trans cycloadduct (**10**) were obtained.

The absolute stereochemistry of these trans cycloadducts has been confirmed by X-ray diffraction data on pure *trans*-**10**.[15] A comparison of nmr chemical shift data



cis- and trans-**8**–**10**

C

trans-**8**–**10**

D

of these known systems with that of the similarly substituted cycloadducts (Table I, **17**–**20**) shows definite trends and similarities and allows for unambiguous stereochemical assignments.[28]

Conclusion

The question of whether or not sulfene reactions with enamines are concerted or stepwise processes is still not definitively resolved. Certainly these are limiting cases and perhaps the course of the reaction of sulfenes with enamines depends on the nature of the reactants. In those cases where electron-withdrawing groups are present to stabilize a zwitterionic intermediate, perhaps the reactions are more stepwise in character, whereas, when these groups are absent, such as with sulfene itself, there is a "substantial degree of concertedness"[5] to the cycloaddition. The nature of the reactive sulfenes and the instability of the cis enamines makes this problem even more difficult to resolve. The reaction could indeed be a concerted process and the stereochemical consequences dependent on the properties of the cycloaddends as suggested by Epiotis,[9] and not a consequence of a dipolar intermediate. The mechanism of this reaction thus remains obscure but the steroechemical outcome of these reactions is indeed interesting to note.

Experimental Section

All reactions were performed in a nitrogen atmosphere. The nmr spectra were recorded on a Varian A-60A instrument in $CDCl_3$ with trimethylsilane as the internal standard and the data for cis isomers were obtained from mixtures except where noted. The infrared (ir) spectra were recorded on a Beckman IR-33 or a Perkin-Elmer Infracord. All melting points and boiling points are uncorrected. Ethanesulfonyl, butanesulfonyl, and α-toluenesulfonyl chlorides were obtained from Eastman Organic Chemicals (White Label). The following sulfonyl chlorides were prepared according to the literature: haloalkanesulfonyl chlorides,[16-19] cyanoalkanesulfonyl chlorides,[20] α-carbethoxyethanesulfonyl chloride,[2b] β-phenylethanesulfonyl chloride,[10] benzoylmethanesulfonyl chloride,[21] and para-substituted α-toluenesulfonyl chlorides.[22] Triethylamine, obtained from Matheson Coleman and Bell, was distilled from α-naphthyl isocyanate (2%), bp 88–89°, and stored over sodium hydroxide prior to use.[23] The enamines were also prepared according to the literature, enamines I, II, and III by the reaction of isobutyraldehyde (flash distilled, Aldrich) with the appropriate freshly distilled amine in the presence of $TiCl_4$[24] and IV [bp 55–56° (17 mm), $n^{30}{}_D$ 1.4310] by the reaction of the aldehyde with diisopropylamine (Matheson Coleman and Bell) in the presence of molecular sieves.[25] No attempt was made to maximize the isolated purified yields of the cycloadducts. Microanalyses were performed by Dr. C. S. Yeh and staff.

General Procedure for Preparing Thietane 1,1-Dioxide Derivatives from Monosubstituted Sulfonyl Chlorides. To an ethereal solution of 1.0 equiv of the enamine and 1.0 equiv of triethylamine at room temperature, an ethereal solution of 1.0 equiv of the sulfonyl chloride was added dropwise over a period of 10–30 min. After the addition was complete, the reaction was stirred for an additional 30 min. Triethylammonium chloride was then filtered and washed with several small portions of diethyl ether. The combined filtrate and washings were then evaporated *in vacuo*, affording a crude residue which after drying over P_2O_5 under reduced pressure for several hours was dissolved in $CDCl_3$. After an aliquot of this was analyzed *via* nmr the solvent was again removed *in vacuo* and the residue was recrystallized from a suitable solvent. Pure trans isomers were obtained by stirring isomeric mixtures (~2.0 g) with a catalytic amount of potassium *tert*-butoxide (~0.1 g) in *tert*-butyl alcohol for a period of from 1 day to 2 weeks. Recrystallization or sublimation gave analytically pure products.

2,2-Dimethyl-3-(*N,N*-dimethylamino)-4-*p*-tolylthietane 1,1-Dioxide (1). The cis–trans mixture was prepared on a 0.1-molar scale according to the general procedure. The isomeric mixture would not crystallize: nmr ($CDCl_3$) cis δ 1.58 and 1.72 (s, 3 H each, *gem*-dimethyl groups), 2.03 [s, 6 H, $N(CH_3)_2$] 2.29 (s, 3 H, $PhCH_3$), 3.13 (d, J = 10 Hz, 1 H, NCH), 5.25 (d, J = 10 Hz, 1 H, $CHSO_2$), 7.13 and 7.53 (m, 2 H each, ortho and meta aromatic H). An analytical sample of the trans isomer was obtained after isomerization of the crude material for 1 day as described above, recrystallization from methanol, and sublimation at 100° (0.4 mm): mp 134°; ir (KBr) (SO_2) 1305, 1285, 1160, 1110, and 1045 cm^{-1}; nmr ($CDCl_3$) δ 1.61 and 1.67 (s, 3 H each, *gem*-dimethyl groups), 2.06 [s, 6 H, $N(CH_3)_2$], 2.33 (s, 3 H, $PhCH_3$), 2.92 (d, J = 10 Hz, 1 H, CHN), 5.06 (d, J = 10 Hz, 1 H, $CHSO_2$), and 7.27 (m, 4 H, aromatic H).

Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.88; H, 7.92; N, 5.24; S, 11.99. Found: C, 62.87; H, 8.07; N, 5.02; S, 12.20.

2,2-Dimethyl-3-(*N,N*-dimethylamino)-4-phenylthietane 1,1-Dioxide (2). A cis–trans mixture was obtained on a 0.1-molar scale in an 82% yield after recrystallization from 95% ethanol: nmr ($CDCl_3$) cis δ 1.63 and 1.75 (s, 3 H each, *gem*-dimethyl groups), 2.08 [s, 6 H, $N(CH_3)_2$], 3.18 (d, J = 10 Hz, 1 H, CHN), 5.29 (d, J = 10 Hz, 1 H, $CHSO_2$), and 7.25–7.80 (m, 5 H, aromatic H). Equilibration of a 2.0-g sample of the isomeric mixture with 0.1 g of potassium *tert*-butoxide in 50 ml of *tert*-butyl alcohol for 3 days followed by solvent removal afforded 2.0 g of the isomerically pure trans cycloadduct. Recrystallization from 95% ethanol afforded an analytically pure sample: mp 164° (lit.[26] mp 165–166); ir (KBr) (SO_2) 1290, 1115, and 1050 cm^{-1}; nmr ($CDCl_3$) δ 1.63 and 1.67 (s, 3 H each, *gem*-dimethyl groups), 2.05 [s, 6 H, $N(CH_3)_2$], 2.95 (d, J = 10 Hz, 1 H, CHN), 5.09 (d, J = 10 Hz, 1 H, $CHSO_2$), and 7.39 (s, 5 H, aromatic H).

Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53; S, 12.65. Found: C, 61.80; H, 7.29; N, 5.50; S, 12.77.

2,2-Dimethyl-3-(*N*-pyrrolidino)-4-phenylthietane 1,1 Dioxide (3). This material was isolated on a 0.01-molar scale as the trans cycloadduct after stirring the initial crude reaction products with 0.2 g of potassium *tert*-butoxide in 50 ml of *tert*-butyl alcohol for 40 hr and recrystallization from 95% ethanol: nmr ($CDCl_3$) cis δ 1.60 and 1.70 (s, 3 H each, *gem*-dimethyl groups), 1.42 and 2.20 (m, 8 H, pyrrolidino H), 3.28 (d, J = 10 Hz, 1 H, CHN), 5.28 (d, J = 10 Hz, 1 H, $CHSO_2$), 7.23–7.82 (m, 5 H, aromatic H). Pure trans cycloadduct had mp 136–137.5° [lit.[27] mp 161° (ligroin)]; ir (KBr) (SO_2) 1310, 1300, and 1105 cm^{-1}; nmr ($CDCl_3$) δ 1.65 (s, 6 H, *gem*-dimethyl groups), 1.42 and 2.10 (m, 8 H, pyrrolidino H), 3.05 (d, J = 10 Hz, 1 H, CHN), 5.08 (d, J = 10 Hz, 1 H, $CHSO_2$), and 7.40 (s, 5 H, aromatic H).

2,2-Dimethyl-3-(*N*-morpholino)-4-phenylthietane 1,1-Dioxide (4). This reaction was carried out on a 0.01-molar scale to give a quantitative yield of an isomeric mixture of products: nmr ($CDCl_3$) cis δ 1.62 and 1.73 (s, 3 H each, *gem*-dimethyl groups), 2.26 [m, 4 H, $(CH_2)_2N$], 3.30 (d, J = 10 Hz, 1 H, CHN), 3.55 [m, 4 H, $(CH_2)_2O$], 5.33 (d, J = 10 Hz, 1 H, $CHSO_2$), and 7.25–7.78 (m, 5 H, aromatic H). The crude material was dissolved in 75 ml of *tert*-butyl alcohol and 0.2 g of potassium *tert*-butoxide was added. After stirring at room temperature for 2 days, work-up and recrystallization from 95% ethanol afforded a 73% overall yield of pure trans cycloadduct: mp 181–182.5°; ir (KBr) (SO_2) 1310 and 1110 cm^{-1}; nmr ($CDCl_3$) δ 1.60 and 1.63 (s, 3 H each, *gem*-dimethyl groups), 2.23 [m, 4 H, $(CH_2)_2N$], 3.08 (d, J = 10 Hz, 1 H, CHN), 3.55 [m, 4 H, $(CH_2)_2O$], 5.10 (d, J = 10 Hz, 1 H, $CHSO_2$), and 7.37 (s, 5 H, aromatic H).

4-*p*-Chlorophenyl-2,2-dimethyl-3-(*N,N*-dimethylamino)thie-

tane 1,1-Dioxide (5). A mixture of cis and trans cycloadducts was obtained in a 75% yield on a 0.05-molar scale according to the general procedure: nmr ($CDCl_3$) cis δ 1.63 and 1.73 (s, 3 H each, *gem*-dimethyl groups), 2.10 [s, 6 H, $N(CH_3)_2$], 3.15 (d, *J* = 10 Hz, 1 H, CHN), 5.25 (d, *J* = 10 Hz, 1 H, $CHSO_2$), and 7.22–7.72 (m, 5 H, aromatic H). Recrystallization of the mixture from methanol afforded a 45% yield of trans cycloadduct which was purified further by sublimation at 121° (0.4 mm): mp 138°; ir (KBr) (SO_2) 1310, 1118, and 1050 cm^{-1}; nmr ($CDCl_3$) δ 1.64 and 1.68 (s, 3 H each, *gem*-dimethyl groups), 2.08 [s, 6 H, $N(CH_3)_2$], 2.88 (d, *J* = 10 Hz, 1 H, CHN), 5.08 (d, *J* = 10 Hz, 1 H, $CHSO_2$), and 7.42 (s, 5 H, aromatic H).

Anal. Calcd for $C_{13}H_{18}ClNO_2S$: C, 54.25; H, 6.30; Cl, 12.32; N, 4.87; S, 11.14. Found: C, 54.50; H, 6.46; Cl, 12.54; N, 4.76; S, 11.18.

2,2-Dimethyl-3-(*N,N*-dimethylamino)-4-*p*-nitrophenylthietane 1,1-Dioxide (6). The starting sulfonyl chloride (*p*-nitro-α-toluenesulfonyl chloride) is only slightly soluble in Et_2O; so 0.05 mol was suspended in 250 ml of Et_2O and a solution containing the enamine I (0.05 mol) and triethyamine (0.05 mol) was slowly added to it. In this fashion only trans cycloadduct was obtained. According to the general procedure, employing a large volume of Et_2O (800 ml) to dissolve the acid chloride, only trans isomer was again obtained. Products **1**, **2**, and **5** were also prepared by this inverse addition route but no differences were observed in the cis/trans ratios. The product **6** was also only moderately soluble in Et_2O but an nmr analysis of the solid filtered off indicated only trans isomer along with triethylammonium chloride. An analytical sample was obtained by sublimation at 110° (0.1 mm): mp 154–155°; ir (KBr) (SO_2) 1300, 1118, 1050 and (NO_2) 1520 and 1345 cm^{-1}; nmr ($CDCl_3$) δ 1.67 and 1.70 (s, 3 H each, *gem*-dimethyl groups), 2.08 [s, 6 H, $N(CH_3)_2$], 2.98 (d, *J* = 10 Hz, 1 H, CHN), 5.21 (d, *J* = 10 Hz, 1 H, $CHSO_2$), and 7.63 and 8.27 (m, 2 H each, ortho and meta aromatic H).

Anal. Calcd for $C_{13}H_{18}N_2O_4S$: C, 52.33; H, 6.08; N, 9.39; S, 10.75. Found: C, 52.49; H, 6.24; N, 9.16; S, 10.88.

4-Chloro-2,2-dimethyl-3-(*N,N*-dimethylamino)thietane 1,1-Dioxide (7). Fractional recrystallization of the crude reaction product obtained from 0.1 mol of reactants according to the general procedure afforded 13.5% pure cis cycloadduct: mp 102–103°; ir (KBr) (SO_2) 1330, 1310, 1180, and 1060 cm^{-1}; nmr ($CDCl_3$) δ 1.56 and 1.75 (s, 3 H each, *gem*-dimethyl groups), 2.30 [s, 6 H, $N(CH_3)_2$], 2.94 (d, *J* = 7 Hz, 1 H, CHN), 5.33 (d, *J* = 7 Hz, 1 H, $CHSO_2$).

Anal. Calcd for $C_7H_{14}ClNO_2S$: C, 39.71; H, 6.64; Cl, 16.76; N, 6.61; S, 15.15. Found: C, 40.00; H, 6.76; Cl, 16.85; N, 6.59; S, 15.42.

Further crystallizations afforded only cis–trans mixtures (20.5%), which were then equilibrated (as described previously) for 4 days to yield pure trans product: mp 82–83°; ir (KBr) (SO_2) 1320, 1170, 1120, and 1060 cm^{-1}; nmr ($CDCl_3$) δ 1.56 and 1.58 (s, 3 H each, *gem*-dimethyl groups), 2.27 [s, 6 H, $N(CH_3)_2$], 2.63 (d, *J* = 8 Hz, 1 H, CHN), 5.27 (d, *J* = 8 Hz, 1 H, $CHSO_2$).

4-Bromo-2,2-dimethyl-3-(*N,N*-dimethylamino)thietane 1,1-Dioxide (12). A cis–trans mixture was obtained in a 43% yield on a 0.1-molar scale after recrystallization from 95% ethanol: nmr ($CDCl_3$) cis δ 1.54 and 1.78 (s, 3 H each, *gem*-dimethyl groups), 2.30 [s, 6 H, $N(CH_3)_2$], 2.83 (d, *J* = 7 Hz, 1 H, CHN), 5.48 (d, *J* = 7 Hz, 1 H, $CHSO_2$). Equilibration as before for 3 days afforded pure trans cycloadduct, which was purified by sublimation at 58° (0.3 mm): mp 83–84°; ir (KBr) (SO_2) 1315, 1160, 1110, and 1050 cm^{-1}; nmr ($CDCl_3$) δ 1.56 and 1.58 (s, 3 H each, *gem*-dimethyl groups), 2.28 [s, 6 H, $N(CH_3)_2$], 2.77 (d, *J* = 8 Hz, 1 H, CHN), 5.35 (d, *J* = 8 Hz, 1 H, $CHSO_2$).

Anal. Calcd for $C_7H_{14}BrNO_2S$: C, 32.81; H, 5.47; Br, 31.22; N, 5.47; S, 12.53. Found: C, 33.10; H, 5.64; Br, 31.00; N, 5.20; S, 12.70.

4-Bromo-2,2-dimethyl-3-(*N*-pyrrolidino)thietane 1,1-Dioxide (13). The cis–trans mixture was obtained in a crude quantitative yield on a 0.01-molar scale: nmr ($CDCl_3$) cis δ 1.56 and 1.77 (s, 3 H each, *gem*-dimethyl groups), 1.57 and 2.40 (broad m, 8 H, pyrrolidino H), 2.88 (d, *J* = 6.5 Hz, 1 H, CHN), 5.47 (d, *J* = 6.5 Hz, 1 H, $CHSO_2$). Equilibration of the crude material for 6 days and recrystallization from 95% ethanol gave a 64% yield of the trans isomer: mp 81–82°; ir (KBr) (SO_2) 1320, 1310, 1175, and 1110 cm^{-1}; nmr ($CDCl_3$) δ 1.57 and 1.62 (s, 3 H each, *gem*-dimethyl groups), 1.56 and 2.43 (broad m, 8 H, pyrrolidino H), 2.90 (d, *J* = 8 Hz, 1 H, CHN), 5.33 (d, *J* = 8 Hz, 1 H, $CHSO_2$).

4-Bromo-2,2-dimethyl-3-(*N*-morpholino)thietane 1,1-Dioxide (14). The crude cis–trans mixture was obtained in a quantitative yield on a 0.01-molar scale according to the general procedure: nmr ($CDCl_3$) cis δ 1.57 and 1.78 (s, 3 H each, *gem*-dimethyl groups), 2.52 [m, 4 H, $(CH_2)_2N$], 2.96 (d, *J* = 7 Hz, 1 H, CHN), 3.77 [m, 4 H, $(CH_2)_2O$], 5.52 (d, *J* = 7 Hz, 1 H, $CHSO_2$). After equilibration, as before, for 4 days the pure trans isomer was obtained in a 50% yield recrystallized from 95% ethanol: mp 141–143°; ir (KBr) (SO_2) 1310, 1110, and 880 cm^{-1}; nmr ($CDCl_3$) δ 1.57 and 1.78 (s, 3 H each, *gem*-dimethyl groups), 2.50 [m, 4 H, $(CH_2)_2N$], 2.90 (d, *J* = 8.5 Hz, 1 H, CHN), 3.72 [m, 4 H, $(CH_2)_2O$], 5.39 (d, *J* = 8.5 Hz, 1 H, $CHSO_2$).

2,2-Dimethyl-3-(*N,N*-dimethylamino)-4-iodothietane 1,1-Dioxide (15). The crude mixture of cis and trans cycloadducts was obtained in an 83% yield on a 0.01-molar scale: nmr ($CDCl_3$) cis δ 1.51 and 1.83 (s, 3 H each, *gem*-dimethyl groups), 2.31 [s, 6 H, $N(CH_3)_2$], 2.24 (d, *J* = 7.5 Hz, 1 H, CHN), 5.73 (d, *J* = 7.5 Hz, 1 H, $CHSO_2$). Pure trans isomer was obtained only after equilibration, as before, for 2 weeks. The cycloadduct was very hygroscopic: ir ($CHCl_3$) (SO_2) 1330, 1170, and 1055 cm^{-1}. It was, therefore, converted to the picrate for analysis: mp 152–156°; ir (KBr) (NO_2) 1645, 1630, and 1340, (SO_2) 1328 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}IN_4O_9S$: C, 29.55; H, 3.21; I, 23.80. Found: C, 29.65; H 3.49; I, 23.98.

4-Cyano-2,2-dimethyl-3-(*N,N*-dimethylamino)thietane 1,1-Dioxide (16). The crude reaction material was obtained in a 42% yield according to the general procedure on a 0.02-molar scale. The crude material, mp 95–108°, was sublimed at 65° (2 mm) to yield a product, mp 98–108°. Equilibration for 3 days had no effect on the nmr and an attempt to prepare the picrate was unsuccessful: ir (KBr) (CN) 2270, (SO_2) 1335, 1170, 1125, and 1065 cm^{-1}; nmr ($CDCl_3$) δ 1.60 and 1.63 (s, 3 H each, *gem*-dimethyl groups), 2.30 [s, 6 H, $N(CH_3)_2$], 2.91 (d, *J* = 9 Hz, 1 H, $CHSO_2$).

3-(*N,N*-Dimethylamino)-2,2,4-trimethylthietane 1,1-Dioxide (21). A cis–trans mixture of this material was obtained according to the general procedure after distillation of the crude material: bp 118–120° (2.5 mm); nmr ($CDCl_3$) cis δ 1.44 (d, *J* = 7 Hz, 3 H, $CHCH_3$), 1.48 and 1.58 (s, 3 H each, *gem*-dimethyl groups), 2.20 [s, 6 H, $N(CH_3)_2$], 2.72 (d, *J* = 8.5 Hz, 1 H, CHN), 4.03 (m, 1 H, $CHSO_2$). Equilibration for 1 day under the usual conditions afforded pure trans cycloadduct: bp 89° (0.3 mm); ir (salt plates) (SO_2) 1300, 1285, 1110, and 1040 cm^{-1}; nmr ($CDCl_3$) δ 1.43 (d, *J* = 7 Hz, 3 H, $CHCH_3$), 1.49 and 1.52 (s, 3 H each, *gem*-dimethyl groups), 2.18 (d, *J* = 9 Hz, 1 H, CHN), 2.20 [s, 6 H, $N(CH_3)_2$], 4.03 (octet, *J* = 9 and 7 Hz, 1 H, $CHSO_2$).

Anal. Calcd for $C_8H_{17}NO_2S$: C, 50.23; H, 8.96; N, 7.32; S, 16.76. Found: C, 50.00; H, 8.94; N, 7.29; S, 16.56.

2,2-Dimethyl-3-(*N,N*-dimethylamino)-4-*n*-propylthietane 1,1-Doxide (22). A cis–trans mixture was obtained from the crude reaction material on a 0.1-molar scale after distillation: bp 113° (0.05 mm); nmr ($CDCl_3$) cis δ 0.97 (t, *J* = 6.5 Hz, 3 H, CH_2CH_3), 1.2–2.45 (m, 4 H, CH_2's), 1.51 and 1.62 (s, 3 H each, *gem*-dimethyl groups), 2.20 [s, 6 H, $N(CH_3)_2$], 2.74 (d, *J* = 9 Hz, 1 H, CHN), 3.91 (m, 1 H, $CHSO_2$). Equilibration for 1 day afforded pure trans cycloadduct: bp 95–100° (0.4 mm); ir (salt plates) (SO_2) 1300, 1115, and 1050 cm^{-1}; nmr ($CDCl_3$) δ 0.97 (t, *J* = 6.5 Hz, 3 H, CH_2CH_3), 1.2–2.3 (m, 4 H, CH_2's), 1.50 and 1.53 (s, 3 H each, *gem*-dimethyl groups), 2.20 [s, 6 H, $N(CH_3)_2$], 2.19 (d, *J* = 9 Hz, 1 H, CHN), 3.88 (m, *J* = 9 Hz, 1 H, $CHSO_2$).

Anal. Calcd for $C_{10}H_{21}NO_2S$: C, 54.78; H, 9.61; N, 6.39; S, 14.63. Found: C, 54.54; H, 9.52; N, 6.21; S, 14.43.

4-Benzyl-2,2-dimethyl-3-(*N,N*-dimethylamino)thietane 1,1-Dioxide (23). The crude cis–trans mixture of the cycloadduct, prepared on a 0.1-molar scale, defied crystallization: nmr ($CDCl_3$) cis δ 1.47 and 1.62 (s, 3 H each, *gem*-dimethyl groups), 2.15 [s, 6 H, $N(CH_3)_2$], 2.74 (d, *J* = 9 Hz, 1 H, CHN), 2.95–3.45 (m, 2 H, $PhCH_2$), 3.9–4.35 (m, 1 H, $CHSO_2$), 7.23 (s, 5 H, aromatic H). The crude material was therefore equilibrated for 1 week and the resulting residue was recrystallized from methanol to give a 57% yield of the trans isomer: mp 97–98°; ir (KBr) (SO_2) 1300, 1290, and 1115 cm^{-1}; nmr ($CDCl_3$) δ 1.53 (s, 6 H, *gem*-dimethyl groups), 2.23 [s, 6 H, $N(CH_3)_2$], 2.36 (d, *J* = 8.5 Hz, 1 H, CHN) 2.77–3.72 (nine-peak ABC pattern, 2 H, $PhCH_2$), 4.21 (octet, 1 H, $CHSO_2$), and 7.28 (s, 5 H, aromatic H). An analytical sample was obtained by sublimation at 80° (0.3 mm).

Anal. Calcd for $C_{14}H_{21}NO_2S$: C, 62.88; H, 7.92; N, 5.24; S, 11.99. Found: C, 62.67; H, 7.98; N, 5.20; S, 12.20.

4-Benzoyl-2,2-dimethyl-3-(*N,N*-dimethylamino)thietane 1,1-Dioxide (24). This material was prepared on a 0.1-molar scale by the inverse addition method owing to the low solubility of benzoylmethanesulfonyl chloride in Et_2O. The product was identified by the nmr of the crude reaction material but was too unstable to give a satisfactory melting point or analysis. Equilibration had no effect on the nmr: ir (KBr) (SO_2) 1310 (C=O), 1680 cm^{-1}; nmr δ

1.60 and 1.69 (s, 3 H each, *gem*-dimethyl groups), 2.18 [s, 6 H, $N(CH_3)_2$], 3.44 (d, *J* = 9.2 Hz, 1 H, $CHSO_2$), 7.47–7.68 (m, 3 H, meta and para aromatic H), and 8.0–8.2 (m, 2 H, ortho aromatic H).

4-Benzoyl-2,2-dimethyl-3-(*N*-pyrrolidino)thietane 1,1-Dioxide (25). Only the trans isomer of this material was obtained in a 64% yield on a 4.6-millimolar scale. Recrystallization from 95% ethanol gave the pure trans isomer: mp 112–115°; ir (KBr) (SO_2) 1315 (C=O), 1690 cm^{-1}; nmr ($CDCl_3$) δ 1.60 and 1.67 (s, 3 H each, *gem*-dimethyl groups), 1.47 and 2.27 (broad m, 8 H, pyrrolidino H), 3.48 (d, *J* = 9.5 Hz, 1 H, CHN), 5.58 (d, *J* = 9.5 Hz, 1 H, $CHSO_2$), 7.50 (m, 3 H, meta and para aromatic H), and 8.08 (m, 2 H, ortho aromatic H).

4-Benzoyl-2,2-dimethyl-3-(*N*-pyrrolidino)thietane 1,1-Dioxide (26). The crude reaction material obtained in this reaction according to the general procedure on a 4.6-millimolar scale contained only trans isomer. Recrystallization from 95% ethanol afforded an analytically pure material: mp 168–171°; ir (KBr) (SO_2) 1315 and 1120, (C=O) 1688 cm^{-1}; nmr ($CDCl_3$) δ 1.58 and 1.67 (s, 3 H each, *gem*-dimethyl groups), 2.35 [m, 4 H, $(CH_2)_2N$], 3.54 (d, *J* = 9 Hz, 1 H, CHN), 3.63 [m, 4 H, $(CH_2)_2O$], 5.58 (d, *J* = 9 Hz, 1 H, $CHSO_2$), 7.53 (m, 3 H, meta and para aromatic H), and 8.08 (m, 2 H, ortho aromatic H).

Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.55; N, 4.33; S, 9.92. Found: C, 59.24; H, 6.49; N, 4.36; S, 9.92.

Postequilibration Experiment on 2. A sample of 2 (2.6 g, 0.01 mol) containing 74% cis isomer was dissolved in acetonitrile and stirred with an equimolar amount of triethylamine for 16 hr. Removal of the solvent and triethylamine *in vacuo* afforded a quantitative recovery of cycloadducts which now contained only 64% cis cycloadduct, demonstrating a slow postisomerization under these conditions.

General Procedure for Preparing Thietane 1,1-Dioxide Derivatives from α,α-Disubstituted Sulfonyl Chlorides. These thietane 1,1-dioxide derivatives were prepared as described for the monosubstituted sulfene reactions with the exception that the reactions were carried out in an ice–salt bath maintained between 0 and 5°.

2-Chloro-3-(*N,N*-dimethylamino)-2,4,4-trimethylthietane 1,1-Dioxide (8). A cis–trans mixture of this material was prepared on a 0.05-molar scale according to the general procedure: mp 88–94°; nmr ($CDCl_3$) cis δ 1.57 and 1.75 (s, 3 H each, *gem*-dimethyl groups), 1.97 [s, 3 H, $C(Cl)CH_3$], 2.32 [s, 6 H, $N(CH_3)_2$], and 2.58 (s, 1 H, CHN). Refluxing a 2.0-g (8.8 mmol) sample of this mixture with a threefold excess of sodium hydroxide in 50% aqueous ethanol for 6 hr followed by removal of the organic phase *in vacuo* afforded 1.5 g of a mixture of cycloadducts and the enamine C as indicated by ir absorption for this double bond at 1620 cm^{-1}. Subsequent treatment of this mixture with 8 ml of 30% H_2SO_4 in 8 ml of absolute ethanol and removal of the organic solvent afforded 0.7 g (49%) of 2,4,4-trimethylthietan-3-one 1,1-dioxide: mp 105–106 (lit.[26] mp 104–105°; nmr ($CDCl_3$) δ 1.56 (d, *J* = 7 Hz, 3 H, $CHCH_3$), 1.57 and 1.70 (s, 3 H each, *gem*-dimethyl groups), and 5.12 (q, *J* = 7 Hz, 1 H, $CHCH_3$). Neutralization of the aqueous phase with 10% sodium hydroxide then afforded predominantly trans cycloadduct (~18% cis): mp 69–70°; ir (KBr) (SO_2) 1320, 1120, and 1060 cm^{-1}; nmr ($CDCl_3$) δ 1.60 and 1.64 (s, 3 H each, *gem*-dimethyl groups), 2.07 [s, 3 H, $C(Cl)CH_3$], 2.29 [s, 6 H, $N(CH_3)_2$], and 2.84 (s, 1 H, CHN).

2-Chloro-3-(*N*-pyrrolidino)-2,4,4-trimethylthietane 1,1-Dioxide (9). This material was prepared as a cis–trans mixture on a 0.05-molar scale and after recrystallization from 95% ethanol a 71% yield of isomeric cycloadducts was realized: mp 78–83°; nmr ($CDCl_3$) cis δ 1.55 and 1.72 (s, 3 H each, *gem*-dimethyl groups), 1.95 [s, 3 H, $C(Cl)CH_3$], 1.57 and 2.42 (broad m, 8 H, pyrrolidino H), and 2.67 (s, 1 H, CHN). Treatment of a 5.1-g (0.02 mol) sample of this mixture as described for 8 yielded a product that was predominantly trans (18% cis): mp 86–92°; ir (KBr) (SO_2) 1320 and 1110 cm^{-1}; nmr ($CDCl_3$) δ 1.58 and 1.62 (s, 3 H each, *gem*-dimethyl groups), 2.02 [s, 3 H, $C(Cl)CH_3$], 1.59 and 2.40 (broad m, 8 H, pyrrolidino H), and 2.92 (s, 1 H, CHN).

2-Chloro-3-(*N*-morpholino)-2,4,4-trimethylthietane 1,1-Dioxide (10). The cis–trans mixture was obtained in a 60% yield after recrystallization from 95% ethanol on a 0.05-molar scale: mp 138–145°; nmr ($CDCl_3$) cis δ 1.53 and 1.70 (s, 3 H each, *gem*-dimethyl groups), 1.93 [s, 3 H, $C(Cl)CH_3$], 2.48 [m, 4 H, $CH_2)_2N$], 2.70 (s, 1 H, CHN), and 3.73 [m, 4 H, $(CH_2)_2O$]. Treatment of a 6.1-g sample (0.023 mol) of this mixture as described above for 8 yielded the keto sulfone D as well as pure *trans*-**10**: mp 184–185° (lit.[26] mp 186°); ir (KBr) (SO_2) 1320 and 1120 cm^{-1}; nmr δ 1.60 and 1.63 (s, 3 H each, *gem*-dimethyl groups), 2.03 [s, 3 H, $C(Cl)CH_3$], 2.50 [m, 4 H, $(CH_2)_2N$], 3.00 (s, 1 H, CHN), and 3.77 [m, 4 H, $(CH_2)_2O$].

2-Chloro-3-(*N,N*-diisopropylamino)-2,4,4-trimethylthietane 1,1-Dioxide (11). This material was obtained as a cis–trans mixture in an 83% yield after recrystallization from 95% ethanol on a 0.02-molar scale, mp 96–122°. Attempts to isolate pure trans adduct as for **8–10** were unsuccessful and repeated recrystallizations only afforded a product containing 86% cis and a product containing 46% cis isomer: ir (KBr) (SO_2) 1310, 1160, and 1105 cm^{-1}; nmr ($CDCl_3$) (*cis*-**11**) δ 1.06 and 1.12 (d, *J* = 6.5 Hz, 6 H each, isopropyl *gem*-dimethyl groups), 1.50 and 1.80 (s, 3 H each, ring *gem*-dimethyl group), 1.92 [s, 3 H, $C(Cl)CH_3$], 3.58 [septet, *J* = 6.5 Hz, 2 H, $CH(CH_3)_2$], and 3.60 (s, 1 H, CHN); (*trans*-**11**) δ 1.06 and 1.15 (d, *J* = 6.5 Hz, 6 H each, isopropyl *gem*-dimethyl groups), 1.62 and 1.65 (s, 3 H each, ring *gem*-dimethyl groups), 2.05 [s, 3 H, $C(Cl)CH_3$], 3.46 [d, *J* = 6.5 Hz, 2 H, $CH(CH_3)_2$], and 3.80 (s, 1 H, CHN).

2-Cyano-3-(*N,N*-dimethylamino)-2,4,4-trimethylthietane 1,1-Dioxide (17). The cis–trans mixture was prepared on a 0.01-molar scale according to the general procedure in a 63% yield. Recrystallization from 95% ethanol gave a cis–trans mixture in a 49% yield: mp 106–109°; ir (KBr) (CN) 2260 (SO_2) 1327 and 1115 cm^{-1}; nmr ($CDCl_3$) (*cis*-**17**) δ 1.59 and 1.82 (s, 3 H each, *gem*-dimethyl groups), 1.85 [s, 3 H, $C(CN)CH_3$], 2.33 [s, 6 H, $N(CH_3)_2$), and 2.46 (s, 1 H, CHN); (*trans*-**17**) δ 1.63 and 1.69 (s, 3 H, each, *gem*-dimethyl groups), 1.93 [s, 3 H, $C(CN)CH_3$], 2.30 [s, 6 H, $N(CH_3)_2$], and 2.70 [s, 1 H, CHN]. An analytical sample was obtained by sublimation at 87° (0.3 mm).

Anal. Calcd for $C_9H_{16}N_2O_2S$: C, 49.98; H, 7.46; N, 12.95; S, 14.83. Found: C, 50.23; H, 7.56; N, 12.74; S, 14.74.

2-Cyano-3-(*N*-pyrrolidino)-2,4,4-trimethylthietane 1,1-Dioxide (18). This material was prepared on a 0.01-molar scale and isolated as a cis–trans mixture in a 56% yield after recrystallizing the crude reaction products from 95% ethanol: mp 140–143° (83% cis); ir (KBr) (CN) 2260, (SO_2) 1330, 1175, and 1030 cm^{-1}; nmr ($CDCl_3$) (*cis*-**18**) δ 1.58 and 1.78 (s, 3 H each, *gem*-dimethyl groups), 1.83 [s, 3 H, $C(CN)CH_3$], 1.60 and 2.38 (broad m, 8 H, pyrrolidino H), and 2.57 (s, 1 H, CHN); (*trans*-**18**) δ 1.62 and 1.65 (s, 3 H each, *gem*-dimethyl groups), 1.88 [s, 3 H, $C(CN)CH_3$], 1.60 and 2.38 (broad m, 8 H, pyrrolidino H), and 3.07 (s, 1 H, CHN).

2-Cyano-3-(*N*-morpholino)-2,4,4-trimethylthietane 1,1-Dioxide (19). The material was prepared on a 0.01-molar scale according to the general procedure as a cis–trans mixture. Recrystallization from 95% ethanol afforded the pure cis isomer in a 50% yield: mp 134–135°; ir (KBr) (CN) 2260 (SO_2) 1327 and 1115 cm^{-1}; nmr ($CDCl_3$) δ 1.60 and 1.78 (s, 3 H each, *gem*-dimethyl groups), 1.83 [s, 3 H, $C(CN)CH_3$], 2.52 [m, 4 H, $CH_2)_2N$], 2.65 (s, 1 H, CHN), and 3.80 [m, 4 H, $CH_2)_2O$]; nmr ($CDCl_3$) (*trans*-**19**) δ 1.63 and 1.67 (s, 3 H each, *gem*-dimethyl groups), 1.88 [s, 3 H, $C(CN)CH_3$], 2.40 [m, 4 H, $CH_2)_2N$], 3.12 (s, 1 H, CHN), and 3.73 [m, 4 H, $(CH_2)_2O$].

2-Cyano-3-(*N,N*-diisopropylamino)-2,4,4-trimethylthietane 1,1-Dioxide (20). This material was obtained as a cis–trans mixture on a 0.01-molar scale. Recrystallization from pentane afforded almost pure cis isomer: mp 92–99°; ir (KBr) (CN) 2255 (SO_2) 1325, 1170, 1120, and 1100 cm^{-1}; nmr ($CDCl_3$) δ 1.08 and 1.10 (d, *J* = 6.5 Hz, 6 H each, isopropyl *gem*-dimethyl groups), 1.49 (s, 3 H, ring *gem*-dimethyl group trans to CN), 1.81 and 1.83 [two s, 3 H each, $C(CN)CH_3$ and ring *gem*-dimethyl group cis to CN], 3.47 (s, 1 H, CHN), and 3.58 [q, 2 H, *J* = 6.5 Hz, $CH(CH_3)_2$].

2-Carbethoxy-3-(*N*-pyrrolidino)-2,4,4-trimethylthietane 1,1-Dioxide (27). This material was obtained as the trans isomer according to the general procedure on a 3-millimolar scale. Recrystallization from hexane afforded the pure material in a 23% yield: mp 77–79°; ir (KBr) (C=O) 1748 (SO_2) 1315, 1260, and 1110 cm^{-1}; nmr ($CDCl_3$) δ 1.32 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 1.57 and 1.63 (s, 3 H each, *gem*-dimethyl groups), 1.82 [s, 3 H, $C(SO_2)CH_3$], 1.55 and 2.30 (broad m, 8 H, pyrrolidino H), 3.38 (s, 1 H, CHN), and 4.28 (q, *J* = 7 Hz, 2 H, CH_2CH_3).

2-Carbethoxy-3-(*N*-morpholino)-2,4,4-trimethylthietane 1,1-Dioxide (28). This material was obtained as a cis–trans mixture according to the general procedure on a 7.5-millimolar scale. Recrystallization from 95% ethanol afforded the pure trans isomer in a 35% yield: mp 109–111°; ir (KBr) (C=O) 1750 (SO_2) 1310 and 1260 cm^{-1}; nmr ($CDCl_3$) δ 1.32 (t, *J* = 7 Hz, 3 H, CH_2CH_3), 1.57 and 1.65 (s, 3 H each, *gem*-dimethyl groups), 1.82 [s, 3 H, $C(SO_2)CH_3$], 3.40 (s, 1 H, CHN), 3.70 [m, 4 H, $(CH_2)_2N$], 4.07 [m, 4 H, $(CH_2)_2O$], and 4.28 (q, *J* = 7 Hz, 2 H, CH_2CH_3).

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Registry No.—I, 6906-32-7; II, 2403-57-8; III, 2403-55-6; IV, 23297-04-3; *cis*-**1**, 50640-23-8; *trans*-**1**, 50640-24-9; *cis*-**2**, 50640-25-0; *trans*-**2**, 50640-26-1; *cis*-**3**, 50640-27-2; *trans*-**3**, 50640-28-3; *cis*-**4**, 50640-29-4; *trans*-**4**, 50640-30-7; *cis*-**5**, 50640-31-8; *trans*-**5**, 50640-32-9; *trans*-**6**, 50640-33-0; *cis*-**7**, 41959-68-6; *trans*-**7**, 41959-69-7; *cis*-**8**, 50640-34-1; *trans*-**8**, 50640-35-2; *cis*-**9**, 50640-36-3; *trans*-**9**, 50640-37-4; *cis*-**10**, 50640-38-5; *trans*-**10**, 31752-27-9; *cis*-**11**, 50640-39-6; *trans*-**11**, 50640-40-9; *cis*-**12**, 50640-41-0; *trans*-**12**, 50640-42-1; *cis*-**13**, 50640-43-2; *trans*-**13**, 50640-44-3; *cis*-**14**, 50640-45-4; *trans*-**14**, 50640-46-5; *cis*-**15**, 50640-47-6; *trans*-**15** picrate, 50640-49-8; *trans*-**16**, 50640-50-1; *cis*-**17**, 50640-51-2; *trans*-**17**, 50640-52-3; *cis*-**18**, 50640-53-4; *trans*-**18**, 50640-54-5; *cis*-**19**, 50640-55-6; *trans*-**19**, 50640-56-7; *cis*-**20**, 50640-57-8; *trans*-**20**, 50640-58-9; *cis*-**21**, 50640-59-0; *trans*-**21**, 50640-60-3; *cis*-**22**, 50640-61-4; *trans*-**22**, 50640-62-5; *cis*-**23**, 50640-63-6; *trans*-**23**, 50640-64-7; *trans*-**24**, 50640-65-8; *trans*-**25**, 50640-66-9; *trans*-**26**, 50640-67-0; *trans*-**27**, 50640-68-1; *cis*-**28**, 50640-69-2; *trans*-**28**, 50640-70-5; 2,4,4-trimethylthietan-3-one 1,1-dioxide, 31686-74-5.

References and Notes

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Preparation of 3,4-Dimethylenepyrrolidine and 1-Alkyl-3,4-dimethylenepyrrolidines by the Thermal Elimination of Sulfur Dioxide

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The reaction of 3,4-bis(bromomethyl)-2,5-dihydrothiophene 1,1-dioxide with primary alkylamines gives 5-alkyl-1,3,4,6-tetrahydrothieno[3,4-c]pyrrole 2,2-dioxides as well as 1,4-HBr elimination products. These bicyclic thienopyrroles were thermally decomposed, eliminating sulfur dioxide, to give 3,4-dimethylenepyrrolidine and the corresponding *N*-alkyl-3,4-dimethylenepyrrolidines, which have been characterized spectrally and analytically.

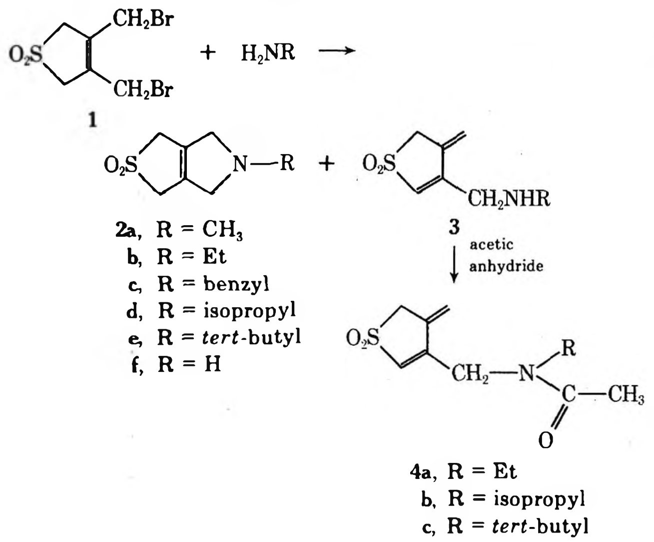
The preparation of 1-substituted 3,4-dimethylenepyrrolidines and their sulfone precursors has recently been of considerable interest.[1-5] These compounds have specific utility as reactants in the Diels–Alder reaction,[6] as monomers in polymerization reactions, and for their medicinal applications. The synthetic utilization of sulfur dioxide as a protecting agent for the synthesis of 1-aryl-3,4-dimethylenepyrrolidines has been demonstrated.[2,4] This report describes the extension of this method to the preparation of the novel secondary amine, 3,4-dimethylenepyrrolidine as well as 1-alkyl-3,4-dimethylenepyrrolidines.

In the nucleophilic reaction of primary amines with 3,4-bis(bromomethyl)-2,5-dihydrothiophene 1,1-dioxide, it has been proposed[2,4] that a competing reaction was a 1,4-HBr elimination due to the acidic character of the sulfolene protons. We found no evidence for this type of elimination in our earlier study[2] of this reaction with monosubstituted anilines. However, this elimination appears to be more facile with primary alkylamines, and subsequently we were able to isolate for the first time the 1,4-HBr elimination product for a series of such amines from this reaction.

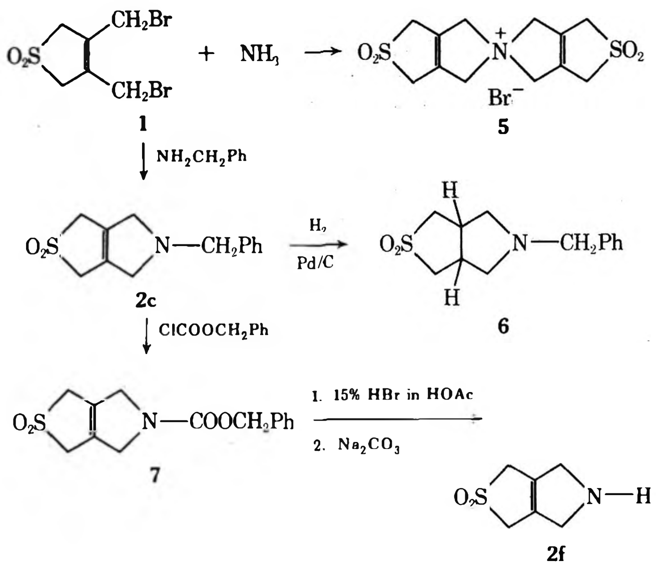
Results and Discussion

The reaction of alkylamines with **1** was carried out as previously described[1] and the bicyclic compounds (**2**) were isolated in moderate yields (21–40%) (Scheme I). The 1,4-HBr elimination products (**3**) were observed in the reaction mixtures for all cases by nmr. We were not able to isolate these compounds (**3**)[7] directly from the reaction

Scheme I



Scheme II



mixtures; consequently, their acetylated derivatives (4) were isolated by the method of McElvain.[8] These acetylated derivatives were characterized in the cases of **4a–4c**. The amount of 1,4-HBr elimination product formed appears to be sensitive to the reaction conditions. Under our usual reaction conditions[1] (3:1 molar ratio of amine to **1** in acetonitrile), considerable amounts of both **2** and **3** were obtained in all cases. However, we found that an almost quantitative yield (determined by nmr) of the elimination product was obtained when the reactions were carried out in MeOH with a 3.5:1 molar ratio of amine to **1**.

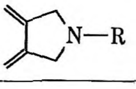
An initial attempt to prepare 1,3,4,6-tetrahydrothieno-[3,4-*c*]pyrrole 2,2-dioxide (**2f**) involved reacting **1** with ammonia (Scheme II). Using a method similar to Bobbitt, *et al.*,[9] the dibromo sulfone (**1**) was added to an ammonia-acetonitrile solution (50:1 molar ratio of ammonia to **1**), but only an intractable oil was obtained. When a 10:1 molar ratio of ammonia to **1** in acetonitrile was used, the 5,5-spirobis(1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrolidinium 2,2-dioxo) bromide (**5**) was obtained in 70% yield. Similarly, lower concentrations of ammonia also gave the spiro product.

Indirect approaches to the synthesis of **2f** were next employed (Scheme II). The first attempt involved catalytic cleavage of the benzyl group in **2c**, similar to the procedure of Mattocks and Hartung.[10] It was found, however, that reduction of the tetrasubstituted double bond took place more readily than the cleavage of the benzyl group. This gave compound **6** in good yield (70%). Since catalytic cleavage of the benzyl group proved ineffective in this case, the benzyl group was replaced by a carbobenzyloxy group[11] by treating **2c** with benzylchloroformate to yield compound **7**. Cleavage of the carbobenzyloxy group was accomplished by treating **7** with 15% HBr in glacial acetic acid to give the amine hydrobromide salt which was neutralized with sodium carbonate to give the sulfone precursor **2f**.

Thermal decomposition (120°) of these masked exocyclic dienes (**2a–2f**) under reduced pressure (0.1 mm) led to the elimination of sulfur dioxide and recovery of the exocyclic dienes (**8a–8f**) as well as some polymeric material[12] (Scheme III). These dienes were liquids (~room temperature) and polymerized readily upon standing to give white, brittle, water-soluble polymers (**9**). The dienes (**8a–8f**) were characterized by their nmr spectra (Table I). Picrate derivatives (**10a** and **10b**) of **8f** and **8a** gave sharp melting points. The exocyclic dienes (**8a, 8c, 8d**) reacted readily with methyl iodide (Scheme III) to give their corresponding pyrrolidinium iodide salts (**11a–11c**) in good yields (55–67%).

In conclusion, primary alkylamines react with the dibromo sulfone (**1**) to give the corresponding pyrroline compounds (**2**) in lower yields (21–40%) than the previously

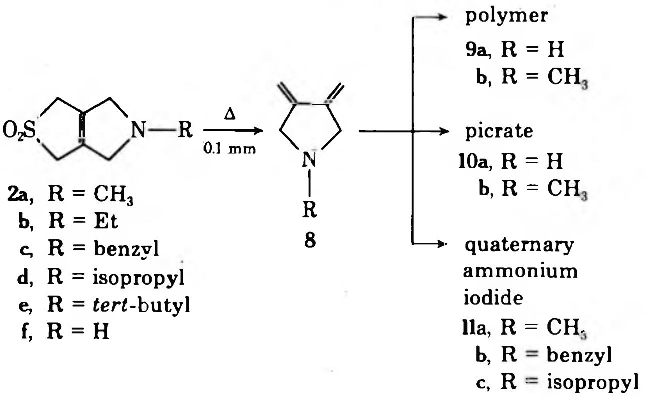
Table I
3,4-Dimethylenepyrrolidines (8)



Compd	Yield, %	Nmr spectra[a] Endo vinyl hydrogens	Exo vinyl hydrogens	Methylene hydrogens adjacent to N	R
8f	40	5.54 (t, J = 2 Hz)	5.12 (m)	3.72 (t, J = 2 Hz)	5.95 (bs, N–H)
8a[b]	65	5.32 (t, J = 2 Hz)	4.85 (m)	3.24 (t, J = 2 Hz)	2.34 (s, CH_3)
8b	56	5.43 (t, J = 2 Hz)	5.00 (m)	3.54 (t, J = 2 Hz)	2.71 (q, J = 7 Hz, $-CH_2CH_3$), 1.18 (t, J = 7 Hz, $-CH_2CH_3$)
8c	67	5.43 (t, J = 2 Hz)	4.97 (m)	3.44 (t, J = 2 Hz)	7.35 (s, $-CH_2C_6H_5$), 3.66 (s, $-CH_2C_6H_5$)
8d	55	5.44 (t, J = 2 Hz)	5.00 (m)	3.57 (t, J = 2 Hz)	2.86 [h, J = 7 Hz, $-CHC(CH_3)_2$], 1.17 [d, J = 7 Hz, $-CHC(CH_3)_2$]
8e	60	5.46 (t, J = 2 Hz)	5.00 (m)	3.62 (t, J = 2 Hz)	1.18 [s, $-C(CH_3)_3$]

[a] Determined with $CDCl_3$ solution except **8f** for which DMSO-d_6 was used. Chemical shifts (δ) are relative to TMS (δ = 0.0). Signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; h, heptet; m, multiplet. [b] This compound has been characterized by Gaoni.[5] Our nmr spectrum for this compound is in agreement with Gaoni except for the chemical shift (δ) of the exo vinyl hydrogens which he assigned a value of 4.39.

Scheme III



studied[2] monosubstituted anilines (50–83%). This is caused by a 1,4-HBr elimination reaction which competes with the nucleophilic cyclization process. Furthermore, it is difficult to prevent substantial polymerization of 1-alkyl-3,4-dimethylenepyrrolidines under our conditions for the thermal elimination of sulfur dioxide from **2**. Consequently, the use of sulfur dioxide as a protecting agent for the preparation of 1-alkyl-3,4-dimethylenepyrrolidines is not as advantageous as it is with their aryl counterparts.[2] This method, however, is presently the only available procedure for the preparation of 3,4-dimethylenepyrrolidine itself.

Experimental Section

Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60 and a Perkin-Elmer R-24. Chemical shifts (δ) are relative to TMS (δ = 0.0). Nmr signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; h, heptet; bs, broad singlet. Ir spectra (potassium bromide pellets) were recorded on a Perkin-Elmer 337, and elemental analysis were carried out on a Perkin-Elmer 240. Uv spectra were recorded on a Beckman DK-2. All the compounds in Table I were prepared by essentially the same procedure given below for 3,4-dimethylenepyrrolidine.

5-*tert*-Butyl-1,3,4,6-tetrahydrothieno[3,4-c]pyrrole 2,2-Dioxide (2e). A solution of the dibromo sulfone (**1**) (3.04 g, 10 mmol) and 35 mmol of *tert*-butylamine in 200 ml of acetonitrile was stirred at rm temperature for 1 hr. The reaction mixture was filtered to remove the *tert*-butylamine hydrobromide which precipitated and the filtrate was evaporated to dryness. The residue was dissolved in methanol and neutralized with sodium carbonate. The methanol was removed under reduced pressure and the resultant residue was triturated with 150 ml of ether. The ethereal extracts were reduced in volume to 20 ml, and petroleum ether was added to make the solution cloudy. The petroleum ether–ether solution was allowed to stand in a freezer overnight, and 0.45 g (21%) of the bicyclic product was obtained: mp 100–102°; ir max 1322, 1262, 1180, 1115 cm^{-1}; nmr ($CDCl_3$) δ 3.77 and 3.66 (fused singlets, 8 H), 1.14 (s, 9 H).

Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96; N, 6.51. Found: C, 55.80; H, 8.02; N, 6.33.

Acetylated Derivative of 4-(*N-tert*-Butylaminomethyl)-2-hydro-3-methylenethiophene 1,1-Dioxide (4c). The petroleum ether–ether solution from the procedure of **2e** was evaporated to dryness, and the resulting oil was stirred with 3 ml of acetic anhydride for 4 hr. The reaction mixture was diluted with 20 ml of 3 *N* HCl and extracted with methylene chloride. The methylene chloride was removed under vacuum to give an oil. Crystallization from ether gave 0.35 g (14%) of **4c**: mp 194–196° dec; ir max 1636, 1392, 1290, 1222, 1115 cm^{-1}; nmr ($CDCl_3$) δ 6.63 (m, 1 H), 5.47 (m, 2 H), 4.28 (m, 2 H), 4.06 (m, 2 H), 2.03 (m, 3 H), 1.45 (s, 9 H).

Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.02; H, 7.44, N, 5.44. Found: C, 55.46; H, 7.57, N, 5.33.

5-Isopropyl-1,3,4,6-tetrahydrothieno[3,4-c]pyrrole 2,2-Dioxide (2d). Procedure same as for **2e**: yield 41%; mp 118–120° dec; ir max 2778, 1295, 1262, 1172, 1103, 1094 cm^{-1}; nmr ($CDCl_3$) δ 3.79 and 3.62 (fused singlets, 8 H), 2.79 (h, *J* = 7 Hz, 1 H), 1.11 (d, *J* = 7 Hz, 6 H).

Anal. Calcd for $C_9H_{15}NO_2S$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.78; H, 7.50; N, 6.90.

Acetylated Derivative of 4-(*N*-Isopropylaminomethyl)-2-hydro-3-methylenethiophene 1,1-Dioxide (4b). Procedure same as for **4c**: yield 22%; mp 155–156°; ir max 1626, 1440, 1404, 1280, 1224, 1187, 1110 cm^{-1}; uv λ_{max} (CH_3OH) 233 mμ (ε 19,450); nmr ($CDCl_3$) δ 6.50 (m, 1 H), 5.70–5.3 (m, 2 H), 4.45–3.8 (m, 5 H), 2.4–1.8 (m, 3 H), 1.15 (d, *J* = 7 Hz, 6 H).

Anal. Calcd for $C_{11}H_{17}NO_3S$: C, 54.31; H, 7.04; N, 5.76. Found: C, 53.95; H, 7.21; N, 5.69.

Acetylated Derivative of 4-(*N*-Ethylaminomethyl)-2-hydro-3-methylenethiophene 1,1-Dioxide (4a). Procedure same as for **4c**: yield 15%; mp 125–126°; ir max 1646, 1633, 1441, 1397, 1273, 1220, 1105 cm^{-1}; nmr ($CDCl_3$) δ 6.46 (m, 1 H), 5.7–5.3 (m, 2 H), 4.35 (m, 2 H), 4.00 (m, 2 H), 3.37 (q, *J* = 7 Hz, 2 H), 2.3–2.00 (m, 3 H), 1.19 (t, *J* = 7 Hz, 3 H).

Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.40; H, 6.60; N, 6.11. Found: C, 52.28; H, 6.55; N, 5.95.

5,5′-Spirobis(1,3,4,6-tetrahydrothieno[3,4-c]pyrrolidinium 2,2-dioxo) Bromide (5). Ammonia (1.02 g, 60 mmol) was dissolved in 100 ml of acetonitrile and added to a solution of 3.04 g (10 mmol) of **1** in 200 ml of acetonitrile. The reaction mixture was allowed to stand for 1 hr during which time the spiro compound and ammonium bromide precipitated. The precipitate was washed with 100 ml of hot methanol to yield 1.33 g (70%) of the spiro compound as a residue; no melting point up to 300°; ir max 1318, 1281, 1269, 1181, 1114, 1093 cm^{-1}; nmr (D_2O) δ 4.73 (m, 8 H), 4.12 (m, 8 H); mol wt[13] 371, 375 (actual 382).

Anal. Calcd for $C_{12}H_{16}NS_2O_4Br$: C, 37.90; H, 4.22; N, 3.70. Found: C, 38.10; H, 4.40; N, 4.00.

5-Benzyl-1,3,3a,4,6,6a-hexahydrothieno[3,4-c]pyrrole 2,2-Dioxide (6). A 3.0-g solution of compound **2c** in 50 ml of glacial acetic acid was hydrogenated over 2.0 g of 10% Pd/C and 0.5 g of platinum oxide at 47 psi of hydrogen pressure for 24 hr. The acetic acid solution was filtered to remove the catalyst and evaporated to dryness. The residue remaining was diluted with H_2O and neutralized with sodium carbonate. The H_2O solution was evaporated and its residue triturated with 200 ml of ether. From this ether extract, 2.1 g (70%) of product was obtained; mp 94–96°; ir max 1320, 1283, 1241, 1217, 1140, 1129, 1095, 737 cm^{-1}; nmr ($CDCl_3$) δ 7.31 (s, 5 H), 3.63 (s, 2 H), 3.4 to 2.5 (m, 10 H).

Anal. Calcd for $C_{13}H_{17}NSO_2$: C, 62.20; H, 6.82; N, 5.52. Found: C, 61.90; H, 6.84; N, 5.36.

5-Carbobenzyloxy-1,3,4,6-tetrahydrothieno[3,4-c]pyrrole 2,2-Dioxide (7). A solution of 1.2 g of **2c** in 5 ml of benzyl chloroformate was allowed to stand for 10 hr at room temperature. The reaction mixture was diluted with ether, and the product was collected by filtration. Recrystallization in acetone–ether yielded 1.13 g (80%) of **7**: mp 134° dec; ir max 1750 (broad), 1730, 1445, 1410 (broad), 1332, 1300, 1173, 1030, 945, 756, 695 cm^{-1}; nmr (acetone-d_6) δ 7.35 (s, 5 H), 5.11 (s, 2 H), 4.27 (s, 4 H), 3.88 (s, 4 H).

Anal. Calcd for $C_{14}H_{15}NSO_4$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.55; H, 5.35; H, 4.48.

1,3,4,6-Tetrahydrothieno[3,4-c]pyrrole 2,2-Dioxide (2f). To 1.0 g of compound **7** dissolved in 10 ml of glacial acetic acid was added 10 ml of 30% HBr in glacial acetic acid. The reaction mixture was allowed to stir for 3 hr and then diluted with 100 ml of ether. The amine hydrobromide salt (70%) precipitated and was collected by filtration. The amine hydrobromide salt was dissolved in H_2O and neutralized with Na_2CO_3. The free amine (64%) was extracted from the water solution with methylene chloride: mp 116° dec; ir max 3360, 1414, 1280 (broad), 1173, 1119, 1093, 753 cm^{-1}; nmr ($CDCl_3$) δ 3.83 (s, 8 H), 1.86 (s, 1 H); nmr (CF_3COOH) δ 4.57 (s, 4 H), 4.17 (s, 4 H).

Anal. Calcd for $C_6H_9NSO_2$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.37; H, 5.51; N, 8.53.

3,4-Dimethylenepyrrolidine (8f). The sulfone precursor (**2f**) was thermally decomposed at 120° under vacuum (0.1 mm). The exocyclic diene was trapped in a flask cooled to Dry Ice–acetone temperatures with some polymerization occurring. The reaction flask was connected to the cooled flask by a U-tube wrapped with heating tape to prevent appreciable sublimation: yield 40%; nmr (D_2O) δ 5.70 (t, *J* = 2 Hz, 2 H), 5.22 (m, 2 H), 4.08 (t, *J* = 2 Hz, 4 H).

Polymer (9a) of 3,4-Dimethylenepyrrolidine. Compound **8f** (liquid) polymerized readily upon standing at room temperature to give a water-soluble polymer: nmr (D_2O) δ 4.05 (bs, 4 H), 2.31 (bs, 4 H).

Picrate (10a) of 3,4-Dimethylenepyrrolidine. The exocyclic diene (**8f**) (~0.09 g) was dissolved in 2 ml of MeOH and added to

2 ml of MeOH saturated with picric acid. The solution was filter to remove polymeric material which had precipitated and then allowed to stand for 2 hr at room temperature. Ether (50 ml) was added to the solution, which was then left in a freezer for 36 hr. During this time, 0.065 g (20%) of orange picrate crystals precipitated: mp 118–119°; nmr (acetone-d_6) δ 8.6 (s, 2 H), 5.79 (m, 2 H), 5.28 (m, 2 H), 5.07 and 4.37 (m, 4 H) (N–H not observed).

Anal. Calcd for $C_{12}H_{12}N_4O_7$: C, 44.44; H, 3.70; N, 17.24. Found: C, 44.69; H, 3.64; N, 17.24.

Polymer (9b) of 1-Methyl-3,4-dimethylenepyrrolidine. Compound **8a** (liquid) polymerized readily upon standing at room temperature to give a water-soluble polymer: nmr (D_2O) δ 4.14 (bs, 4 H), 3.0 (bs, 3 H), 2.34 (bs, 4 H).

Picrate (10b) of 1-Methyl-3,4-dimethylenepyrrolidine. To a solution of the exocyclic diene **8a** (~0.25 g) in 5 ml of methanol was added 5 ml of methanol saturated with picric acid. The solution was allowed to stand for 3 hr at room temperature after which time 60 ml of ether was added. The solution was left in a freezer for 48 hr and during this time 0.52 g (67%) of yellow picrate crystals precipitated: mp 101–103°; nmr (acetone-d_6) δ 8.67 (s, 2 H), 5.74 (m, 2 H), 5.29 (m, 2 H), 4.37 (m, 4 H), 3.18 (s, 3 H) (N–H not observed).

Anal. Calcd for $C_{13}H_{14}N_4O_7$: C, 46.15; H, 4.14; N, 16.56. Found: C, 46.06; H, 4.09; N, 16.36.

1,1-Dimethyl-3,4-dimethylenepyrrolidinium Iodide (11a). Compound **2a** (0.6 g) was decomposed by the same procedure used for the preparation of **8f**. The 1-methyl-3,4-dimethylenepyrrolidine recovered was dissolved in 3 ml of methylene chloride. To this solution was added 3 ml of methyl iodide. The reaction was allowed to stand overnight and 0.52 g (65%) of **11a** was collected by filtration: mp 179° dec; ir max 916 cm^{-1}; nmr (DMSO-d_6) δ 5.78 (m, 2 H), 5.33 (m, 2 H), 4.31 (m, 4 H), 3.12 (s, 6 H).

Anal. Calcd for $C_8H_{14}NI$: C, 38.24; H, 5.60; N, 5.58. Found: C, 37.94; H, 5.54; N, 5.52.

1-Methyl-1-benzyl-3,4-dimethylenepyrrolidinium Iodide (11b). Procedure same as for **11a**: yield 67%; mp 146–147° dec; ir max 907, 750, 696 cm^{-1}; nmr (DMSO-d_6) δ 7.42 (s, 5 H), 5.72 (m, 2 H), 5.26 (m, 2 H), 4.7–3.8 (m, 6 H), 2.8 (s, 3 H).

Anal. Calcd for $C_{14}H_{18}NI$: C, 51.36; H, 5.50; N, 4.28. Found: C, 51.16; H, 5.40; N, 4.10.

1-Methyl-1-isopropyl-3,4-dimethylenepyrrolidinium Iodide (11c). Procedure same as for **11a**: yield 55%; mp 250–252° dec; ir max 1429, 913 cm^{-1}; nmr (DMSO-d_6) δ 5.81 (m, 2 H), 5.30 (m, 2 H), 4.38 (m, 4 H), 3.84 (h, J = 7 Hz, 1 H), 2.75 (s, 3 H), 2.03 (d, J = 7 Hz, 6 H).

Anal. Calcd for $C_{10}H_{18}NI$: C, 43.02; H, 6.50; N, 5.01. Found: C, 43.33; H, 6.43; N, 4.91.

Acknowledgment. The authors wish to thank Texaco Incorporated for their fellowship support of P. V. Alston, and the National Science Foundation for their financial support through Grant No. GP 26616.

Registry No.—**1**, 18214-57-8; **2a**, 35105-72-7; **2b**, 35105-73-8; **2c**, 35105-74-9; **2d**, 50586-20-4; **2e**, 50586-21-5; **2f**, 50586-22-6; **4a**, 50586-23-7; **4b**, 50586-24-8; **4c**, 50586-25-9; **5**, 50586-26-0; **6**, 50586-27-1; **7**, 50586-28-2; **8a**, 50521-42-1; **8b**, 50586-29-3; **8c**, 505086-30-6; **8d**, 50586-31-7; **8e**, 50586-32-8; **8f**, 50586-16-8; **9a**, 50586-17-9; **9b**, 50678-88-1; **10a**, 50586-33-9; **10b**, 50586-34-0; **11a**, 50586-35-1; **11b**, 50586-36-2; **11c**, 50586-37-3; *tert*-butylamine, 75-64-9; isopropylamine, 75-31-0.

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(12) In the thermal decomposition of **2d** and **2e**, some rearranged product[2] (~5%) was observed by nmr; however, this compound did not interfere with further reactions of the intermediate exocyclic dienes (**8d** and **8e**).

(13) Determined by the Mohr method: D. A. Skoog and D. M. West, "Analytical Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1965, p 218.

Synthesis of 1,3,4,5,6,7,8,8a-Octahydro-2-methyl-4a-phenylisoquinolin-6-ols. Novel Fragments of the Morphine Molecule

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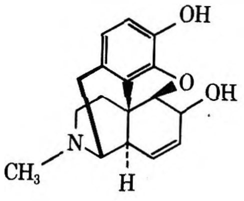
Received August 13, 1973

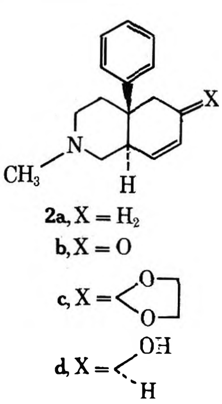
Renewed efforts were made to gain access to the long neglected morphine fragment **2d**, *trans*-1,3,4,5,6,7,8,8a-octahydro-2-methyl-4a-phenylisoquinolin-6-ol. Previous efforts by McElvain involved an unsuccessful attempt at the conjugate addition of phenylmagnesium bromide to the enone **17**, 1,3,4,7,8,8a-hexahydro-2-methylisoquinolin-6-one. Our first attempt involved intramolecular alkylation of the ketal **8b**, which was not successful. Use of diphenylcopper lithium, however, enabled us to achieve conjugate addition to the enone **17**, giving stereospecifically the cis ketone **18**, 1,3,4,7,8,8a-hexahydro-2-methyl-4a-phenylisoquinolin-6-one, whose structure was confirmed by X-ray analysis of the methobromide. The stereochemistry of reduction and methyllithium addition to this ketone **18** is discussed.

In the search for new structural types possessing analgetic activity the pentacyclic structure of morphine (**1**) has been subjected to many modifications. One of these, compound **2a**, represents an interesting target type, which has been subjected to only one additional study since compound **2a** was reported.[1] A study by McElvain described an unsuccessful attempt to gain access to this type by a synthetic approach which was quite similar to our successful route.[2]

The reason for this apparent neglect of otherwise attractive target compounds such as **2a–d** while other modifications have been extensively explored[3] is perhaps the synthetic difficulties posed by a bridgehead aryl group. This cannot be introduced by an intramolecular process, as in the classical Grewe synthesis of the morphinans.[3] The Boekelheide synthesis of compound **2a**, on the other hand, involved six steps and yielded a material of uncertain stereochemistry.[1] Therefore, it seemed appropriate for us to consider application of newer synthetic methodology.

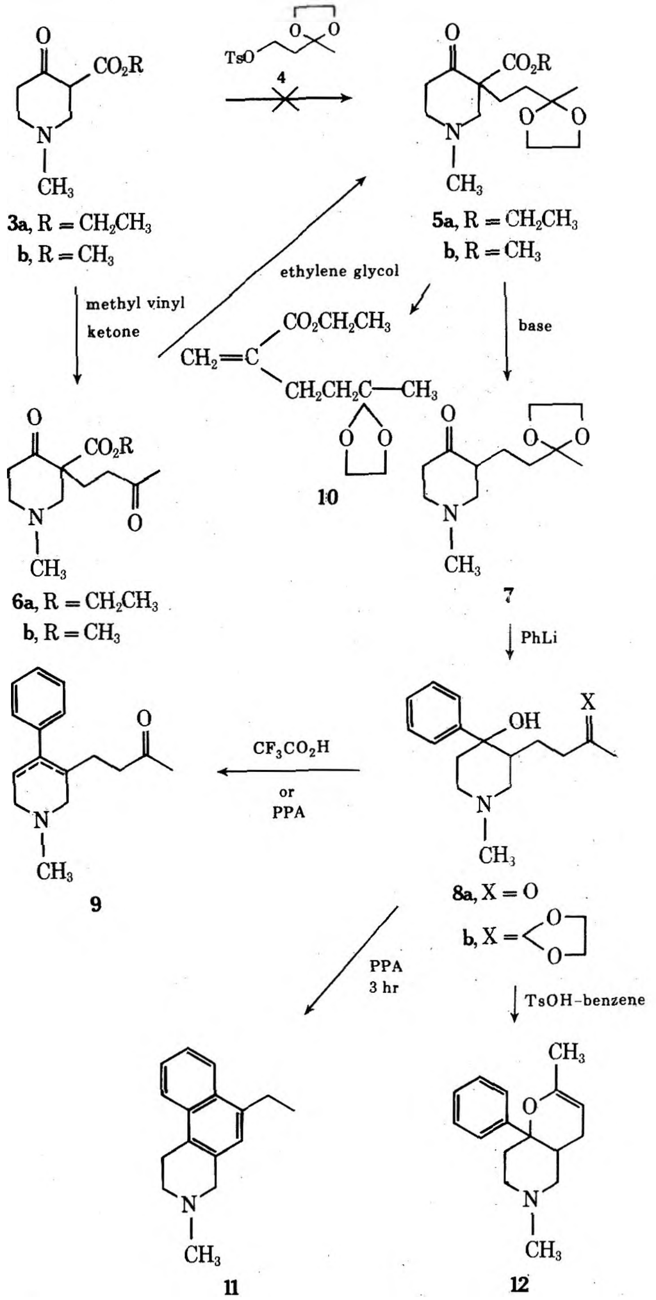


1
morphine



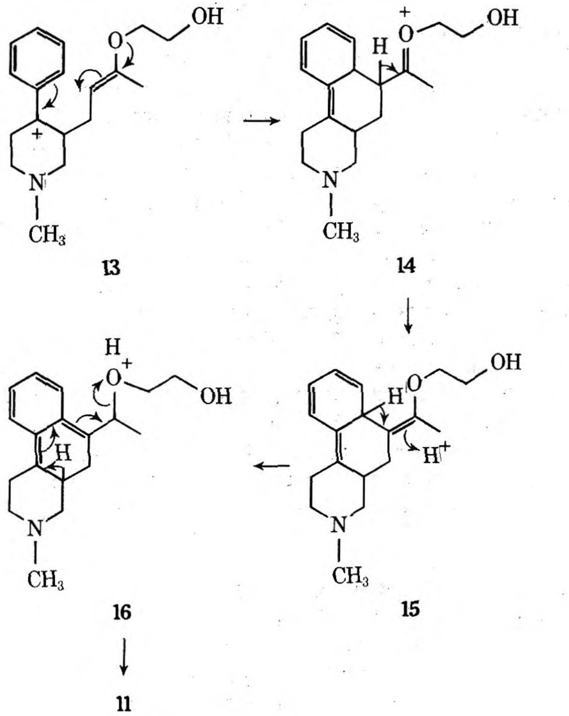
2a, X = H_2
b, X = O
c, X =
d, X =

Scheme I

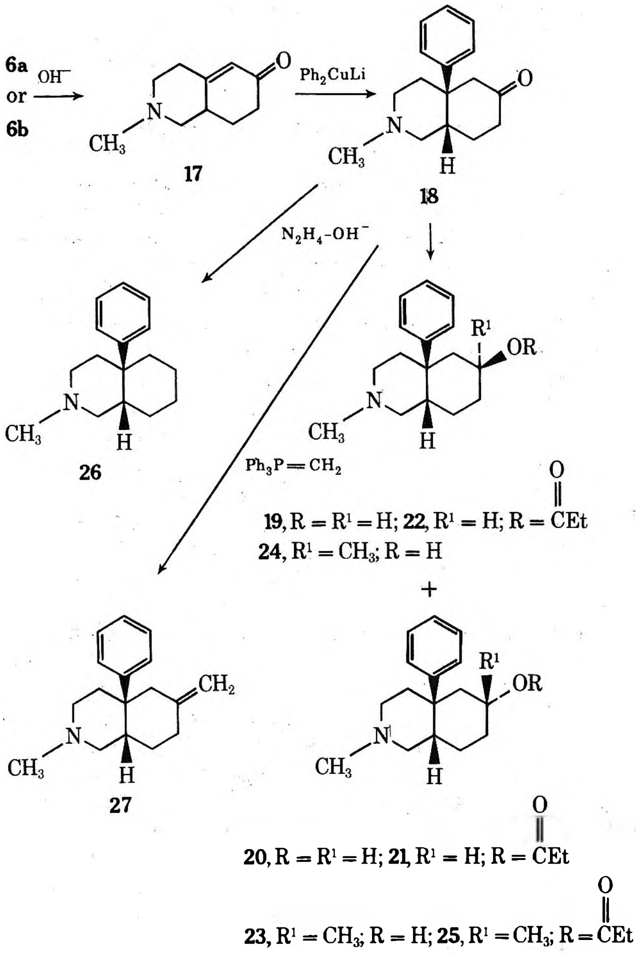


Two schemes were considered. The first was a variant of one used by Wenkert for the synthesis of lupinine.[4] This essentially involves the acid-catalyzed intramolecular alkylation of the α carbon atom of an ethylene ketal. Two routes were selected for the synthesis of an appropriate ketal precursor **8b**. Both routes were designed to provide the 4-piperidone **7** which could be reacted with phenyllithium to give **8b**. The first was an unsuccessful attempt to alkylate 1-methyl-4-oxonipecotate (**3a**) with 3-oxobutyl *p*-toluenesulfonate ethylene ketal (**4**), which had been used by Wenkert.[4] The second provided access to the desired 4-piperidone **7** *via* selective ketalization of the methyl vinyl ketone adduct **6a** of ethyl 1-methyl-4-oxonipecotate (**3a**)[5] followed by basic hydrolysis and decarboxylation (Scheme I). Unfortunately, this decarboxylation process proceeded in very poor yield, the major product **10** being derived by ring cleavage of the nonenolizable β-keto ester and a reverse Michael reaction on the resulting ring-opened product. A better yield (35%) of **7** was obtained from the methyl ester **5b**, derived by methyl vinyl ketone addition to methyl 1-methyl-4-oxonipecotate (**3b**). Use of the more readily hydrolyzable methyl ester **5b** favored the desired pathway. Addition of phenyllithium to the 4-piperidone **7** proceeded well but the ketal in the product **8b** was quite acid sensitive. Merely extraction by 2 *N* hydrochloric acid and rebasification with sodium carbonate was sufficient to deketalize it to give **8a**. A good yield (65%) of the desired ketal **8b** could be obtained by avoiding any treatment with acid. Several attempts to cyclize **8b** to the target compounds **2b** or **2c** were, however, unsuccessful (Scheme I). The most common products were mixtures of the deketalized tetrahydropyridines **9**, *i.e.*, simple dehydration products. Forcing conditions on **8b** with polyphosphoric acid and separation of the products by preparative glc yielded an interesting compound, which was assigned the structure **11** based on spectral evidence. Such a product could be formed by closure not onto the benzylic carbon but the ortho position of the aromatic ring (Scheme II). Unfortunately, complete characterization of this material was not possible, as it yielded consistently unsatisfactory elemental analysis. Conditions similar to those used by Wenkert[4] did give a product **12** derived by alkyla-

Scheme II



Scheme III



17 **18** **26** **27**

19, $R = R^1 = H$; **22**, $R^1 = H$; $R = \overset{O}{\overset{\|}{C}}Et$
24, $R^1 = CH_3$; $R = H$

20, $R = R^1 = H$; **21**, $R^1 = H$; $R = \overset{O}{\overset{\|}{C}}Et$

23, $R^1 = CH_3$; $R = H$; **25**, $R^1 = CH_3$; $R = \overset{O}{\overset{\|}{C}}Et$

tion by the benzylic cation but, alas, this was derived by alkylation on oxygen of an intermediate such as **13** (Scheme II). At this point our efforts were, therefore, directed to another scheme to obtain access to the primary target **2b**, or a derivative thereof. Treatment of the methyl vinyl ketone-piperidone adducts **6a** or **6b** with potassium hydroxide or, better, potassium carbonate yielded 1,3,4,7,8,8a-hexahydro-2-methylisoquinolin-6-one (**17**) which had been obtained previously by McElvain by a slightly different procedure[5] (Scheme III). Conjugate addition of diphenylcopper lithium to the enone **17** should now yield **2b** and/or the cis-fused isomer **18**.[6] High stereoselectivity favoring the cis product had been observed in the copper salt catalyzed conjugate addition of phenylmagnesium bromide to $\Delta^{1(9)}$-2-octalone, which is to our knowledge the only angular arylation of this type reported.[2] Such reaction conditions, when applied by McElvain to the enone **17**, failed to give conjugate addition.[2] However, diphenylcopper lithium in our hands gave a good yield (75%) of a crystalline saturated ketone **18**. This ketone was assigned the cis stereochemistry based on an nmr study of the alcohols **19** and **20** obtained by borohydride reduction and their propionate esters **21** and **22**. In the epimeric pairs, the signal due to the proton attached to the carbon atom bearing the alcohol or propionate functionality was clearly visible in the nmr spectra of these substances. In all the spectra this signal was broadened by the large axial coupling with the neighboring protons. Thus, the substituent is equatorial in both isomers. This is only possible if the ring fusion is conformationally mobile, *i.e.*, cis. In view of the importance of this stereochemical assignment it was confirmed by an X-ray analysis of the methobromide of the ketone **18**.

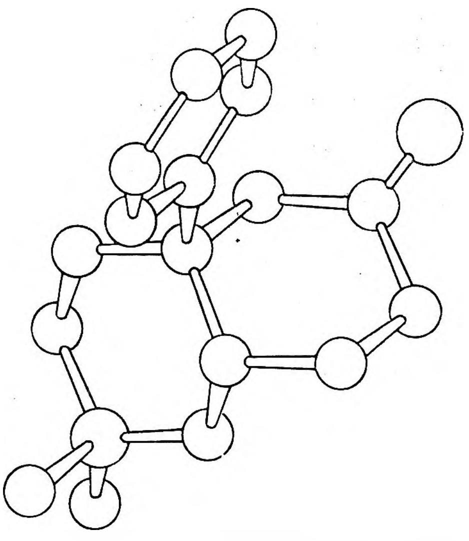


Figure 1. Atomic positions in crystal of methobromide of **18**.

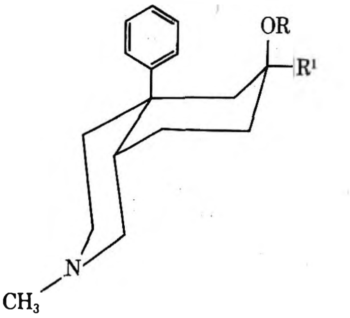
Thin platelet crystals of the quaternary methyl bromide derivative of ketone **18** were obtained from methanol solution. The crystal data for $C_{17}H_{24}BrNO$, mol wt 338.29, are monoclinic, $I2/a$, a = 11.766 (7), b = 9.312 (6), c = 30.46 (2), β = 92.48°, d_{obsd} = 1.34 (2), d_{calcd} = 1.35 g/cm^3 (Z = 8). A total of 1977 reflections were scanned using the θ-2θ technique and Cu Kα radiation on a Picker automated diffractometer; 1577 of these were judged to be above background. There was no significant decay in intensity of the four standard reflections monitored during the course of data collection (see paragraph at end of paper regarding supplementary material).

The bromide ion was located in a straightforward manner from the Patterson synthesis and all other nonhydrogen atoms were evident on an electro-density map phased on the bromide position. Full-matrix least-squares refinement assigning anisotropic thermal parameters to the bromide ion and isotropic parameters to all other atoms resulted in a conventional R factor of 15.8%. Further refinement of the structure was not deemed justifiable in light of the relatively poor quality of the crystals and owing to the fact that the objective of determination of the geometric stereochemistry of the molecule had been achieved. The conformation of the methobromide of ketone **18** as it exists in the crystal is depicted in Figure 1 and clearly agrees with the proposed cis ring fusion.

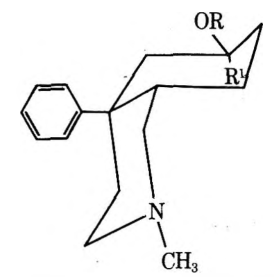
The stereochemical course of the conjugate addition of diphenylcopper lithium to the enone **17** is therefore the same as that observed by McElvain in the copper-catalyzed conjugate addition of phenylmagnesium bromide to $\Delta^{1(9)}$-2-octalone;[2] *i.e.*, addition creates a cis-fused ring system. Analogous results have recently been reported for the addition of dimethylcopper lithium to the enone **17**.[7] The cis ring fusion of the conjugate addition product in this instance was proven by conversion of a derivative to an azatwistane. Wolff-Kishner reduction on ketone **18** yielded a base **26** which could be characterized as a picrate. This picrate was directly compared (tlc, melting point, mixture melting point) with that obtained by Boekelheide,[1,8] and they were not identical. Thus, the compound prepared by Boekelheide[1] has the trans stereochemistry and can be assigned structure **2a**, although a trace of the cis isomer **18** could be detected by tlc.

The chemistry of the diphenylcopper lithium product **18** was explored further. The compound **18** reacted normally with a Wittig reagent, triphenylmethylenephosphorane, to yield **27**.

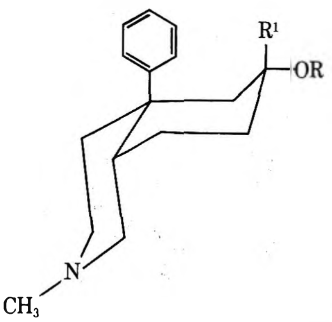
The remaining problem for us was to make stereochemical assignments to the two alcohols **19** and **20** which had



19a, $R = R^1 = H$; **22a**, $R^1 = H$, $R = CH_3CH_2CO$;
24a, $R^1 = CH_3$, $R = H$; **25a**, $R^1 = CH_3$, $R = CH_3CH_2CO$

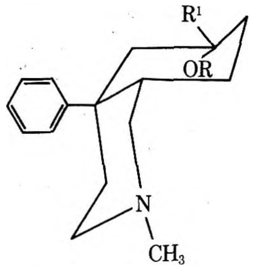


19b, $R^1 = R = H$; **22b**, $R^1 = H$, $R = CH_3CH_2CO$;
24b, $R^1 = CH_3$, $R = H$; **25b**, $R^1 = CH_3$, $R = CH_3CH_2CO$



20a, $R^1 = R = H$; **21a**, $R^1 = H$, $R = CH_3CH_2CO$;
23a, $R^1 = CH_3$; $R = H$

a conformations



20b, $R^1 = R = H$; **21b**, $R^1 = H$, $R = CH_3CH_2CO$;
23b, $R^1 = CH_3$; $R = H$

b conformations

been obtained from sodium borohydride reduction of the ketone **18** (Scheme III).

Catalytic reduction in acetic acid of the ketone **18** gave a single product identical (tlc, vpc) with compound **19**, the major product of the borohydride reduction. The identity of the alcohol was also confirmed by comparison of the crystalline propionate hydrochloride **22**. Catalytic reduction of cyclohexanones under acidic conditions has been shown to generate the axial alcohol and the addition of hydrogen can generally be expected to take place from the less hindered side.[9] If we assume that the conformation of **18** on the catalyst is that with the phenyl axial to the carbocyclic ring, *i.e.*, an **a** conformation, then the initial product would be **19a**, which conformationally flips to **19b**.[10] With the assignment of the major borohydride product as the all-cis compound **19b**, the minor product is then necessarily the cis-trans compound **20a**.

Assignment of configuration to the methyllithium adducts **23** and **24** of ketone **18** has been made tentatively by comparison of their nmr spectra with those of the borohydride products **19** and **20**. The major differences in the nmr spectra of **19b** and **20a** are in the pattern of the aromatic protons. The spectrum of compound **19b** shows a multiplet for the five aromatic protons, whereas compound **20a** shows a singlet. If this is assumed to be due to the fact that the compounds have different conformations, then the nmr spectrum of the major methyl carbinol **24** suggests that it has a **b** conformation predominantly whereas the minor methyl carbinol **23** has an **a** conformation. As **24b** readily forms a propionate **25b** it can be assumed to be an equatorial tertiary alcohol; therefore it has an all-cis configuration and the isomeric carbinol **23a** is cis-trans. It had been hoped to confirm these tentative stereochemical assignments by an X-ray crystallographic analysis. Several unsuccessful attempts to grow suitable crystals of an appropriate derivative were made.

An attempt to extend the similarity with the morphine skeleton was thwarted by our inability to prepare *m*-anisyllithium. As were those of McElvain,[2] our attempts to achieve conjugate addition of *m*-anisylmagnesium bromide to the ketone **18** by means of copper catalysis were unsuccessful.

Experimental Section[11]

Attempted Preparation of Ethyl 1-Methyl-4-oxo-3-(3-oxobutyl)nipecotate Monoketal (5a) with Ethylene Glycol. To a suspension of 2.11 g of 57% NaH in 100 ml of toluene and 25 ml of DMF, a solution of 9.1 g (0.049 mol) of ethyl 1-methyl-4-oxonipecotate (**3a**) in 50 ml of toluene was added. After stirring for 2 hr a solution of 0.049 mol of 3-oxobutyl *p*-toluenesulfonate ethylene ketal (**4**) in toluene was added and the mixture was heated for 18 hr to 80°. After cooling, the reaction mixture was poured into water. The toluene layer was repeatedly washed with water and dried. The solvent was removed *in vacuo*, leaving 4.5 g of an oil. The mass spectrum showed no molecular ion for **5a** present. Tlc showed that it was a mixture.

Ethyl and Methyl 4-Oxo-3-(3-oxobutyl)nipecotate (6a and 6b). A mixture of 129 g (0.697 mol) of ethyl 1-methyl-4-oxonipecotate (**3a**), 1 g of 57% NaH, and 550 ml of benzene was stirred at 25° for 1 hr. A solution of 48.7 g (0.697 mol) of methyl vinyl ketone was added dropwise over 30 min. The temperature was kept below 30°. After an additional 45 min the reaction mixture was washed twice with 25 ml of water, dried over Na_2SO_4, and concentrated and the residue was distilled *in vacuo*. The fraction boiling at 142–146° (0.5 mm) was collected, yield of **6a** 178 g (83% of theory), nmr ($CDCl_3$) δ 4.24 (q, 2, CH_2, $J = 7$ Hz).

Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49. Found: C, 61.32; H, 8.37; N, 5.35.

The methyl ester **6b** was analogously prepared using the above procedure: yield 66.5% of theory; bp 142–145° (0.5 mm); nmr ($CDCl_3$) δ 3.76 (s, 3, $-COOCH_3$), 3.5–1.2 (m, 16-CH), 2.35 (s, 3, NCH_3), 2.13 (s, 3, $COCH_3$); ir ν_{max} (liquid) 1713, 1230, 745 cm^{-1}.

Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.90; H, 8.18; N, 5.87.

Monoketalization of 6a and 6b with Ethylene Glycol. 5a and 5b. An ethyl acetate solution of 165.2 g (0.685 mol) of methyl 1-methyl-4-oxo-3-(3-oxobutyl)nipecotate (**6b**) was treated with anhydrous HCl. The crude hydrochloride was filtered off and refluxed with 72.1 g (1.03 mol) of ethylene glycol in 1.3 l. of benzene for 12 hr using a water separator (15 ml of H_2O collected). After cooling, 500 ml of ether was added and the precipitated crude ketal hydrochloride was filtered off. It was converted to the free base and distilled *in vacuo*: yield 138.8 g; bp 156–158° (0.5 mm) (70.6% of theory); nmr ($CDCl_3$) δ 3.92 (s, 4, $-OCH_2CH_2O-$), 3.77 (s, 3, $OCOCH_3$), 3.5–1.4 (m, 13, –CH–), 2.37 (s, 3, NCH_3), 1.31 (s, 3, CH_3); ir ν_{max} (liquid) 1720 and 1230 cm^{-1}.

Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 59.05; H, 8.39; N, 4.82.

The ethyl ester **5a** was prepared analogously by the above procedure: nmr ($CDCl_3$) δ 4.5-1 (m, CH_x), 4.26 (t, J = 7 Hz, CH_2), 4.92 (s, 4, $-OCH_2CH_2O-$), 2.33 (s, 3, $-NCH_3$), 1.3 (s, 3, CH_3); ir ν_{max} (liquid) 1720, 1225 cm^{-1}.

Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.20; H, 8.34; N, 4.97.

The hydrochloride had mp 157° dec.

Anal. Calcd for $C_{15}H_{25}NO_5HCl$: C, 53.64; H, 7.80; N, 4.17. Found: C, 53.61; H, 7.93; N, 4.30.

Hydrolysis with KOH of Ethyl Ester 5a to 7 and 10. The reaction mixture, containing 17.2 g (0.057 mol) of the ethyl ester ketal **5a**, 3.23 g of KOH, and 75 ml of water, was refluxed for 2.5 hr. After cooling, 15 g of K_2CO_3 was added and the solution was extracted repeatedly with ether. The ether extracts were dried over K_2CO_3, filtered, and concentrated. The residue (7.4 g) was distilled *in vacuo* (0.2 mm). Two main fractions, 1.8 g (bp 115-125°) and 0.5 g (bp 126-134°), were obtained. The higher boiling fraction, **7**, was purified by preparative gas chromatography [Dexsil GS 300, 3% on Chromosorb G (acid washed and silanized) mesh 60/80 at 180°]: m/e 227 (M^+); nmr ($CDCl_3$) δ 3.92 (s, 4, OCH_2CH_2O), 2.38 (s, 3, NCH_3), 1.31 (s, 3, CCH_3).

Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.40; H, 9.31; N, 6.16. Found: C, 63.03; H, 9.58; N, 5.89.

The lower boiling material present was identified by mass spectrum, nmr, and analysis as ethyl 2-methyl-α-methylene-1,3-dioxolane-2-butyrate (**10**): nmr ($CDCl_3$) δ 6.17 (s, 1, $CH_2{=}C$), 5.57 (s, 1, $CH_2{=}C$), 4.24 (q, 2, CH_2, J = 7 Hz), 3.97 (s, 4, OCH_2CH_2O, 2.65-1.65 (m, 4, 2 CH_2), 1.37 (s, 3, CH_3).

Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.68; H, 8.53.

Hydrolysis with K_2CO_3 of Ethyl Ester 5a to 7. A mixture of 9.0 g (0.03 mol) of ethyl ester ketal **5a**, 12.4 g (0.09 mol) of K_2CO_3, 75 ml of water, and 30 ml of ethanol was refluxed gently for 14 hr. The solution was cooled, 20 g of K_2CO_3 was added, and the solution was extracted three times with ether. The combined ether extracts were dried and concentrated. The residue was distilled *in vacuo*, yield 1.4 g, bp 126-128° (0.5 mm). Gas chromatography indicated that the product was essentially pure and identical with the material obtained by KOH hydrolysis and purified by gas chromatography [glc Dexsil GC 300, 3% on Chromosorb G (acid washed and silanized) mesh 60/80, retention time 1.8 min at 210°]. This was identical with the minor product **7** obtained from **5a** and KOH.

4-Hydroxy-1-methyl-3-(3-oxobutyl)-4-phenylpiperidine (8a). A solution of phenyllithium was prepared from 0.625 g (0.09 mol) of Li wire and 6.92 g (0.044 mol) of bromobenzene in 30 ml of ether. With stirring and cooling, a solution of 9.2 g (0.04 mol) of oxo ketal **7** in 25 ml of ether was added dropwise. The reaction mixture was stirred for 4 hr at 25°. After an additional 48 hr at room temperature, water was added dropwise with cooling. The ether layer was separated, dried, and concentrated. The residue was redissolved in ether and extracted with 2 N HCl. After addition of Na_2CO_3 solution the aqueous extracts were extracted with ether. The ether extracts were dried and concentrated and the residue, 6.5 g, was distilled *in vacuo*. The main fraction boiled at 175-182° (0.7 mm): yield 4.2 g (40.2% of theory), 97% by glc, of compound **8a** [DC 530, 5% on Chromosorb G (acid washed and silanized) mesh 60/80, retention time 5.5 min at 270°]; nmr ($CDCl_3$) δ 7.7-7.2 (m, 5, ArH), 2.28 (s, 3, NCH_3), 1.87 (s, 3, CH_3); ir ν_{max} (liquid) 3440, 1710, 855, 700 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.52; H, 8.87; N, 5.36. Found: C, 73.59; H, 8.82; N, 5.36.

4-Hydroxy-1-methyl-3-(3-oxobutyl)-4-phenylpiperidine Ketal (8b). To a stirred, cooled solution of phenyllithium prepared from 1.4 g (0.2 mol) of Li wire and 15.7 g (0.1 mol) of bromobenzene in 75 ml of anhydrous ether, a solution of 14.6 g (0.0643 mol) of **7** in 50 ml of anhydrous ether was added dropwise. The reaction mixture was stirred for 4 hr at 25°. After an additional 48 hours at room temperature, water was added dropwise with cooling, and the ether layer was separated, dried, and concentrated, yielding an oil that was distilled at 170-181° (0.3 mm), yield 12.8 g (65.9% of theory) of compound **8b**: nmr ($CDCl_3$) δ 7.7-7 (m, 5, ArH), 3.72 (s, 4, OCH_2CH_2O), 3.1-0.7 (m, 18, CH), 2.24 (s, NCH_3), 1.08 (s, 3, CH_3); glc DC 500, 5% on Chromosorb G (acid washed and silanized) mesh 60/80, retention time 6.0 min at 265°. The deketalized material **8a** had a retention time of 4 min under these conditions.

Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.78; H, 8.91; N, 4.59. Found: C, 70.60; H, 8.71; N, 4.56.

4a,5,7,8-Tetrahydro-2,6-dimethyl-8a-phenyl-4*H*-pyrano[3,2-*c*]pyridine (12). A solution of 4.3 g of ketal **8b** and 3.42 g of $TsOH{\cdot}H_2O$ in 400 ml of benzene was refluxed for 12 hr. After 6 hr at room temperature the reaction mixture was poured into aqueous Na_2CO_3. After mixing well, the layers were separated. The aqueous layer was extracted once with $CHCl_3$. The combined organic fractions were dried and concentrated. The residue was distilled in a Kugelrohr apparatus at 150° (0.4 mm), yield 1.7 g of compound **12**: m/e 243 (M^+); nmr ($CDCl_3$) δ 7.32 (s, 5, ArH), 4.38 (d, 1, J = 4 Hz, C=CH), 2.32 (s, 3, NCH_3), 1.86 (s, 3, CCH_3); ir ν_{max} (liquid) 1684, 756, 697 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.51; H, 8.74; N, 5.97.

A hydrochloride was prepared by dissolving 1.5 g of **12** in ethyl acetate and adding anhydrous HCl. After recrystallization from isopropyl alcohol it melted at 255° dec, nmr ($CDCl_3$) δ 7.37 (s, 5, ArH), 4.41 (d, 1, J = 4 Hz, C=CH).

Anal. Calcd for $C_{16}H_{21}NO{\cdot}HCl$: C, 68.65; H, 7.92; N, 5.00. Found: C, 68.77; H, 8.12; N, 4.90.

1-Methyl-3-(3-oxobutyl)-4-phenyltetrahydropyridine (9). Polyphosphoric acid (25 g) was liquified by heating to 95°, 1 g of ketal **8b** was added with stirring, and the temperature was maintained for 10 min. The reaction mixture was cooled by adding ice and made basic by addition of NH_4OH. Repeated extraction with $CHCl_3$ yielded an oil which was distilled *in vacuo*: bp 170-180° (0.5 mm); m/e 243 (M^+); nmr ($CDCl_3$) δ 7-7.6 (m, 5, aromatic), 5.92 (t, 2, J = 3.5 Hz, CH=CH), 2.4 (s, 3, NCH_3), 1.97 (s, 3, $COCH_3$); ir ν_{max} (liquid) 1710, 1660, 760, 700 cm^{-1}; glc DC 530, 5% on Chromosorb G (acid washed and silanized) mesh 60/80, retention time 6.8 (69.5%), 7.6 min (30.5%) at 230°. Spectral data suggested that the major product was the $\Delta^{3,4}$ isomer and the minor product was the $\Delta^{4,5}$ isomer.

The same product was obtained when 1 g of ketal **8b** was refluxed for 3 hr in a mixture of 20 ml of trifluoroacetic acid and 2 ml of trifluoroacetic anhydride. It was identified by glc and nmr.

Reaction of the Ketal 8b with PPA to give 11. To 26 g of polyphosphoric acid heated to 95°, 1 g of ketal **8b** was added with stirring. After heating for 3 hr, ice and water were added, and the solution was made basic by adding NH_4OH. Repeated extraction of the aqueous solution with $CHCl_3$ yielded 0.5 g of an oil which was subjected to preparative glc. One fraction was identified by nmr and mass spectrum [m/e 243 (M^+)] as the dehydration products **9**, retention times 3.5 and 4.3 min [DC 550, 5% on Chromosorb G (acid washed and silanized) mesh 60/80 at 235°]. The second fraction, retention time 7.5 min, had a molecular ion of m/e 225 corresponding to compound **11**: nmr ($CDCl_3$) δ 8.2-7.3 (m, 5, ArH), 7.0 (s, 1, ArH), 3.67 (s, 2, $-CH_2-$), 3.3-2.6 (m, 6, 3 CH_2), 2.49 (s, 3, NCH_3), 1.33 (t, 3, J = 7 Hz, $-CH_3$); ir ν_{max} (CS_2) 1655, 750 cm^{-1}; uv λ_{max} (MeOH) 231 nm (ϵ 48,600), 286 (5790), 323 (680).

Anal. Calcd for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22. Found: C, 84.19; H, 8.65; N, 5.90.

1,3,4,7,8,8a-Hexahydro-2-methylisoquinolin-6-one (17). To a solution of 185 g (0.77 mol) of diketo ester **6b** in 1800 ml of water was added 428 g (3.1 mol) of K_2CO_3 and the reaction mixture was refluxed under N_2 for 2 hr, then stirred for an additional 1 hr at room temperature. Following addition of 400 g of K_2CO_3, the solution was cooled in an ice bath and extracted four times with a total of 1.6 l. of ether. The ether extracts were combined, dried over K_2CO_3, and concentrated. The residue was distilled *in vacuo*, yield 74 g (58.2% of theory) of **17**:[5] bp 103-111° (0.2-0.3 mm); 98-99% pure by glc [VC-W98, 3% on Chromosorb G (acid washed and silanized) mesh 60/80, retention time 3.6 min, 180°]; nmr ($CDCl_3$) δ 5.81 (s, 1, CH=C), 2.3 (s, 3, NCH_3); ir ν_{max} (liquid) 1670, 1626 cm^{-1}.

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.23; H, 9.85; N, 8.67.

1,3,4,7,8,8a-Hexahydro-2-methyl-4a-phenylisoquinolin-6(8*H*)-one (18). To a stirred suspension of 38 g of cuprous iodide (previously washed with anhydrous ether) in 150 ml of anhydrous ether under nitrogen and cooled to 0-5° was added over a period of 20 min a solution of phenyllithium freshly prepared by allowing 69 g of bromobenzene and 6.1 g of lithium wire to react in 375 ml of anhydrous ether. The mixture was stirred for 30 min at 0°; then a solution of 16.5 g of **17** in 100 ml of anhydrous ether was added dropwise over a 30-min period. After stirring for 30 min at 0-5° and 1.5 hr at room temperature the reaction mixture was poured into a stirred mixture of 75 g of ammonium chloride in 200 ml of water and ice. The mixture was well shaken and filtered and the layers were separated. The aqueous layer was extracted with ether, and the combined ether extracts were washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure, leaving an oil that was distilled, bp 145-155° (0.3 mm), yield 18.2 g (75%). The oil was crystallized from 50 ml of hexane, yield 13.8 g (57%) of the ketone 18: mp 72-74°; *m/e* 243 (M^+); nmr ($CDCl_3$) δ 7.6-7.1 (m, 5, ArH), 2.34 (s, 3, NCH_3); ir ν_{max} (liquid) 1703, 754, 695 cm^{-1}.

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.91; H, 8.41; N, 5.40.

This was further characterized as the methobromide, mp 300°.

Anal. Calcd for $C_{17}H_{24}BrNO$: C, 60.39; H, 7.15; N, 4.14. Found: C, 60.31; H, 7.16; N, 4.20.

This methobromide was crystallized from methanol to obtain a crystal for X-ray crystallographic analysis.

1,3,4,7,8,8a-Hexahydro-6-hydroxy-6-(*m*-methoxyphenyl)-2-methylisoquinoline. A 15-g portion of *m*-bromoanisole was treated with 2 g of magnesium turnings in 50 ml of anhydrous THF. Reagent was added to a stirred suspension of CuI in 40 ml of THF under N_2 and cooled in an ice bath. After stirring for 45 min at 5° a solution of 6.6 g of the hexahydroisoquinolone 17 in 20 ml of THF was added dropwise over a 20-min period. The reaction mixture was stirred for 1 hr at 5° and 2.5 hr at room temperature, and then was poured into a stirred solution of 20 g of ammonium chloride in 150 ml of ice water. Ether was added, the mixture was well shaken and filtered, and the layers were separated. The aqueous layer was extracted once more with ether, and the combined ether extracts were washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo*, leaving a dark brown oil which was purified by preparative tlc. The only pure identifiable product was the 1,2-addition product: mp 109-111°; nmr ($CDCl_3$) δ 7.8-6.6 (m, 4, ArH), 5.51 (s, 1, C=CH), 3.82 (s, 3, OCH_3), 2.22 (s, 3, NCH_3); ir ν_{max} (Nujol) 3115, 1666, 1253 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 75.01; H, 8.54; N, 5.06.

1,3,4,5,6,7,8,8a-Octahydro-2-methyl-4a-phenylisoquinolin-6-ol (19). A mixture of 2.4 g of 18 and 1 g of 10% Pd/C in 25 ml of glacial acetic acid was hydrogenated at 60° (1000 psi) for 6 hr. The mixture was filtered and concentrated *in vacuo*, and the residue was dissolved in water, basified with 10% Na_2CO_3, and extracted three times with ether. The combined ether extracts were washed with water, dried over K_2CO_3, filtered, and concentrated *in vacuo*, yielding 2.1 g (86% of theory) of an oil, the alcohol 19, nmr ($CDCl_3$) δ 7.7-7.0 (m, 5, ArH), 4.0-3.2 (m, 1, CHOH), 2.3 (s, 3, NCH_3).

1,3,4,5,6,7,8,8a-Octahydro-2-methyl-4a-phenylisoquinolin-6-ols (19 and 20). To a stirred solution of 2.4 g of 18 in 50 ml of anhydrous ethanol, 1.13 g of sodium borohydride was added in several portions. After stirring for 75 min at room temperature the solution was concentrated *in vacuo*, water and ether were added, and the layers were separated. The aqueous layer was extracted once with ether, and the combined ether extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*, leaving 2.3 g (94% of theory) of an oil that was an isomeric mixture of compounds 20 and 19: nmr ($CDCl_3$) δ 7.71-7.1 (m, 5, ArH), 4.17-3.0 (m, 1, CHOH), 2.31 (s, 3, NCH_3); ir ν_{max} ($CHCl_3$) 3610 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.53; H, 9.91; N, 5.71.

1,3,4,5,6,7,8,8a-Octahydro-2-methyl-4a-phenylisoquinolin-6-ol Propionates (21 and 22). A solution of 4.8 g of a mixture of the octahydroquinolinols 20 and 19 in 3.75 ml of propionic anhydride and 6 ml of pyridine was allowed to stand at room temperature for 4 days. The solution was diluted with toluene and concentrated *in vacuo*. The residue was dissolved in ether, treated with ice and 10% aqueous Na_2CO_3, filtered, and concentrated *in vacuo*, leaving 4.4 g (74.5%) of an oil. This oil was dissolved in acetone and the solution was acidified by addition of HCl-EtOAc solution. Two isomers were obtained by fractional crystallization from acetone-ether. The major isomer 22 (1.7 g, 25.7% had mp 247-248° dec; nmr ($CDCl_3$) δ 7.9-7.1 (m, 5, ArH), 5.2-4.7 (m, 1 -CHO-), 2.96 (d, 3, J = 4.5 Hz, NCH_3), 1.13 (t, 3, J = 7 Hz, CCH_3).

Anal. Calcd for $C_{19}H_{27}NO_2 \cdot HCl$: C, 67.54; H, 8.35; N, 4.15. Found: C, 67.20; H, 8.14; N, 4.30.

The minor isomer 21 (0.45 g, 6.8%) had mp 233° dec; nmr ($CDCl_3$) δ 7.43 (s, 5, ArH), 5.33-4.77 (m, 1, -CHO-), 2.68 (d, 3, NCH_3), 1.06 (t, 3, J = 7 Hz, CCH_3).

Anal. Calcd for $C_{19}H_{27}NO_2 \cdot HCl$: C, 67.54; H, 8.35; N, 4.15. Found: C, 67.45; H, 8.46; N, 3.96.

The alcohol 19 obtained from catalytic reduction was acylated under the same conditions. Only a single propionate hydrochloride could be obtained identical (melting point, mixture melting point, nmr, ir) with 22.

1,3,4,5,6,7,8,8a-Octahydro-2,6-dimethyl-4a-phenylisoquinolin-6-ol (23 and 24). A stirred solution of methyllithium (prepared from 17 g of methyl iodide and 1.7 g of lithium in 200 ml of anhydrous ether) under nitrogen was cooled to −70° and a solution of 9.6 g of 18 in 50 ml of anhydrous ether was added dropwise over a 30-min period. The reaction mixture was stirred for 15 min at −70° and then allowed to warm to room temperature overnight. The mixture was cautiously poured into a stirred solution of 50 g of ammonium chloride in 150 ml of ice water. The mixture was shaken in a separating funnel and the layers were separated. The aqueous layer was extracted twice with methylene chloride, the combined organic layers were dried, filtered and concentrated *in vacuo*, and the residue was triturated with ether, leaving a mixture of two solid isomers which were separated by fractional crystallization from acetone-ether. The major isomer 24 (28%) had mp 177-181°; nmr ($CDCl_3$) δ 7.3 (broad s, 5, ArH), 2.10 (s, 3, NCH_3), 1.04 (s, 3, CCH_3); ir ν_{max} (Nujol) 3190, 765, 693 cm^{-1}.

Anal. Calcd for $C_{17}H_{25}NO$: C, 78.71; H, 9.72; N, 5.40. Found: C, 79.07; H, 9.26; N, 5.50.

The minor isomer 23 (5.7%) had mp 91-93°; nmr ($CDCl_3$) δ 7.6-7.0 (m, 5, ArH), 2.28 (s, 3, NCH_3), 1.18 (s, 3, CCH_3). As a satisfactory elemental analysis could not be obtained on this material, it was characterized as the maleate, mp 175-176°.

Anal. Calcd for $C_{17}H_{25}NO \cdot C_4H_4O_4$: C, 67.18; H, 7.78; N, 3.73. Found: C, 67.40; H, 7.91; N, 3.61.

The major isomer 24 was also converted to a maleate, mp 198-203° dec, for comparison purposes.

Anal. Calcd for $C_{17}H_{25}NO \cdot C_4H_4O_4$: C, 67.18; H, 7.78; N, 3.73. Found: C, 67.40; H, 7.53; N, 3.87.

1,3,4,5,6,8a-Octahydro-2,6-dimethyl-4a-phenylisoquinolin-6-ol Propionate (25). A solution of 4 g of 24 in 6 g of propionic anhydride and 20 ml of pyridine was refluxed for 8 hr and then allowed to stand at room temperature for 16 hr. The solution was concentrated *in vacuo*, and the residue was dissolved in methylene chloride, washed with cold 10% sodium carbonate solution and water, and dried over sodium sulfate. Filtration and concentration *in vacuo* left an oil that was triturated with ether-hexane (1:1) and the insoluble solid was filtered off and identified as starting material. The filtrate was concentrated and the maleate salt was prepared from the oil, yield 3.3 g (68%) of oil, 3.6 g (53%) of the maleate: mp 185-186°; nmr ($CDCl_3$) δ 7.38 (s, 5, ArH), 6.27 (s, 2, maleate), 2.66 (s, 3, NCH_3), 1.42 (s, 3, CCH_3), 1.12 (t, 3, J = 7 Hz, CCH_3).

Anal. Calcd for $C_{20}H_{29}NO_2$: C, 66.80; H, 7.71; N, 3.35. Found: C, 66.81; H, 7.55; N, 3.46.

Wolff-Kishner Reduction of 18. A mixture of 2.4 g of 18, 2 g of hydrazine hydrate (99-100%), 2 g of KOH, and 30 ml of diethylene glycol was heated to 100° until the KOH dissolved. The solution was heated to reflux (200° oil bath) for 1 hr, then material was distilled until the temperature of distillate rose to 175° (internal) and the solution was refluxed for 1.5 hr. After cooling to room temperature the solution was diluted with water and extracted four times with ether. Combined extracts were washed with water, dried over K_2CO_3, filtered, and concentrated under reduced pressure. The oily residue was dissolved in ethyl acetate and acidified with HCl-EtAc solution. The precipitate was recrystallized from acetone-isopropyl alcohol to yield 1.15 g (43.3%), mp 222-224°, of compound 26: nmr ($CDCl_3$), δ 7.7-7.0 (m, 5, ArH); ir ν_{max} (Nujol) 761, 698 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}N \cdot HCl$: C, 72.29; H, 9.10; N, 5.27. Found: C, 72.49; H, 9.02; N, 5.52.

The hydrochloride was converted to the free base and a picrate formed, mp 144-146°.

Anal. Calcd for $C_{16}H_{23}N \cdot C_6H_3N_3O_7$: C, 57.63; H, 5.72; N, 12.22. Found: C, 57.51; H, 5.76; N, 12.26.

The picrate, mp 212-213°, obtained from Professor Boekelheide[8] was reanalyzed in view of its age.

Anal. Calcd for $C_{16}H_{23}N \cdot C_6H_3N_3O_7$: C, 57.63; H, 5.72; N, 12.22. Found: C, 57.62; H, 5.41; N, 12.26.

The two picrates were not identical by melting point and the depression of melting point on admixture. Tlc was carried out on the two picrates (Al_2O_3 GF254 Merck, $CHCl_3$; detection Dragendorff reagent): R_f 0 (picric acid), 0.3 (major), 0.53 (trace) (Boekelheide sample); R_f 0 (picric acid), 0.53 (major) (picrate of 26).

Wittig Reaction of 18 to 27. To a stirred solution of the triphenylmethylenephosphorane under N_2 (prepared by treating 17.4 g of triphenylmethylphosphonium bromide with 32 ml of 1.6 *M* *n*-butyllithium) in 150 ml of anhydrous ether a solution of 18 (9.6 g) in 50 ml of anhydrous ether was added dropwise. A pale yellow solid precipitated. After stirring for 20 hr at room temperature the solids were filtered off and washed with ether. The combined ether fractions were washed with water until the water filtrate was neutral and then dried over anhydrous Na_2SO_4. Filtration and concentration under reduced pressure left 6.5 g of an oil that was distilled, bp 120–135° (0.3 mm), to give **27**: 4.3 g (43%); nmr ($CDCl_3$) δ 7.6–7.0 (m, 5, ArH), 4.67 (d, 2, J = 4 Hz, $=CH_2$), 2.16 (s, 3, NCH_3).

Anal. Calcd for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.24; H, 9.33; N, 5.73.

This oil **27** was further characterized as the hydrochloride, mp 208–209° dec.

Anal. Calcd for $C_{17}H_{23}N \cdot HCl$: C, 73.49; H, 8.71; N, 5.04. Found: C, 73.12; H, 8.98; N, 5.06.

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Registry No.—**3a**, 25012-72-0; **3b**, 13221-89-1; **5a**, 50640-99-8; **5a** hydrochloride, 50641-00-4; **5b**, 50641-01-5; **6a**, 50641-02-6; **6b**, 50641-03-7; **7**, 50641-04-8; **8a**, 50641-05-9; **8b**, 50641-06-0; **9**, 50640-72-7; **10**, 50640-73-8; **11**, 50641-07-1; **12**, 50641-08-2; **12** hydrochloride, 50641-09-3; **17**, 19608-59-4; **18**, 50640-74-9; **18** methobromide, 50640-75-0; **19**, 50640-76-1; **20**, 50640-77-2; **21** hydrochloride, 50640-78-3; **22** hydrochloride, 50640-79-4; **23**, 50640-80-7; **23** maleate, 50640-81-8; **24**, 50640-82-9; **24** maleate, 50640-83-0; **25** maleate, 50640-85-2; **26** hydrochloride, 50640-86-3; **26** picrate, 50790-98-2; **27**, 50640-87-4; **27** hydrochloride, 50640-88-5; 1,3,4,7,8,8a-hexahydro-6-hydroxy-6-(*m*-methoxyphenyl)-2-methylisoquinoline, 50790-99-3.

Supplementary Material Available. A table with the final atomic positional and thermal parameters and a figure with bond angles and bond lengths will appear following these pages in the microfilm edition of this volume of the journal. The standard deviations and observed structure factors are no longer available. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-1118.

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(10) As was pointed out by a referee, **18** is probably a mixture of both conformers. An approximate calculation suggests a 2:1 mixture of **18a** and **18b**.

(11) Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. Ir spectra were obtained with Perkin-Elmer spectrophotometers, Models 21 and 521. Nmr spectra were obtained with a Varian A-60 nmr instrument. Mass spectra were obtained with an AEI MS 902 mass spectrometer at 70 eV.

Reaction of Acetylenes with Hydrogen Chloride in Acetic Acid. Effect of Structure upon AdE2 and Ad3 Reaction Rates

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Studies of the initial reaction rate and product composition for the reaction of phenylacetylene, 1-phenylpropyne, 1-hexyne, and *tert*-butylacetylene with HCl in HOAc at 25° are reported. The stereochemistry of HCl addition to 1-hexyne-*1-d* at 50° was also examined. The results are found to be consistent with reaction *via* competing AdE2 and anti Ad3 reaction mechanisms. The results show that the AdE2 and Ad3 mechanisms involve different regiospecificity, as well as stereospecificity. The effect of structure upon reaction rate is found to be quite different in the two mechanisms, implicating significantly different transition-state structures.

In previous papers[1-6] we have presented evidence for two distinct mechanisms for addition of HCl to olefins and acetylenes in acetic acid. Reaction *via* the AdE2 mechanism[1-3] occurs by slow protonation of the unsaturated compound to form a carbonium chloride ion pair intermediate

$$\text{olefin (acetylene)} + \mathrm{HCl} \longrightarrow [\mathrm{R^+Cl^-}] \longrightarrow \mathrm{RCl} + \mathrm{ROAc} \longrightarrow \text{(ketone)}$$

which collapses to a mixture composed mainly of chloride and some acetate, the vinyl acetates formed from acetylenes undergoing a rapid subsequent reaction to form a ketone. The rate of reaction depends upon unsaturated reactant and HCl concentrations, but the ratio of the RCl to ROAc is not influenced by the HCl concentration. Moreover, the presence of chloride salt does not increase the percentage of RCl formed and, at 0.2 *M*, causes a less than threefold rate increase. This shows that, once formed, the ion-pair intermediate collapses rapidly to a product mixture determined solely by the structure of the ion pair and not significantly influenced by the composition of the external reaction solution. The effect of salt upon the rate results from a salt effect upon the rate of formation of the carbonium ion pair. Styrene and *tert*-butylethylene react exclusively *via* this mechanism.[3]

Other olefins and acetylenes exhibit different behavior under the same reaction conditions. Thus, the ratio of RCl to ROAc obtained from 3-hexyne[2] and also from cyclohexene[4,5] varies with the HCl concentration. The presence of chloride salt not only markedly increases the ratio of RCl to ROAc but gives rise to a rate increase indicative of catalysis by chloride ion. Under these conditions addition occurs with anti stereochemistry. The observations imply that an Ad3 addition, formally the reverse of E2 elimination, is involved.

The reaction of 1,2-dimethylcyclohexene has been found to involve AdE2 addition, giving largely syn HCl adduct, at low HCl concentration, but in the presence of chloride salt a more rapid anti Ad3 addition of HCl dominates.[6]

An understanding of how structure influences reactivity in each of these mechanisms is important in designing synthetic procedures and also in understanding the electronic structure of the transition states. We report here studies designed to provide information concerning the effect of structure upon reactivity for reaction of acetylenes with HCl in HOAc. Stereochemistry of addition and the effect of chloride salt upon rate and product composition are employed as the criteria of mechanism.

Experimental Section

An Aerograph Model 200 gas chromatograph equipped with thermal conductivity detectors and a Disc integrator was employed for all glpc analyses. Chromosorb P (acid washed) was used as solid support. Pmr spectra were measured on a Varian T-60 spectrometer as approximately 15% v/v solutions in CCl_4; chemical shifts are reported in parts per million downfield from tetramethylsilane as internal standard.

Materials. Acetophenone, 1-phenyl-2-propanone, *p*-xylene, chlorobenzene, and pinacolone were obtained from Matheson Coleman and Bell. Phenylacetylene, 1-phenylpropyne, and 1-hexyne were obtained from Farchan and purified by vacuum distillation on a spinning band column. These purified acetylenes and *tert*-butylacetylene (Farchan) were shown to be ≥99.9% pure by analytical glpc. Samples of (*Z*)- and (*E*)-2-chloro-1-phenylpropene were prepared as described previously.[7] A sample of 2,2-dichlorohexane was obtained from the reaction of 2-hexanone with PCl_5;[8] the product was first purified by vacuum distillation through a glass helix column and then by preparative glpc. All other materials were as described in previous studies.[1,2]

Preparation of 1-Hexyne-*1-d*. A 3 *M* ethereal solution (250 ml) of methylmagnesium bromide (Arapahoe) was added dropwise with stirring to 30 g of 1-hexyne in 50 ml of ether, after which the mixture was refluxed for 3 hr. The mixture was cooled to 0°, 60 ml of D_2O was added, the mixture was stirred for 2 hr, and 100 ml of 2.5 *M* HCl was added. An additional 100 ml of ether was added and the ether layer was separated, dried over anhydrous $MgSO_4$, and concentrated by removal of ether through a Vigreux column. Spinning-band distillation of the concentrated ether fraction yielded 14 g of 1-hexyne-*1-d*, bp 70.5–71.0°, found by glpc to be 99.6% pure (0.4% ether) and by pmr to contain ≥98% deuterium at *C-1*.

Addition to Phenylacetylene. Reaction mixtures containing 0.8 *M* phenylacetylene, 0.75 *M* HCl, and 0.039 *M* 1-phenyl-2-propanone (internal standard) were prepared with and without tetramethylammonium chloride (TMAC) (0.2 *M*) in volumetric flasks as described previously and placed in a 25° thermostated bath. Samples (5 ml) were withdrawn at intervals and quenched by mixing with 25 ml of 10% aqueous NaCl and 10 ml of pentane. The aqueous fraction was washed with two 5-ml portions of pentane; the combined pentane fractions were washed with 10 ml of 10% aqueous $NaHCO_3$ and dried over anhydrous K_2CO_3. The pentane fraction was concentrated by evaporation and analyzed by glpc on a 0.125-in. column packed with 20% SE-52 (first 4 ft) and 20% DEGS (last 8 ft) operated at 150° with a helium flow rate of 15 ml/min. Retention times in minutes follow: phenylacetylene, 4; α-chlorostyrene, 9; acetophenone, 14.5; 1-phenyl-2-propanone, 18. Initial rates and product compositions were determined at 1–9% conversion. The two major products were isolated by preparative glpc from a sample of a reaction mixture without added TMAC at near complete reaction. The pmr spectrum of the major product was identical with that of authentic α-chlorostyrene, while the pmr spectrum of the minor product was identical with that of authentic acetophenone. Calibrations with the internal standard accounted for 95–100% of the starting acetylene as product or recovered starting material.

Addition to 1-Hexyne. Reaction solutions were prepared and reaction samples were worked up in the same fashion as described previously[1,2] for addition to 3-hexyne; *p*-xylene was employed as an internal standard. Analysis by glpc was carried out on a 25 ft × 0.125 in. 10% XF1150 column operated at 100° and 13 ml/min of helium. Retention times in minutes follow: 1-hexyne, 6; (*Z*)-2-chloro-2-hexene and 2-chloro-1-hexene, 10; (*E*)-2-chloro-2-hexene, 13; *p*-xylene, 23; 2,2-dichlorohexane, 27; 2-hexanone, 29. Quantitative measurements were made at 1–9% conversion (Figure 1).

Products were isolated by preparative glpc from runs at higher temperatures so that significant conversion could be obtained in reasonable time periods. Reaction of 0.87 *M* 1-hexyne with HCl (0.82 *M*) in the presence of TMAC (0.42 *M*) at 50° for 6 days gave 60% conversion of 1-hexyne. Samples of 2-chloro-1-hexene, (*E*)-2-chloro-2-hexene, 2,2-dichlorohexane, and 2-hexanone were isolated from the product mixture and their pmr spectra were measured. The spectrum of 2-hexanone proved to be identical with that of an authentic sample. Pmr spectral data for 2-chloro-1-hexene in CCl_4 exhibited a narrow multiplet (δ 5.10, 2 H), a broad triplet (δ, 2.35, 2 H, J = 7 Hz), a multiplet (δ 1.2–1.7, 4 H), and an unsymmetrical triplet (δ 0.93, 3 H). In benzene the spectrum gave a doublet (δ 5.05, 1 H, J = 1 Hz), an approximate quartet (δ 4.82, 1 H, J = 1 Hz), a broad triplet (δ 2.13, 2 H, J = 7 Hz), a multiplet (δ 1.0–1.6, 4 H), and another multiplet (δ 0.77, 3 H). The pmr spectrum (CCl_4) of (*E*)-2-chloro-2-hexene consisted of a broad triplet (δ 5.58, 1 H, J = 2 Hz), a broad singlet overlapping a multiplet (δ 2.05 and 2.0, 5 H), a sextet (δ 1.43, 2 H, J = 7 Hz), and an unsymmetrical triplet (δ 0.93, 3 H, J = 7 Hz). The pmr spectrum of 2,2-dichlorohexane showed a multiplet (δ 2.18, 2 H), a singlet (δ 2.13, 3 H), a multiplet (δ 1.2–1.8, 4 H), and an unsymmetrical triplet (δ 0.98, 3 H, J = 7 Hz). A sample (30% of product) consisting of 95% (*Z*)-2-chloro-2-hexene and 5% 2-chloro-1-hexene was isolated by glpc from a reaction of 0.8 *M* 1-hexyne with 0.8 *M* HCl at 125° for 4 days; the pmr spectrum of the major isomer exhibited a broad triplet (δ 5.43, 1 H, J = 7 Hz), a broad doublet (δ 2.14, 2 H, J = 7 Hz), a doublet (δ 2.10, 3 H, J = 1 Hz), a broad sextet (δ 1.43, 2 H, J = 7 Hz), and an unsymmetrical triplet (δ 0.94, 3 H, J = 7 Hz). For reactions carried to >50% conversion at 50°, calibration with internal standard showed that ≥97% of the initial 1-hexyne was accounted for as products or unreacted starting material.

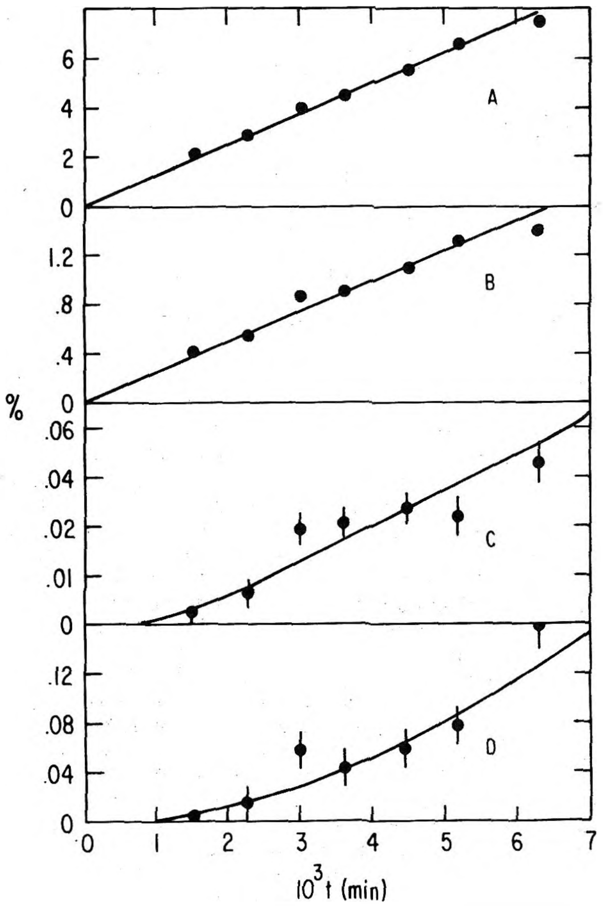


Figure 1. Appearance of products as a function of time in the reaction of 1-hexyne (0.8 *M*) with HCl (0.75 *M*) in the presence of TMAC (0.2 *M*) at 25.0° in HOAc: (A) 2-chloro-1-hexene plus (*Z*)-2-chloro-2-hexene; (B) 2-hexanone; (C) (*E*)-2-chloro-2-hexene; (D) 2,2-dichlorohexane. Solid lines represent the calculated values (see text).

Addition to 1-Hexyne-1-d. Reactions of 1-hexyne-*1-d* (0.8 *M*) with HCl (0.75 *M*) in the presence and absence of TMAC (0.2 *M*) were conducted in ampoules at 50° for 2–3 weeks. The peak corresponding to 2-chloro-1-hexene was isolated by preparative glpc and the pmr spectrum was determined in benzene as solvent. The relative amounts of syn and anti adduct were determined from the ratio of the peak areas for the resonances at 5.05 and 4.82 ppm.

Addition to 2-Hexyne. Reaction of 2-hexyne (0.9 *M*) with HCl (0.8 *M*) in the presence of TMAC (0.4 *M*) in a sealed ampoule at 50° was allowed to proceed for 6 days and then worked up. Analysis by glpc as described for addition to 1-hexyne indicated ~75%

Table I
Initial Rates and Product Composition for the Reaction of Acetylenes (0.8 *M*) with HCl (0.75 *M*) in Acetic Acid at 25° in the Absence and Presence of TMAC

Registry no.	Acetylene	[TMAC], *M*	10^7 *R*, *M* sec^{-1}	Products (%) Chloride	Ketone
536-74-3	PhC≡CH	0	79	**1** (92)	**2** (8)
		0.2	174	**1** (88)	**2** (12)
693-02-7	1-Hexyne	0	0.29	**3** (35)	**4** (65)
		0.2	2.2	**3** (82)	**4** (18)
917-92-0	*tert*-Butylacetylene	0	0.094	**8** (26)	**9** (74)
		0.2	0.48	**8** (75)	**9** (25)
928-49-4	3-Hexyne[a]	0	0.87	(47)[b]	3-HO[c] (53)
		0.21	16.7	(96)[b]	3-HO[c] (4)

[a] From ref 2; 0.81 *M* 3-hexyne, 0.78 *M* HCl. [b] *trans*-3-Chloro-3-hexene. [c] 3-Hexanone; ≤1% *cis*-3-chloro-3-hexene formed.

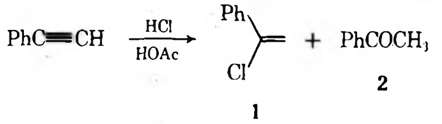
conversion of 2-hexyne with a peak having a retention time identical with that of 2-chloro-1-hexene accounting for 97% of the product. The pmr spectrum of material obtained by glpc purification of the major product peak was consistent with an equal mixture of (*E*)-2-chloro- and (*E*)-3-chloro-2-hexene. Comparison with the spectrum of the 2-chloro-2-hexene obtained from reaction of 1-hexyne with HCl at 125° (see above) gave rise to an nmr assignment for (*E*)-3-chloro-2-hexene having a broad quartet (δ 5.48, 1 H, *J* = 7 Hz), a broad triplet (δ 2.27, 2 H, *J* = 7 Hz), a doublet (*J* = 7 Hz) of triplets (*J* = 1 Hz) (δ 1.73, 3 H), a multiplet (δ 1.46, 2 H), and an unsymmetrical triplet (δ 0.92, 3 H, *J* = 7 Hz).

Addition to *tert*-Butylacetylene (3,3-Dimethyl-1-butyne). Reaction solutions were prepared and worked up as described for 1-hexyne but using chlorobenzene as internal standard. Analysis by glpc was carried out on a 25 ft × 0.125 in. 10% XF1150 column operated at 97° and 12 ml/min of helium. Retention times in minutes follow: *tert*-butylacetylene, 4; 2-chloro-3,3-dimethyl-1-butene, 6.5; pinacolone, 14; chlorobenzene, 27. Two unidentified minor products with retention times of 10 and 23 min were observed at less than 10% conversion and contributed about 2 and 3.5%, respectively, of the total product. The two major products were isolated from a reaction of *tert*-butylacetylene (0.8 *M*) with HCl (0.75 *M*) carried out in a sealed ampoule at 50° for 3 weeks. The pmr spectrum of glpc-purified product with 6.5-min retention time (2-chloro-3,3-dimethyl-1-butene) exhibited an AB multiplet at 5.09 ppm (2 H) and a singlet at 1.17 ppm (9 H). The pmr spectrum of the product with 14-min retention time was identical with that of authentic pinacolone.

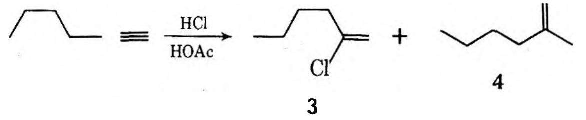
Addition to 1-Phenylpropyne. Reaction mixtures were prepared and worked up as described previously.[1,2] Analysis by glpc was conducted on a 25 ft × 0.125 in. 20% XF1150 column operated at 170° and 18 ml/min of helium. Retention times in minutes follow: 1-phenylpropyne, 12.5; (*E*)-1-chloro-1-phenylpropene, 17.5; (*E*)-2-chloro-1-phenylpropene, 20; (*Z*)-1-chloro-1-phenylpropene, 22.5; (*Z*)-2-chloro-1-phenylpropene, 24.2; propiophenone, 39; (*E*)-1-acetoxy-1-phenylpropene, 45; (*Z*)-1-acetoxy-1-phenylpropene, 51. To check for isomerization, a 0.85:1 mixture of (*E*)- to (*Z*)-2-chloro-1-phenylpropene (0.06 *M*) was allowed to react in 0.75 *M* HCl containing 0.34 *M* TMAC for 28 hr at 50°; analysis by glpc showed that the ratio of isomers was unchanged.

Results

Phenylacetylene. The reaction of phenylacetylene with HCl in HOAc at 25° was found to yield two products, α-chlorostyrene (1) and acetophenone (2). Quantitative measurements at 1-10% conversion showed that the product composition does not vary with time, indicating that secondary reactions of the initial products are unimportant under these conditions. Initial rates and product compositions for reaction in the presence and absence of tetramethylammonium chloride (TMAC) are given in Table I. The reaction yields primarily 1, but the presence of 0.2 *M* TMAC, while causing a slightly greater than twofold increase in rate, results in a decrease in the ratio of 1 to 2.

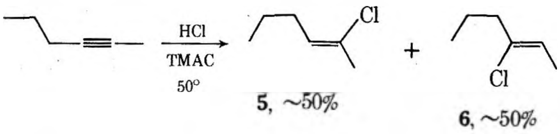


1-Hexyne. The reaction of 1-hexyne with HCl in HOAc was studied in a similar manner. At low conversion only two main products were observed. These were isolated using preparative glpc and their structures were established as 2-chloro-1-hexene (3) and 2-hexanone (4) on the basis of their pmr spectra. At longer reaction times two additional products were observed by glpc. Moreover, the pmr spectrum of the peak corresponding to 3 changed, showing that a third new product with identical glpc retention time with that of 3 was being formed. These three products are observable only after significant (>1%) conversion of 1-hexyne to 3 has occurred and must, therefore, be secondary reaction products.



The structures of the secondary products were established using glpc-purified samples obtained from runs carried out to high conversion. One of the two glpc separable products proved identical in glpc retention time and pmr spectrum with authentic 2,2-dichlorohexane. The other had a pmr spectrum very similar to that of the secondary product having identical retention time with that of 3; both pmr spectra were consistent with the structure 2-chloro-2-hexene and these two secondary products are therefore assigned as the isomeric 2-chloro-2-hexenes.

In order to confirm this assignment and establish the stereochemistry of the 2-chloro-2-hexenes, 2-hexyne was treated with HCl in HOAc containing TMAC. By analogy with the results obtained with 3-hexyne[2] this reaction was expected to yield a mixture of (*Z*)-2-chloro-2-hexene (5) and (*Z*)-3-chloro-2-hexene (6). At 78% conversion three product peaks were observed by glpc, one accounting for 97% of the product and having a retention time identical with that of 3 and the unidentified 2-chloro-2-hexene isomer obtained from 1-hexyne. The pmr spectrum of the glpc-purified material showed that it was composed of essentially equal amounts of 5 and 6. Thus, the 2-chloro-2-hexene obtained from 1-hexyne which has the same retention time as 3 is 5 and the one with different retention time must be (*E*)-2-chloro-2-hexene (7).



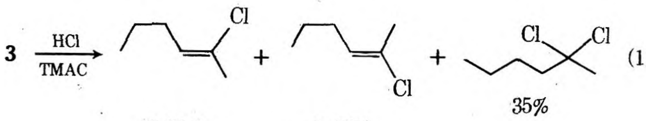
A quantitative study of the 1-hexyne reaction in the presence of TMAC showed that, once formed, 3 reacts with HCl to give the three secondary products in the approximate amounts shown in eq 1. Figure 1 shows the results of glpc analysis of the reaction products at less than

Table II
Effect of TMAC on the Hydrochlorination of 1-Phenylpropyne in Acetic Acid

[HCl], M	[C_9H_8], M	[TMAC], M	$10^9 R$,[a] M sec^{-1}	Product composition, %[b] 10	11	12[c]	14
			0.0°				
0.75	0.80	0.209	24	49	40	7.5	4.1
			25.0°				
0.10	0.10	0	1.1	81	8	11	≤0.3
0.10	0.10	0.080	2.2	59	26	10	4.2
0.10	0.10	0.16	3.2	51	34	8	6.4
0.10	0.10	0.50	5.7	36	46	7	10.6
0.75	0.10	0	26	80	12	8	0.3
0.75	0.10	0.063	34	62	24	11	≤3.2
0.75	0.10	0.167	67	53	33	9	5.5
0.75	0.10	0.50	94	39	45	8	8.4
0.75	0.10	1.00	102	30	51	10	10
0.75	0.80	0	198	77	12	11	0.1
0.75	0.80	0.094	318	59	28	11	2.2
0.75	0.80	0.188	411	52	34	11	3.4
0.75	0.80	0.209	470	51	35	10	3.8
			50.0°				
0.75	0.80	0	2,080	77	12	11	≤0.3
0.75	0.80	0.209	5,580	53	33	10	3.4
			80.0°				
0.75	0.80	0	23,400	74	13	13	≤0.3

[a] Average deviation less than ±5%. [b] In all cases, **13** constituted <0.3% of the products. [c] Includes small amounts of HOAc adducts; *cf.* ref 1.

10% conversion. Also shown are the calculated amounts of products (solid lines) formed assuming that 1-hexyne undergoes a pseudo-first-order reaction to give **3** and **4** as the initial products in a ratio of 83.5:16.5 and that **3** undergoes a secondary reaction (eq 1) following pseudo-first-order kinetics at a rate equal to that of 1-hexyne. The reaction was simulated on a programmable electronic calculator to obtain the calculated product distribution as a function of time. The agreement between calculated and observed values shows that the assumptions concerning the primary product composition, and the rate and products for secondary reaction of **3**, are valid.



(1)

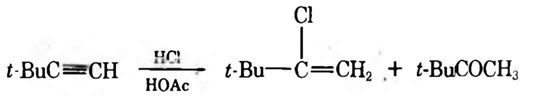
35%

5, 50% **7**, 15%

Values for the initial rate and the product composition for addition of HCl to 1-hexyne in the presence and absence of TMAC are given in Table I. The important features of these results are (1) in the absence of TMAC substantially more ketone than choride is formed; (2) TMAC causes a marked increase in reaction rate which is reflected primarily in increased chloride formation.

In order to establish the stereochemistry of addition to 1-hexyne, the reaction of 1-hexyne-*1-d* with HCl was studied. The syn and anti adducts have different pmr spectra in benzene solution, the proton cis to the alkyl group being shifted to higher field and having a large coupling to the C-3 methylene group relative to the proton trans to the alkyl group.[9-11] Reactions were run at 50°, rather than 25°, so that reasonable amounts of product (25–50% conversion) could be obtained in a period of 2–3 weeks. The peak corresponding to **3** was isolated by preparative glpc and the stereochemistry was established from the relative areas of the two vinylic resonances in the pmr spectrum measured in benzene. For reaction of 1-hexyne-*1-d* (0.8 M) with 0.75 M HCl, the ratio of anti to syn adduct was found to be 40:60, whereas in the same reaction conducted with 0.2 M TMAC present the ratio was 90:10. These results establish that TMAC accelerates the reaction primarily by promoting the anti addition of HCl.

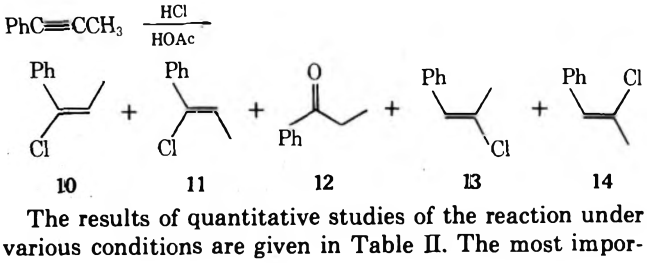
***tert*-Butylacetylene.** A study of addition to *tert*-butylacetylene (3,3-dimethyl-1-butyne) showed that >94% of the product at <10% conversion is 2-chloro-3,3-dimethyl-1-butene (**8**), identified by pmr, and pinacolone (**9**), identified by comparison to an authentic sample. Initial rates and product ratios determined at <3% conversion are given in Table I. As with 1-hexyne, less chloride than ketone is formed in the absence of TMAC, and the presence of TMAC increases the amount of chloride formed with an accompanying increase in reaction rate.



$$t\text{-BuC}{\equiv}\text{CH} \xrightarrow[\text{HOAc}]{\text{HCl}} t\text{-Bu}{-}\overset{\text{Cl}}{\overset{|}{\text{C}}}{=}\text{CH}_2 + t\text{-BuCOCH}_3$$

8 **9**

1-Phenylpropyne. The reaction of 1-phenylpropyne with HCl in HOAc was studied at <10% conversion using methods described in an earlier report.[1] The major products in the absence of chloride salts include the HCl adducts (*E*)- and (*Z*)-1-chloro-1-phenylpropene, and propiophenone as the secondary product formed from the HOAc adducts as initial products.[1] The HCl adducts from proton attack at C-1, (*E*)- and (*Z*)-2-chloro-1-phenylpropene, each account for <0.3% of the product in the absence of chloride salts. However, in the presence of TMAC, significant amounts of **14** (but not **13**) are observed. In a control experiment, it was shown that **13** is stable to the reaction conditions so that **14** is not formed by secondary isomerization of **13**.

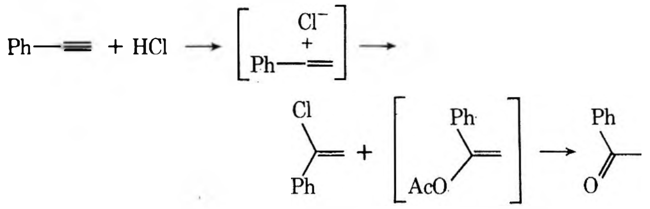


10 **11** **12** **13** **14**

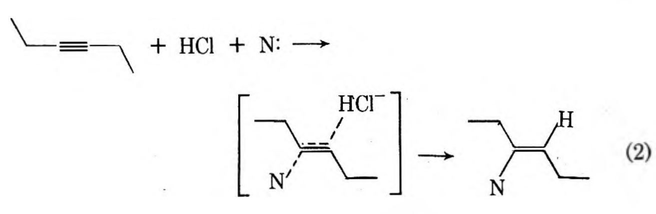
The results of quantitative studies of the reaction under various conditions are given in Table II. The most important feature of the results is that the presence of TMAC in the reaction mixture leads to a marked increase in the amount of 11 formed and causes 14 to become an important reaction product.

Discussion

Addition to Phenylacetylene. The results obtained show that phenylacetylene reacts exclusively *via* the AdE2 mechanism. The high ratio of chloride to ketone (12:1) is consistent with that expected from a collapse of a carbonium-chloride ion pair. The fact that 0.2 *M* chloride salt increases the reaction rate by a factor of only 2 and does not increase the fraction of chloride formed (Table I) implicates the AdE2 process. In fact, the presence of 0.2 *M* chloride salt actually results in a decrease in the ratio of chloride to ketone to 7:1. A similar observation was made in the analogous reaction of styrene.[3] Since capture by added nucleophile is a long-standing criterion for establishing the presence of a carbonium ion intermediate, this seems, at first, a surprising observation. However, it must be remembered that the species formed in the present reaction is a tight ion pair and very probably collapses within the solvent cage without ever encountering external nucleophile. The effect of added salt in reducing the fraction of chloride formed can then be reasonably explained as a medium effect which slightly weakens the ion-pair interaction and thereby increases capture by solvent.

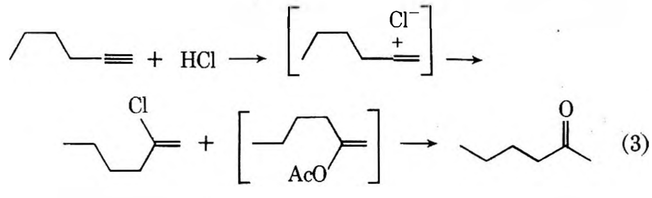


Addition to 1-Hexyne. The results obtained with 1-hexyne are quite different, and resemble those observed previously with 3-hexyne (Table I).[2] Specifically, the low ratio (0.54) of chloride to ketone in the absence of chloride salt, the increase in this ratio with added chloride salt, and the nearly eightfold rate increase caused by 0.2 *M* TMAC are indicative of chloride ion catalysis and reaction primarily *via* competing Ad3 addition of HCl and HOAc (eq 2). Yet, the stereochemical results indicate that a fraction of the reaction does occur *via* an AdE2 path (eq 3). So, at 50° in the absence of chloride salt 40% of the 2-chloro-1-hexene is formed by syn addition. Since the carbonium chloride ion pair favors collapse to syn adduct, the AdE2 mechanism is implicated. Assuming that a comparable fraction of syn adduct obtains at 25° and that no more than an equal amount of ketone derives from the AdE2 process, about 35% of the reaction at 0.8 *M* HCl could occur *via* the vinyl cation, with 15 and 50% occurring *via* Ad3 addition of HCl and HOAc, respectively. On the same basis 95% of the reaction involves *anti* Ad3 addition of HCl when 0.2 *M* TMAC is present.



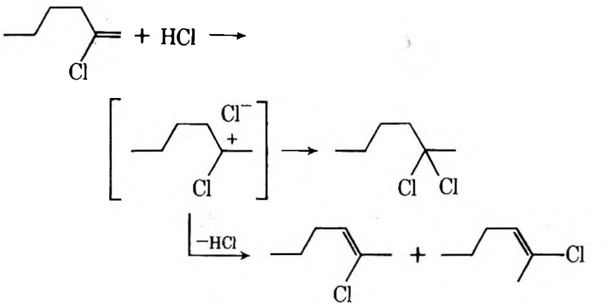
(2)

N: = Cl⁻ or HOAc



(3)

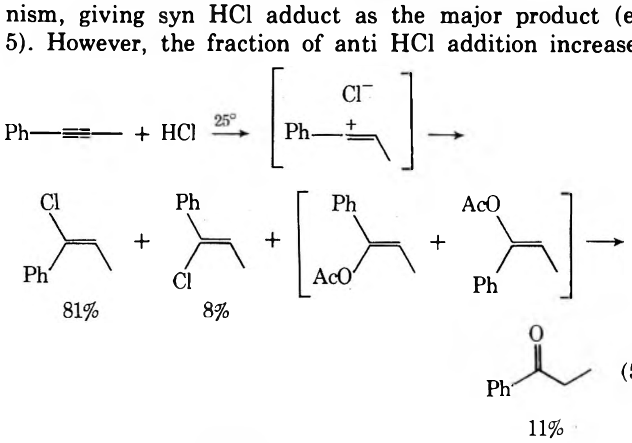
A fairly complete product study was made with 1-hexyne and the results illustrate the complexities that can arise as the result of secondary reactions of the initial products. Thus, 1-chloro-1-hexene is about as reactive as 1-hexyne itself and gives rise to products consistent with an AdE2 reaction of 2-chloro-1-hexene with HCl (eq 4). Reasonable yields of 2-chloro-1-alkenes are obtained from 1-alkynes only at high chloride ion concentration and when the reaction is stopped at 50–75% conversion of 1-alkyne.



(4)

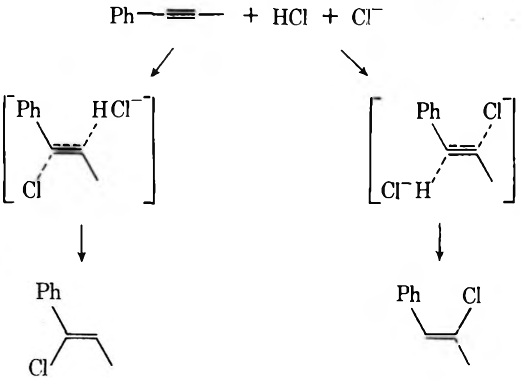
Addition to *tert*-Butylethylene. Since it had been found previously that *tert*-butylethylene reacts with HCl in HOAc *via* an AdE2 mechanism in which Wagner–Meerwein rearrangement accounts for ~40% of the product,[3] it was of some interest to ascertain whether *tert*-butylacetylene would react similarly. However, the substantial effect of chloride salt upon the reaction rate and the ratio of chloride to ketone (Table I) show that reaction of *tert*-butylacetylene occurs primarily *via* competing Ad3 addition of HCl and HOAc rather than *via* the AdE2 mechanism. This conclusion is consistent with the fact that little or no rearrangement accompanies the addition. This observation shows that Ad3 addition is favored, relative to AdE2 addition, to a greater extent for alkynes than for the corresponding alkenes. It is clear, however, that *tert*-butylacetylene can react *via* an AdE2 mechanism involving a cationic intermediate under other reaction conditions. Thus, Griesbaum and Rehman[12] find for reaction of HCl with *tert*-butylacetylene in the absence of solvent that 30–60% of the product derives from an intermediate in which a methyl group has shifted from C-3 to C-2.

Addition to 1-Phenylpropyne. At low HCl concentration and in the absence of chloride salt addition to 1-phenylpropyne occurs predominantly by the AdE2 mechanism, giving syn HCl adduct as the major product (eq 5). However, the fraction of anti HCl addition increases markedly in the presence of chloride salt and a new product appears which arises from anti HCl addition with proton attack at C-1 rather than C-2. At >0.5 *M* chloride salt these two products together account for over half of the total. In view of the fact that chloride salt does not in-



(5)

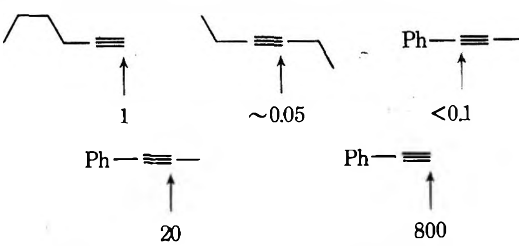
crease the fraction of chloride formed in the reaction of phenylacetylene, where a vinyl cation of similar stability is formed, this observation with 1-phenylpropyne cannot plausibly be attributed to capture of an intermediate vinyl cation by the added chloride salt. These products logically derive from competing anti Ad3 reactions as shown in eq 6.



(6)

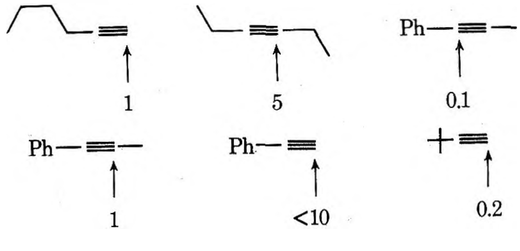
The results with 1-phenylpropyne demonstrate an important difference in the regiospecificity, as well as in stereospecificity, of the AdE2 and Ad3 additions. Thus, while addition *via* the AdE2 mechanism occurs with proton attack at C-2 occurring at least 300 times more rapidly than attack at C-1, the corresponding ratio for attack in the Ad3 mechanism is only about five.

Relative Reactivity in AdE2 Addition. From the results obtained in the absence of chloride salts and the foregoing analysis it is possible to assign relative rates for reaction *via* the AdE2 mechanism. The results are summarized below, arrows indicating the position of proton attack. The value for 3-hexyne[2] has been reduced by the

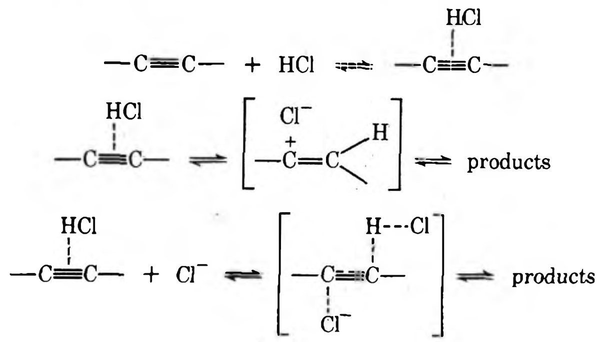


statistical factor of 2. The relative rates vary by a factor of $\sim 10^4$ and we see that substitution of alkyl by phenyl at the incipient cationic carbon results in a rate increase of between 400 and 800. This clearly reflects the ability of the phenyl group to stabilize the intermediate vinyl cation. Replacement of H by alkyl at the position of proton attack results in a rate decrease of between 20-fold and 40-fold. This effect is of the same magnitude as found for hydration of 1-phenylpropyne relative to phenylacetylene[13] and has been attributed to a larger change in C–C than in C–H bond energies as the hybridization of carbon varies from sp to sp^2 upon formation of the vinyl cation.[13]

Relative Reactivity in Ad3 Addition. Using the initial rate data obtained in the presence of 0.2 *M* chloride salt and the mechanistic assignments described above, relative rates were calculated for addition of HCl *via* the Ad3 mechanism. These are summarized as follows.



Scheme I



The relative rates span a range of less than 10^2. We see that substitution of alkyl by phenyl at the site of chloride attachment results in a decrease in rate, in sharp contrast to the large increase found for AdE2 addition. This shows that the Ad3 transition state does not closely resemble a vinyl cation intermediate.

The Ad3 transition state does not appear to be strongly subject to steric effects. The observation that Ad3 addition to 2-hexyne gives essentially equal amounts of anti HCl adduct from attack at C-2 and at C-3 shows that *n*-Pr and Me exhibit no differentiating effect. The comparison of 1-hexyne with *tert*-butylacetylene above shows that even the *t*-Bu group causes only a fivefold reduction in rate.

Comparing 1-hexyne and 3-hexyne we see that replacement of H by alkyl at the site of proton attack results in a modest rate increase for addition *via* the Ad3 mechanism, the effect again being opposite to that found for AdE2 addition. This observation indicates that the transition state for Ad3 addition involves little rehybridization at the site of proton attack.

Reaction Mechanism. These differences in reactivity support the view that the AdE2 and Ad3 mechanism involve distinctly different transition states. The transition state for AdE2 addition must closely resemble the vinyl cation chloride ion pair intermediate. The transition state for Ad3 addition is described as having little cationic character and little rehybridization at the carbon attacked by the proton. These considerations are summarized in Scheme I.

An acetylene–HCl molecular complex is formulated here as a common intermediate to obviate the implication of a termolecular collision in the Ad3 process. There is no direct evidence for involvement of such a complex and association of the reactants within a solvent cage would serve the same purpose. However, the description of the Ad3 transition state as a distorted acetylene–HCl complex associated with chloride ion accommodates the available structure–reactivity data.

The same general scheme applies for reaction of olefins with HCl in HOAc, and some qualitative comparisons of olefin and acetylene reactivity are possible. Both styrene[3] and phenylacetylene react exclusively *via* the AdE2 mechanism with styrene being about threefold more reactive than phenylacetylene under similar conditions. Judging from the rates of syn HCl addition, AdE2 addition to cyclohexene[4,5] is about tenfold faster than AdE2 addition to 3-hexyne.[2] These differences are similar to those found for addition of trifluororoacetic acid addition to alkenes and alkynes.[10,14] The anti Ad3 addition of HCl occurs at about the same rate for cyclohexene and 3-hexyne, and is the dominant reaction in both cases. Reaction of *tert*-butylethylene occurs about fivefold more rapidly than that of *tert*-butylacetylene but the evidence indicates that an AdE2 mechanism operates for the olefin and an Ad3 mechanism for the acetylene. This change in mechanism may arise from the somewhat greater reactivity of olefins than acetylenes *via* the AdE2 mechanism, possibly combined with a lower sensitivity to steric effects for Ad3 addition to acetylenes relative to olefins. For both olefins and acetylenes the balance between AdE2 and Ad3 addition appears to be delicate, so that changes in reactant structure or reaction conditions can lead to a shift from one mechanism to the other as the predominant pathway for reaction.

Acknowledgments. This work was supported by National Science Foundation Grant GP 24562. We thank Mr. Raymond Carrillo for technical assistance with some of the experiments, and Professor Paul E. Peterson for helpful comments.

Registry No.—**3**, 10124-73-9; **5**, 42131-99-7; **7**, 42132-01-4; 2,2-dichlorohexane, 42131-89-5; 1-hexyne-*1-d*, 7299-48-1; 2-hexyne, 764-35-2; (*E*)-3-chloro-2-hexene, 4050-45-7; 1-phenylpropyne, 673-32-5.

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Acid-Catalyzed Hydrolysis of Monoalkyl Xanthates[1]

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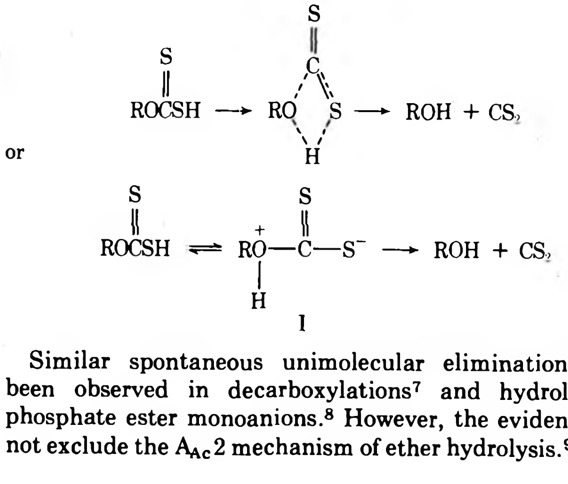
The decomposition of *n*-butyl xanthate in water, pH <5, and in metanolic methanesulfonic acid gives *n*-butyl alcohol and CS_2 by spontaneous elimination from xanthic acid. Similar observations were made on ethyl xanthate in water. At pH <0 the rate decreases because of the formation of unreactive protonated xanthic acid, and acid dissociation constants for both protonation equilibria are calculated. The decomposition of *tert*-butyl xanthate occurs with alkyl–oxygen fission and isobutylene is a major product. The reaction is much faster than that of *n*-butyl xanthate, and the rate is proportional to the concentration of *tert*-butylxanthic acid up to 1 *M* HCl or $HClO_4$, but at higher hydrogen ion concentrations protonation of *tert*-butylxanthic acid increases the rate. The activation parameters for reaction of *n*-butyl- and *tert*-butylxanthic acid are, respectively, $\Delta H^* = 16.3$ and 18.1 kcal mol^{-1}, and $\Delta S^* = -8.4$ and 2 eu.

Monoalkyl xanthates and their derivatives are important in the cellulose industry and in mineral flotation.[2] The acid-catalyzed hydrolyses of ethyl xanthate have been examined by several workers,[4,5] and at pH >2 the first-order rate constant was proportional to the concentration of ethylxanthic acid. It has been suggested that an ion-pair complex of a proton and an alkyl xanthate ion is the reactive species,[6] but such an ion pair seems to be an improbable reactive intermediate and alternative formulations of a unimolecular mechanism are



$$\mathrm{RO\overset{S}{\overset{\|}{C}}SH} \longrightarrow \mathrm{RO\cdots\overset{S}{\overset{\|}{C}}\cdots S\cdots H} \longrightarrow \mathrm{ROH + CS_2}$$

or

$$\mathrm{RO\overset{S}{\overset{\|}{C}}SH} \rightleftharpoons \mathrm{R\overset{+}{O}(H)\text{—}\overset{S}{\overset{\|}{C}}\text{—}S^-} \longrightarrow \mathrm{ROH + CS_2}$$

I

Similar spontaneous unimolecular eliminations have been observed in decarboxylations[7] and hydrolysis of phosphate ester monoanions.[8] However, the evidence does not exclude the $A_{Ac}2$ mechanism of ether hydrolysis.[9]

The rate of hydrolysis of ethylxanthic acid reaches a maximum at *ca.* 0.5 *M* HCl and then decreases. This behavior was treated in terms of formation of a xanthic acid–hydronium ion association,[5] but Iwasaki and Cooke detected a new species spectrophotometrically when the acid concentration was >0.5 *M*, and they suggested that this was the unreactive protonated xanthic acid.[4b] However, similar rate maxima are very common in the acid hydrolysis of weakly basic substrates such as amides, and are explained, at least partially, in terms of decreasing water activity at acidities where the substrate is fully protonated.[10] Rate maxima are also observed in A2 hydrolyses of some weakly basic substrates, such as aryl phosphates[8] and phosphonates.[11] However, these reactions involve nucleophilic attack by water. In the hope of throwing more light on this problem, we used *n*-butyl and *tert*-butyl xanthate, because the ease of formation of the *tert*-butyl cation might introduce a new mechanism of hydrolysis,[12] with a change in the dependence of rate upon acidity. A few experiments were also made with ethyl xanthate.

Experimental Section

Materials. The potassium alkyl xanthates were prepared in the usual way by the reaction of CS_2 with the alkoxide ion in the alcohol or CS_2 as solvent.[13] They were purified by precipitation from the alcohol or acetone by addition of Et_2O followed by recrystallization.

Table I
Decomposition of *n*-Butyl Xanthate in Aqueous Acids[a]

[HCl], *M*	[HClO$_4$], *M*	$10^2 k_\psi$, sec^{-1} Obsd	$10^2 k_\psi$, sec^{-1} Calcd[c]
0.001		0.37	0.38
0.002		0.75	0.74
0.005		1.66	1.67
0.01		2.79	2.90
0.02		4.38	4.59
0.05		6.92	7.02
0.1		9.02	8.60
0.2		10.6	9.66
0.5		9.90	9.58
0.5		9.45[b]	9.58
	0.5	9.01[b]	8.95
1.0		9.05	8.63
1.0		8.70[b]	8.63
	1.00	7.71[b]	8.10
1.25		8.84[b]	8.52
	1.25	7.33[b]	7.65
1.5		8.42[b]	8.33
	1.5	6.13[b]	7.10
2.0		7.28	7.55
2.25		6.72[b]	7.05
	2.25	4.91[b]	5.10
2.5		6.48[b]	6.55
	2.5	4.39[b]	4.35
3.0		6.01[b]	5.55
	3.05	3.63[b]	3.01
4.0		3.93	3.55

[a] At 25.0°. [b] Stopped-flow measurements. [c] Calculated using $k = 0.11$ sec^{-1} and $K_a = 2.9 \times 10^{-2}$; and $K_a' = 14$ in HCl and 9 in HClO$_4$.

Table II
Reaction of *n*-Butyl Xanthate in Acidic Methanol[a]

10^3 [H$^+$], *M*	$10^2 k_\psi$, sec^{-1}
0.82	4.90[b]
0.96	4.85[c]
4.8	4.74
9.6	5.00[b]
19.0	5.08

[a] Followed at 301 nm at 25.0° in MeSO$_3$H–MeOH. [b] Mean of two values. [c] Mean of three values.

Methanesulfonic acid was purified by vacuum distillation, and freshly prepared solutions of it in dried MeOH were used.

Kinetics. The reaction was followed spectrophotometrically, usually at 25.0°, using a Gilford spectrophotometer for the slower reactions and a Durrum-Gibson stopped-flow spectrophotometer for the faster reactions, especially of *tert*-butyl xanthate. Under conditions in which the substrate is present as the xanthate ion the reaction was followed at 301 nm, but in acidic solution where the xanthic acid is present the reaction was followed at 270 nm. These wavelengths correspond to λ_{max} for xanthates and xanthic acids. Using the stopped-flow spectrophotometer we could observe the spectrum of *n*-butylxanthic acid formed by the rapid mixing of HCl and the potassium xanthate and observed λ_{max} 270 nm (ϵ 4520) in 0.05 *M* HCl in agreement with data for ethylxanthic acid in water and in CHCl$_3$.[14]

Ethyl and *n*-butyl xanthate are stable in neutral water, but *tert*-butyl xanthate slowly decomposes under these conditions and freshly made up solutions of it were always used.

The alkyl xanthate concentration was *ca.* 5×10^{-5} *M*, and the first-order rate constants, k_ψ, in reciprocal seconds, were calculated using the integrated first-order rate equation.

For experiments using the Gilford spectrophotometer a small amount of xanthate solution was added to the reaction solution using a square Teflon plunger. For reactions in the stopped-flow spectrophotometer, the xanthate in water was mixed with an equal volume of acid. Heat of dilution of the acid is apparently not causing a problem because rate measurements in both the Gilford and stopped-flow spectrophotometers agreed.

Products. The decomposition of *n*-alkyl xanthates in dilute aqueous acid gives the alcohol and CS$_2$.[4,5] The reaction of *n*-butyl xanthate in methanol containing methanesulfonic acid also gives CS$_2$ (as shown by its absorbance at 206 nm). For the reaction of *n*-butyl xanthate in aqueous 0.05 *M* HCl we identified *n*-butyl alcohol as the reaction product by glc (Carbowax 600 14 ft × 0.125 in. on Chromosorb W 60/80), and found no evidence for butene formation; however, the reaction of *tert*-butyl xanthate gave only a small peak for *tert*-butyl alcohol, and a large peak for isobutylene.

Results and Discussion

Variation of Rate Constant with pH. Our results with ethyl xanthate agree with earlier work,[4,5] and *n*-butyl xanthate behaves very similarly; and the rate–acidity profile fits the following scheme.

$$\mathrm{ROCS_2^-} + \mathrm{H^+} \underset{K_a}{\rightleftharpoons} \mathrm{ROCS_2H} \xrightarrow{k} \text{products}$$

Neglecting activity effects we obtain eq 1, which fits the data up to 0.5 *M* hydrochloric acid (Figure 1 and Table I).

$$k_\psi = k[\mathrm{H^+}]/(K_a + [\mathrm{H^+}]) \qquad (1)$$

The values for up to 0.5 *M* HCl (Table I) were calculated using $k = 0.11$ sec^{-1}, and $K_a = 2.9 \times 10^{-2}$ (measured spectrophotometrically).[15]

The relation between rate and pH is essentially the same for buffers and dilute HCl (Figure 1), with no evidence for general acid catalysis.

For methanesulfonic acid in methanol in the concentration range 1–20 × 10^{-3} *M* the first-order rate constant is independent of the acid concentration (Table II), suggesting that *n*-butylxanthic acid is much weaker in methanol than in water. The formation of CS$_2$ in this reaction confirms that the predominant mechanism of decomposition is a spontaneous elimination, because bimolecular attack would lead to ester exchange and would not be observed spectrophotometrically.

$$n\text{-BuO–S}_2\text{H} + \text{MeOH} \rightleftharpoons n\text{-BuOH} + \text{MeO–CS}_2\text{H}$$

tert-Butyl xanthate is much more reactive than the *n*-alkyl xanthates, although for dilute acid the rate–pH profiles are very similar (Figure 2). There are many examples

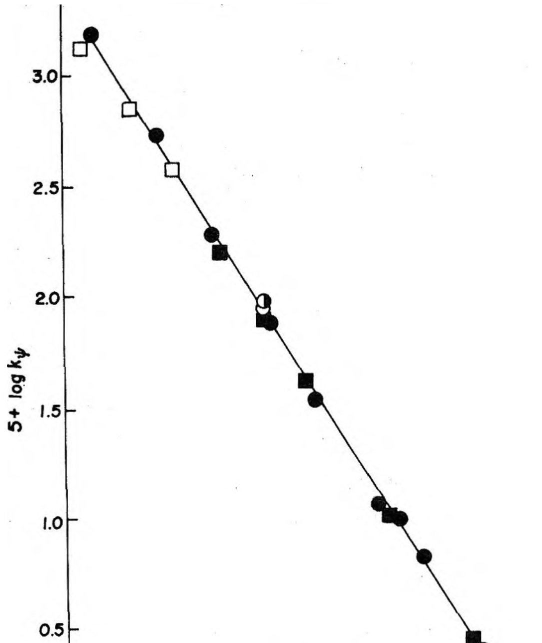


Figure 1. Variation of rate constant and absence of buffer catalysis for the hydrolysis of ethyl xanthate (circles) and *n*-butyl xanthate (squares) at 25.0°. The line is drawn with unit slope: ○, 0.1 *M* acetate; ●, 0.2 *M* acetate; ◑, 0.4 *M* acetate; □, dilute HCl; ■, acetate buffer.

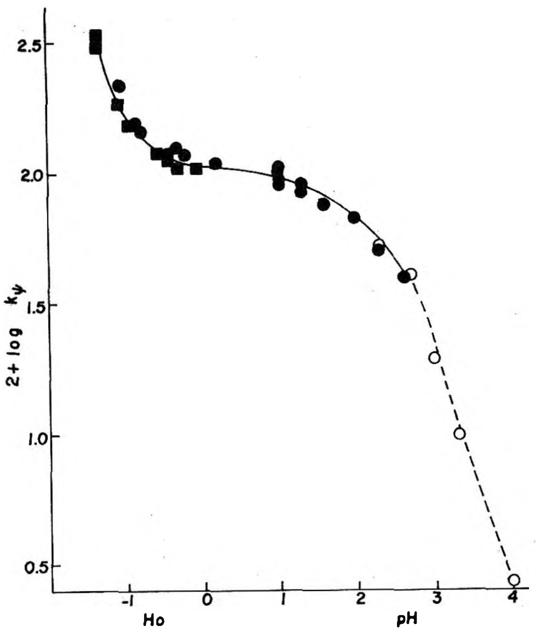


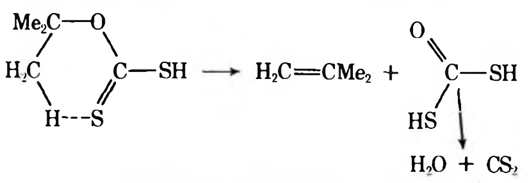
Figure 2. Variation of rate constant with acidity for the decomposition of *tert*-butyl xanthate at 25.0°. The broken line has unit slope. The data represented by solid points were obtained on a stopped-flow spectrophotometer, those represented by open points on a Gilford spectrophotometer: HCl, circles; $HClO_4$, squares.

of ester hydrolyses in which a *tert*-alkyl compound is much more reactive than the corresponding *n*- or *sec*-alkyl compound because of the ease of loss of *tert*-alkyl cations.[9,12] It is therefore tempting to suggest that *tert*-butyl xanthate reacts by an SN1 mechanism

$$t\text{-BuO-CS}_2^- \overset{H^+}{\rightleftharpoons} t\text{-BuO-CS}_2H \xrightarrow{\text{slow}} t\text{-Bu}^+ + \text{OCS}_2H^-$$

and the xanthate monoanion should be a reasonably good leaving group, especially in water.

The reaction of *tert*-butylxanthic acid in dilute acid gives largely isobutene, demonstrating alkyl oxygen fission in the decomposition. Xanthate esters pyrolyze to olefins, by a reaction which is probably a cyclic elimination,[16] although with some carbocation character in the transition state.[17] We could assume that the decomposition of *tert*-butylxanthic acid is similarly concerted with C-O bond breaking assisted by proton loss. Alternatively, we could



assume that an intimate ion pair is formed and then loses a proton either to the solvent or the counterion.[18] Sneen

$$Me_3C\text{-O-CS}_2H \rightleftharpoons [Me_3\overset{+}{C}\ \overset{-}{O}\text{-CS}_2H] \longrightarrow Me_2C{=}CH_2 + CS_2 + H_2O$$

and his coworkers have discussed these types of eliminations (*cf.* ref 19).

Reactions in Moderately Concentrated Acid. The rate maximum in the decomposition of ethylxanthic acid has been explained in terms of protonation of ethylxanthic acid to give an unreactive species.[4b] Alternative explanations are not particularly attractive; for example, there is no obvious reason why small changes in water activity should be important, or why hydronium or chloride ions of HCl should retard the reaction, because salt effects are small. Because it seemed probable that decomposition of *tert*-butylxanthic acid followed an SN1–E1 mechanism, we examined this reaction under conditions in which a protonated xanthic acid (II) should be present, because it should decompose with alkyl oxygen fission more readily than *tert*-butylxanthic acid.

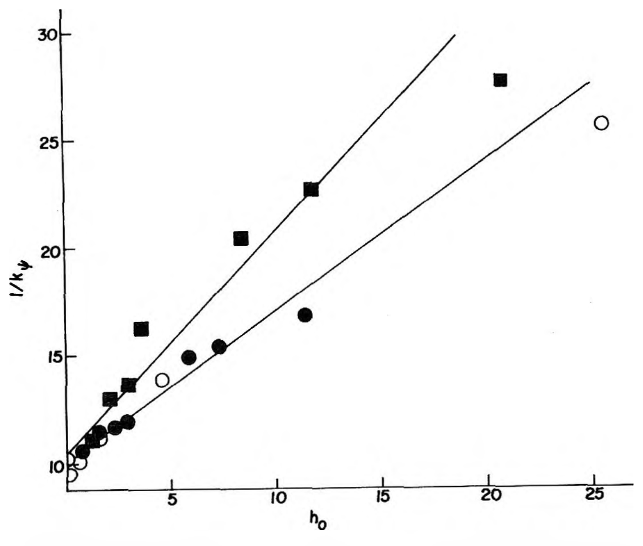
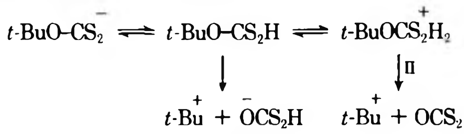


Figure 3. Relation between reaction rate and protonating power for hydrolysis of *n*-butyl xanthate in moderately concentrated acid. The points are calculated from the data in Table I and Figure 2: HCl, circles; $HClO_4$, squares. The solid points use data obtained on the stopped-flow spectrometer.



$$\begin{tikzcd}
t\text{-BuO-}\overset{-}{CS_2} \arrow[r, leftrightharpoons] & t\text{-BuO-CS}_2H \arrow[r, leftrightharpoons] \arrow[d] & t\text{-BuO}\overset{+}{CS_2}H_2 \arrow[d, "\text{II}"] \\
 & t\text{-}\overset{+}{Bu} + \overset{-}{O}CS_2H & t\text{-}\overset{+}{Bu} + OCS_2H_2
\end{tikzcd}$$

(In formulating these reactions we do not specify the position of the protons and we do not know whether isobutene is formed directly or from the *tert*-butyl cation because of the ease of interconversion of these species in strong acid.) The rate of decomposition of *tert*-butylxanthic acid increases sharply with acid concentrations greater than 0.5 *M* (Figure 2 and Table III), whereas that for *n*-butylxanthic acid decreases (Table I) as was found for ethylxanthic acid.[4,5] The most economical explanation for the different kinetic forms is that the decrease of the reaction rate of *n*-butylxanthic acid at hydrogen ion concentrations above 0.5 *M* is indeed due to protonation of the xanthic acid.

In this context we note that the rate decrease for *n*-butylxanthic acid at high acid concentrations is greater for perchloric than for hydrochloric acid (Table I) in accord with the greater protonating power of the former as shown by indicator measurements.[20]

For the decomposition of *tert*-butylxanthic acid at relatively high concentrations of perchloric or hydrochloric acid the situation is opposite to that observed with *n*-butylxanthic acid because the reaction rate in perchloric acid is faster than that in hydrochloric acid (Table III). This is in the expected direction in terms of protonating power of the acids,[20] and in addition it seems that perchloric acid is a more effective catalyst than hydrochloric acid for reactions in which carbocations are generated, probably because of favorable interactions between the carbocation and perchlorate ion.[21] However, the rates of decomposition of *tert*-butylxanthic acid are similar in media of the same protonating power as measured by $-H_0$.[20]

Quantitative Treatment of the Inhibition by Strong Acid. We assume that protonated *n*-butylxanthic acid cannot readily eliminate CS_2, and if protonation of the xanthic acid follows Hammett's acidity function[20] we obtain eq 2, where K_a' is the acid dissociation constant for

Table III
Decomposition of *tert*-Butyl Xanthate in Aqueous Acid[a]

$[H^+]$, *M*	HCl	$HClO_4$
0.05	0.85	
0.10	0.98	
0.50	1.08	1.03
1.00	1.12	1.14
1.25	1.23	1.20
1.50	1.17	1.19
2.25	1.44	1.53
2.50	1.56	1.82
3.00	2.16	
3.05		3.03
3.05		3.44

[a] Values of k_ψ at 25.0°, in reciprocal seconds.

Table IV
Kinetic Salt Effects on the Decomposition of *n*-Butyl Xanthate[a]

$[NaClO_4]$, *M*	0.001 *M* HCl	0.1 *M* HCl
	3.69	90.2
0.05	3.16	
0.08	2.70	
0.10	2.49	75.5
0.20	2.51	75.5

[a] Values of $10^3\ k_\psi$ at 25.0°, in reciprocal seconds.

Table V
Kinetic Salt Effects upon the Decomposition of *tert*-Butyl Xanthate[a]

[NaCl], *M*	$[NaClO_4]$, *M*	0.001 *M* HCl	0.1 *M* HCl
		1.94	9.8
	0.10	1.90	9.44
	0.20	1.60	10.1
0.20		1.89	
	0.40	1.57	8.90
0.40		1.40	
	0.60	1.65	
	0.80	1.79	
0.80		1.52	
	0.98	2.09	
0.98		1.45	

[a] Values of 10 k_ψ, at 25.0°, in reciprocal seconds.

Table VI
Temperature Effects[a]

	Alkyl group	
Temp, °C	*n*-Bu	*t*-Bu
9.4		3.19
14.7	0.13	
14.7	3.14[b]	
16.7		42.6[b]
20.0	0.22	
20.0	5.62[b]	
25.0	0.37	21.3
25.0	9.02[b]	98.5[b]
29.3	0.59	
29.3	12.9[b]	
31.9		210[b]

[a] Values of $10^2\ k_\psi$, in reciprocal seconds, in 10^{-3} *M* HCl unless specified. [b] In 0.1 *M* HCl.

Table VII
Activation Parameters[a]

	Alkyl group	
[HCl], *M*	*n*-Bu	*t*-Bu
10^{-3}	17.7 (3.5)	19.8 (18)
0.1	16.3 (−8.4)	18.1 (2)

[a] Values of ΔH^* are in kilocalories per mole; the values of ΔS^* in entropy units are in parentheses.

protonated *n*-butylxanthic acid and *k* is the first-order rate constant for decomposition of *n*-butylxanthic acid.[22]

$$\frac{1}{k_\psi} = \frac{1}{k} + \frac{h_0}{kK_a'} \qquad (2)$$

Equation 2 is followed reasonably well except that plots of k/k_ψ against h_0 curve at high acid concentrations (Figure 3). From these plots we calculate $k = 0.1\ \text{sec}^{-1}$ and $K_a' = 14$ for reaction in HCl and 9 in $HClO_4$. (The results for ethylxanthic acid[5] can be fitted to $K_a' \cong 10$, although they are too few to test the treatment.) The difference between the values of K_a' in the two acids is not at all unreasonable because there is no reason why the protonation of an alkylxanthic acid should exactly follow h_0, and there could be kinetic salt effects of the acids. These values are slightly larger than that of 7.68 calculated at 20° using "hydrogen ion activity."[4] The value of $k = 0.1\ \text{sec}^{-1}$ agrees with the value of $0.11\ \text{sec}^{-1}$ obtained from results at higher pH (Table I).

Kinetic Salt Effects. Kinetic salt effects are small. The decomposition of *n*-butyl xanthate is retarded by added sodium perchlorate (Table IV), and the retardation at pH 3 can be explained at least in part by increased acid dissociation of *n*-butylxanthic acid; this explanation is consistent with the smaller salt effect at pH 1. At pH 3 the decomposition of *tert*-butyl xanthate is inhibited by sodium chloride, although for sodium perchlorate we observed a rate minimum (Table V). These observations are consistent with the assumption that here the net effect is that of increased acid dissociation of *tert*-butylxanthic acid, and stabilization of a cationoid transition state, especially by perchlorate ion.[21] Transition-state stabilization would become relatively more important with decreasing pH.

Activation Parameters. Values of entropies of activation are useful mechanistic criteria for acid-catalyzed hydrolysis, and generally activation entropies are zero or positive for A1 hydrolyses of weakly basic substrates and 20–30 eu more negative for A2 hydrolyses.[23]

The rate constants for decomposition of *n*- and *tert*-butyl xanthates at various temperatures are given in Table VI. For reactions in 10^{-3} *M* HCl where the xanthate ion is the predominant species the entropies of activation (Table VII) are calculated from the second-order rate constants, but in 0.1 *M* HCl the xanthic acid is the predominant species and the entropies are then calculated from the observed first-order rate constants. (To this extent the two sets of data are not directly comparable.) Although the mechanistic test based on entropies of activation is generally applied to acid-catalyzed hydrolyses, the values which we observe are reasonable for reactions which involve spontaneous heterolysis.[23] The values of ΔS^* are more positive for reactions of *tert*-butyl xanthate, which is understandable because the transition state for decomposition of *n*-butylxanthic acid could have a structure close to that of the dipolar species (I), and should therefore be more strongly hydrated than the transition state for decomposition of *tert*-butylxanthic acid, which should be similar to a carbocation–anion pair. The enthalpies of activation are slightly larger for *tert*-butyl than for *n*-butyl xanthate, as expected if decomposition of the latter involves loss of a carbocation. The values of ΔS^* are more positive for reaction in 10^{-3} *M* than in 0.1 *M* HCl for both esters, and this difference should be related to the entropy of protonation of the alkyl xanthate ions, and therefore be relatively independent of the nature of the alkyl group.

Registry No.—*n*-Butyl xanthate, 110-50-9; *tert*-butyl xanthate, 21807-44-3.

References and Notes

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Acid Chloride Chemistry. I. Phosgenation of Carboxylic Acids, a Catalyst Screening Study[1]

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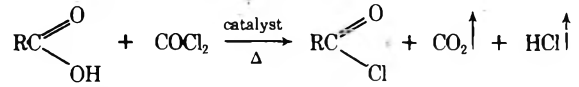
Imidazoles and several related structures with a $-\ddot{X}-Y{=}Z-$ system have been found to be excellent catalysts for phosgenation of lauric acid to lauroyl chloride. In contrast to carboxamide catalysts, imidazole can be recycled from batch to batch without appreciable loss of catalytic activity.

Over the past several decades the catalyzed phosgenation of carboxylic acids has become a prime preparative method (eq 1). Tertiary amines,[2] and more recently carboxamides,[3] have been used as catalysts for this phosgenation reaction. Both catalyst types, however, have restrictions which limit their large-scale application. Catalysis by tertiary amines[2] usually requires a reaction temperature in excess of 120°. Yields are variable, depending upon amine and type of carboxylic acid. Catalysis by carboxamides[3] normally provides high yields at reaction temperatures below 100°. Once the substrate acid has been consumed, however, the carboxamide-derived catalyst decomposes to nonactive tar. The tar can foul equipment[4] and has no catalytic value upon recycle to subsequent reactions.



$$RC(=O)OH + COCl_2 \xrightarrow[\Delta]{\text{catalyst}} RC(=O)Cl + CO_2\uparrow + HCl\uparrow \qquad (1)$$

An ideal phosgenation catalyst should provide acid chlorides in high yield from an assortment of carboxylic acids at moderate reaction temperature and short residence time. Moreover, it should maintain its activity upon recycle with reaction residues from one batch reaction to another. We have found a number of catalysts which fit this description.

Results and Discussion

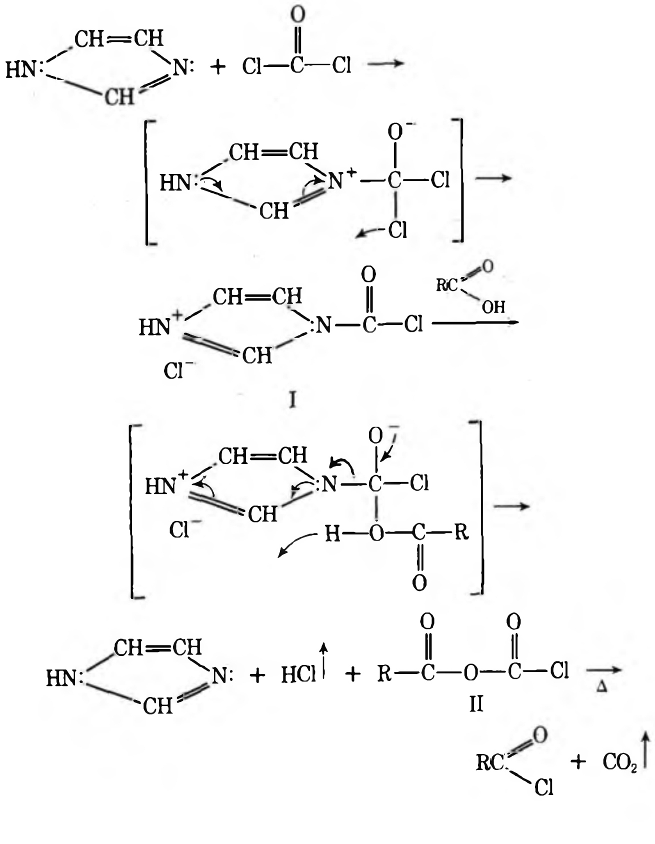
A large number of compounds have been tested as catalysts for the phosgenation of lauric acid to lauroyl chloride. The results of a number of these experiments are recorded in Table I. The catalysts in group A are five-membered heterocyclic compounds containing nitrogen, oxygen, or sulfur atoms adjacent to a carbon–nitrogen double bond. Most of these materials are excellent phosgenation catalysts, providing yields of lauroyl chloride in excess of 90% at reaction temperatures of less than 100°. Group B catalysts are six-membered heterocyclic compounds containing nitrogen, oxygen, or sulfur atoms adjacent to carbon–nitrogen unsaturation. Of those selected, the six-membered heterocyclics were less effective catalysts than the five-membered species. Group C is composed of compounds containing carbon–nitrogen unsaturation. The effectiveness of these materials for conversion of lauric acid to lauroyl chloride varies from excellent to essentially nil. This effectiveness is seen with the series of Schiff bases, isobutylidene-*n*-butylamine, *N*-benzylidenemethylamine, and *N*-benzylideneaniline, wherein the yield of lauroyl chloride varies inversely with aromatic substitution on the carbon–nitrogen double bond. Group D consists of isocyanates and compounds of carbon–carbon unsaturation. *n*-Butyl isocyanate provided an excellent yield of lauroyl chloride, whereas the aromatic specie did not. Carbon–carbon unsaturation provided poor conversion to lauroyl chloride, except for the enamine, 1-dimethylamino-2-methylpropene.

Carbon–nitrogen unsaturation, and in one case nitrogen–nitrogen unsaturation, is present in each compound in Table I which showed high catalytic activity. Usually, this unsaturation is adjacent to an atom possessing an available pair of electrons, the combination of which form the structure $-\ddot{X}-Y{=}Z-$. This XYZ structure is apparently responsible for the observed catalytic activity. Using

Table I
Phosgenation of Lauric Acid to Lauroyl Chloride[a]

Registry no.	Catalyst	Temp, °C	Phosgene consumed, mol %[b]	Yield, %[c]
	Group A			
	1-Butyl-4- (or 5-)methyl-1,2,3-triazole	66–91	100	96.6
143-07-7	2-Benzothiazole	88–95	103	96.4
112-16-3	Imidazole[f]	90–99	102	94.5
26588-27-2	2,5-Dimethyl-1,3,4-oxadiazole	82–100	97	93.8
95-16-9	1,2-Dimethylimidazole	90–105	99	93.0[e]
288-32-4	2-Methylimidazole	90–98	96	90.9
13148-65-7	2-Methylimidazole hydrochloride	93–98	75	69.8
1739-84-0	2-*n*-Butylimidazole	84–94	97	90.0
693-98-1	3,5-Dimethylpyrazole	90–98	93	88.5
36443-78-4	3,5-Dimethylisoxazole	93–103	90	82.9
50790-93-7	2-Thiazoline-2-thiol	94–106	86	77.4
	Group B			
67-51-6	1,5-Diazobicyclo[5.4.0]undec-5-ene	73–105	102	96.0
300-87-8	1,3,5-Triethyltriazine	93–90	103	94.5
96-53-7	Quinoxaline	91–100	92	88.9
6674-22-2	Phenazine	73–94	95	88.2
1009-74-1	Pyridazine	84–100	76	67.1
91-19-0	Pyrimidine	90–100	56	50.9
	Group C			
92-82-0	Isobutylidene-*n*-butylamine	66–94	100	93.0
289-80-5	Bicyclohexylcarbodiimide	78–99	97	95.5
289-95-2	*N*-Benzylidenemethylamine	88–102	70	61.8
6898-75-5	Acetone oxime	87–92	64	57.4
538-75-0	*N*-Benzylideneaniline	90–126	<10	*d*
	Group D			
622-29-7	*n*-Butyl isocyanate	98–100	103	97.8
127-06-0	1-Dimethylamino-2-propene	88–101	101	94.5
111-36-4	Toluene diisocyanate	85–100	66	70.6
2155-94-4	Tetravinylsilane	97–106	50	46.2
1321-38-6	Isobutyl vinyl ether	81–123	<10	*d*
1112-55-6	1-Hexyne	90–109	<10	*d*

[a] Unless otherwise specified 2.0 mol % catalyst based on acid was used. [b] Calculated from averaged flowmeter readings, and presented as mole per cent based on acid. [c] Yields based on lauric acid and 100% conversion of acid to acid chloride. Products distilled directly from completed reaction mixture was generally 99.0–100.5% pure as measured by Mohr (inorganic) chloride analysis. [d] Observed very sluggish reaction. Product not isolated. [e] A flocculant precipitate, apparently a complex of catalyst and acid chloride, was observed in the distilled product. [f] Used 0.5 mol % catalyst based on acid.



imidazole as the model, the depicted mechanism can be written for the catalyzed phosgenation of carboxylic acids to acid chlorides.

This mechanism shows the catalyst as the activator for phosgene in its reaction with carboxylic acid. Imidazole and phosgene yield reactive specie I, which reacts with carboxylic acid to yield acyl chloroformate (II), hydrogen chloride, and catalyst. Acyl chloroformate (II) decomposes at reaction temperature to yield acid chloride and carbon dioxide. Whether the catalyst is complexed with hydrogen chloride is a moot point. As seen in Table I, phosgenation in the presence of 2-methylimidazole is significantly more complete than in the presence of the preformed hydrochloride salt (2-methylimidazole hydrochloride). This data implies that catalyst is not complexed with hydrogen chloride.

The decomposition of the acyl chloroformate is perhaps the rate-determining step. Carbon dioxide is evolved from the reaction mixture at 90–100° following cessation of phosgene feed and hydrogen chloride evolution (see Experimental Section). This evolution indicates the decomposition of an intermediate after the last point at which hydrogen chloride is evolved. This phenomenon was observed with acids of acidities different from that of lauric acid, for instance benzoic and chloroacetic acids.[5]

For Schiff bases, the ease with which phosgene reacts with nitrogen of the carbon–nitrogen unsaturation, and subsequently the yield of acid chloride, should depend upon the ability of the adjacent groups to stabilize the resulting quaternary charge. The all-aliphatic, the aliphatic–aromatic, and the all-aromatic structures (see Table I) provided respective yields of lauroyl chloride of 93.0, 61.8, and <10%. This order of catalytic activity is in keeping with capacity to stabilize the quaternary charge, although steric factors associated with the aromatic groups may also contribute to decreasing activity within the series.

Recycle of Reaction Residues. A significant failure of carboxamide catalysts is the loss of activity once the substrate acid has been consumed.[4] Imidazole, and many of the other catalysts listed in Table I, retain their activity upon consumption of acid. The reaction residues remaining after product distillation can be recycled as useful catalyst for subsequent phosgenations. Data illustrating recycle experiments using imidazole as catalyst and lauric acid as substrate are shown in Table II.

Imidazole, in 0.5 mol % concentration based on acid, was used as catalyst in experiment 1. Upon complete reaction (see Experimental Section), the acid chloride product was removed by distillation under vacuum, and fresh lauric acid was added to the distillation residue. The phosgenation was repeated and the lauroyl chloride was collected as before. The process was repeated a third time. Although catalyst was added only to the initial charge, no difference in rate of reaction or yield and purity of lauroyl chloride was observed throughout the recycle series.

Table II
Preparation of Lauroyl Chloride *via* Recycle of Imidazole Catalyst in Reaction Residues[a]

Expt. no.	Catalyst added[b]	Temp, °C	Time, hr	Phosgene consumed, mole %[c]	Yield, %[d]
1	0.5	89–98	5.0	101	93.4
2	0.0	88–100	5.0	97	93.8
3	0.0	84–97	5.0	99	92.9
					93.4[e]

[a] Lauric acid (1.0 mol) phosgenated neat with 0.5 mol % imidazole catalyst in expt 1. In each succeeding experiment, 1.0 mol of acid was added to distillation residue of the previous reaction. [b] Mole per cent imidazole added during reaction, as based on 1.0 mol of acid added wth each experiment. [c] Calculated from averaged flowmeter readings, and presented as mole per cent based on acid. [d] Calculations based upon lauric acid and 100% conversion of acid to acid chloride. Products distilled directly from completed reaction mixture were of 99.4–100.0% pure as measured by Mohr (inorganic) chloride analysis. [e] Presented as overall yield.

Experimental Section

Typical Phosgenation Experiment. A 500-ml, round-bottomed flask is fitted with a paddle stirrer, a gas inlet tube, a thermowell, and a Dry Ice–acetone deflamator (Dry Ice condenser). The flask and fittings are arranged so that gaseous phosgene could be fed below the surface of the stirred, reacting medium, and that phosgene escaping from the hot medium could be condensed on the Dry Ice–acetone deflamator and returned directly to the medium as a liquid. The deflamator is connected to two Dry Ice–acetone traps in series, the traps are connected to a water scrubber, and the scrubber is open to the atmosphere within the confines of a fume hood. (Caution! Phosgene is not sufficiently irritating at time of exposure to give warning of lethal amounts.) As by-products, hydrogen chloride and carbon dioxide are evolved from the reaction medium; they pass up through the deflamator, through the Dry Ice–acetone trap, and into the top of the water scrubber. In the scrubber, the gases react with a steady stream of water and pass down through a long glass column (4 ft) packed with glass beads. If the rate of phosgenation is too rapid, *i.e.*, an excessive reaction temperature, etc., phosgene entrained in the by-product gases will not be adequately condensed by the deflamator and began to appear in the Dry Ice–acetone trap. To this end, the incorporation of these traps in the off-gas system helps to establish facile reaction conditions.

The flask is charged with lauric acid (200 g, 1.0 mol) and catalyst (2.0 mol %, based on acid), and the mixture is heated with stirring to 90°. The stirred mixture is maintained at 90° for 1 hr, at which time gaseous phosgene (cylinder) is added below the surface of the liquid at a rate necessary to maintain a gentle phosgene reflux from the deflamator. Phosgene addition is regulated and calculated *via* a tubular flowmeter. Reaction is continued, generally within the range of 80–100°, until hydrogen chloride ceases to be evolved (cessation of heat generation at top of water scrubber). Phosgene feed is stopped and the reaction is held at 85–95° with gentle phosgene reflux from the deflamator until evolution of carbon dioxide ceases (30–60 min, as evidenced by cessation of gas at base of scrubber column). Occasionally, additional phosgene is required during this period to maintain phosgene reflux and to complete the reaction.

Following complete reaction, the deflamator is replaced by a 10-in. glass helix packed distillation column fitted with a total reflux head, and dissolved phosgene is removed from the stirred reaction product by sparging at 90° with dry nitrogen for 2 hr. The product is distilled at 10 mm as a single fraction.

The product is analyzed for contained chlorine *via* the Mohr (inorganic) chloride analysis (titration of chloride ion with silver nitrate solution).

Registry No.—$COCl_2$, 75-44-5.

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Kinetics of Proton Transfer Reactions in Aqueous Solution. Alkyl Structural Effect on CH Acids Systems[1]

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The position of the tautomeric keto-enol equilibrium in aqueous solution was studied for the compounds $CH_3COCHRCO_2C_2H_5$ (R = H, CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, i-C_3H_7, s-C_4H_9) by the T-jump relaxation technique under alkaline conditions of catalysis: $EH + OH^- \rightleftharpoons E^- + H_2O \rightleftharpoons CH + OH^-$. The kinetics is characterized by two relaxation times, one in the microsecond range, corresponding to the enol reactivity, and the other in the millisecond range, corresponding to the ketone reactivity. In all cases, the slow relaxation time has been measured. Only for R = H and a substituted compound presenting a similar enol structure (ethyl 2-hydroxycyclohexenecarboxylate) is there a sufficiently high enol content to allow the measurement of the fast relaxation time. Results show that the alkyl substituent effect on the enol content and the ketone acidity and deprotonation rate is large. The α-alkyl substituent effect on the enol form is often explained as being steric in nature. Although we do not completely reject this hypothesis, we present a number of arguments in favor of an electronic effect on the keto form.

Our knowledge of the keto-enol interconversion in aqueous media of β-keto esters bearing alkyl groups in the α position is particularly limited. These compounds ($CH_3COCHRCO_2C_2H_5$ series), which exist in both keto and enol forms, are weak acids dissociating according to the following scheme.

$$\text{Ketone (CH)} + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{Enolate } (E^-) + H_3O^+ \quad K_{CH} = k_1/k_2$$

$$\text{Enol (EH)} + H_2O \underset{k_4}{\overset{k_3}{\rightleftharpoons}} \text{Enolate } (E^-) + H_3O^+ \quad K_{EH} = k_3/k_4 \tag{1}$$

The overall change may be represented as follows.

$$\text{Ketone} \overset{K_T}{\rightleftharpoons} \text{Enol} \qquad K_T = \frac{[EH]}{[CH]} = K_{CH}/K_{EH} \tag{2}$$

The equilibrium constant (K_T = 0.0039 at 20 ± 1°) for the first member of the series, R = H, was measured by Schwarzenbach and Felder.[2] In this case the keto-enol equilibrium strongly favors the keto form. By an indirect method these authors determined the acidity constants of this same compound at 20 ± 1°: $pK_{CH} = 10.49$ and $pK_{EH} = 8.09$. Their method, generally applicable to β-dicarbonyl compounds, allows a calculation of K_{EH} and K_{CH} from the overall acidity ($K_g = [E^-][H_3O^+]/[EH] + [CH]$) and the enol content, according to the following equations.

$$K_{CH} = K_g(1 + K_T) \cong K_g(\text{for } K_T \ll 1) \tag{3}$$

$$K_{EH} = K_g(1 + 1/K_T) \tag{4}$$

Rumpf and Reynaud,[3] identifying the overall acidity with that of the keto form, determined the K_{CH} acidity constants at ambient temperature for R = H, CH_3, C_2H_5, and n-C_4H_9. These values are given in the last column of Table I. They demonstrate an attenuation of the degree of ionization of the keto form as the chain length of R increases. Owing to experimental difficulties the authors were unable to measure the acidity constants for secondary R groups.

From the reactivity of enol toward bromine, Eidinoff[4] as well as Pearson and Mills[5] has measured k_1 for R = H and C_2H_5 (1.2×10^{-3} and 7.5×10^{-6} sec^{-1}, respectively). From determination of K_{CH}, these authors were able to calculate k_2 (5.8×10^7 and 3.8×10^7 M^{-1} sec^{-1}, respectively). These results show that the k_2 constant is not sensitive to the structural effect produced by replacing H by C_2H_5. On the other hand, the ionization constant (k_1) is considerably diminished by the same structural change.

Apart from their structures, the keto form belongs to the class of CH acids while the enol form belongs to that of acids possessing an intramolecular hydrogen bond. From observation of acid reactivity toward bases, Eigen[6] has shown that it is possible to classify the former either in terms of the two classes cited above or as normal acids. We may represent the acid-base transformation as follows.

$$AH + B \underset{k_r}{\overset{k_f}{\rightleftharpoons}} A^- + BH^+ \tag{5}$$

When the equilibrium lies far to the right, it is possible to use the k_f value to classify acids according to these three categories (Figure 1). The order of magnitude of k_f for normal acids is 10^{10} M^{-1} sec^{-1}. This corresponds to the diffusion limit. For acids with an internal hydrogen bond, the ionization reaction is rendered more difficult by the fact that the proton is bound up in this bond. A measurement of k_f constitutes a kinetic means of evaluating the strength of the internal hydrogen bond. In certain cases (*e.g.*, the presence of electron-attracting groups in the vicinity of the acidic hydrogen) the reactivity of CH acids extends into the range of rapid reactions, but does not reach the diffusion limit. There are relatively few kinetic studies of CH acids by fast kinetics methods. However, this area is of great importance since it concerns carbanion formation, vital to organic synthesis.

A complete kinetic study of the keto-enol interconversion of β-dicarbonyls would be very difficult using classical methods but becomes possible using the fast kinetics methods (Figure 1); and this can be a good indirect method to derive in turn the K_T values not easily attainable by direct measurements. Such a study will be carried out on a series of β-keto esters $CH_3COCHRCO_2C_2H_5$ (where R = alkyl) so as to specify the influence of the alkyl groups on the degree of enolization in aqueous media, and to discuss the thermodynamic stabilities of the tautomeric forms.

Experimental Section

Solvent and Reagents. Rate and equilibrium constants have been determined in doubly distilled water. The salts used to adjust the ionic strength, NaBr and $NaClO_4$, were recrystallized, dried, and stored in a desiccator. The β-keto esters were purified by glpc (DEGS and XF 1150 columns) at very low injection temperatures, in order to avoid any decomposition. The final purity was checked by the same method and in every case was better than 99.5%.

Rate Constant Measurement. The stock solutions were pre-

Table I
Rate Constants for the Acid–Base Equilibrium of the Keto Form $CH_3COCHRCO_2C_2H_5$. Ketone Acidity

Init concn, M^{-1}	pH	τ_{32}, sec^{-1}	k_{32}, M^{-1} sec^{-1}	k_{23}, sec^{-1}	pK_{CH}
		I. $CH_3COCH_2CO_2C_2H_5$			
	12.01	87.5			
	12.02	80			
	11.92	67			
	11.82	64			
$\sim 4 \times 10^{-5}$	11.57	29.5			
	11.53	33.5	6.7×10^3	3.0	10.65[a]
	11.36	18			10.49[b]
	11.36	16			10.68[c]
	11.33	16			10.81[d]
	10.52	5.5			10.90[e]
	10.00	4			10.64[f]
		II. $CH_3COCH(CH_3)CO_2C_2H_5$			
	12.92	12.8			
	12.83	10.5			
$\sim 1.4 \times 10^{-4}$	12.72	9.1			
	12.58	6.25	1.07×10^2	1.8	12.25[a]
	12.52	5.6			12.59[e]
	12.26	4.2			12.42[f]
	11.96	3.0			
		III. $CH_3COCH(C_2H_5)CO_2C_2H_5$			
	13.06	11.1			
	12.97	9.5			
	12.90	8.35			
	12.78	5.9			
	12.74	7.1			
$\sim 1.3 \times 10^{-4}$	12.70	4.65	6.4×10^1	1.9	12.50[a]
	12.53	4.3			12.93[e]
	12.27	3.5			12.87[f]
	12.16	2.2			13.01[f]
					12.74[g]
		IV. $CH_3COCH(n\text{-}C_3H_7)CO_2C_2H_5$			
	12.84	6.30			
	12.81	5.90			
	12.75	5.55			
$\sim 2.4 \times 10^{-4}$	12.68	4.00			
	12.56	3.30	5.3×10^1	1.3	12.40[a]
	12.42	2.40			12.98[e]
	12.31	2.30			
	12.24	2.20			
	12.07	2.00			
		V. $CH_3COCH(n\text{-}C_4H_9)CO_2C_2H_5$			
	12.94	4.50			
	12.85	3.45			
$\sim 2.2 \times 10^{-4}$	12.72	3.20			
	12.65	2.90	3.1×10^1	1.45	12.70[a]
	12.50	2.60			13.04[e]
	12.25	2.20			13.20[f]
	12.09	2.05			
		VI. $CH_3COCH(i\text{-}C_3H_7)CO_2C_2H_5$			
	13.08	12.3			
	12.84	9.35			
$\sim 1.7 \times 10^{-3}$	12.71	9.8			
	12.58	9.1			
	12.40	7.15	2.2×10^1	8	13.5[a]
	12.23	8.0			13.24[e]
	12.06	8.35			>15[f]
		VII. $CH_3COCH(sec\text{-}C_4H_9)CO_2C_2H_5$			
	12.90	4.35			
$\sim 1.6 \times 10^{-3}$	12.72	3.60			
	12.50	3.10	1.95×10^1	2.7	13.1[a]
	12.39	3.20			13.31[e]
	12.16	3.30			

[a] Our values. [b] See ref 2. [c] See ref 4. [d] W. Walisch and H. A. Ruppersberg, *Chem. Ber.*, **92,** 2622 (1959). [e] These values have been calculated from the equation $pK_{CH} = 12.59 - 3.44\sigma^*$; see ref 17. [f] See ref 3. [g] See ref 5.

pared by injecting, with a microsyringe, a small quantity of pure β-keto ester in an aqueous solution. The ionic strength was adjusted by using $NaClO_4$; 100 ml of each stock solution was prepared in a graduated flask in order to perform five to six kinetic runs.

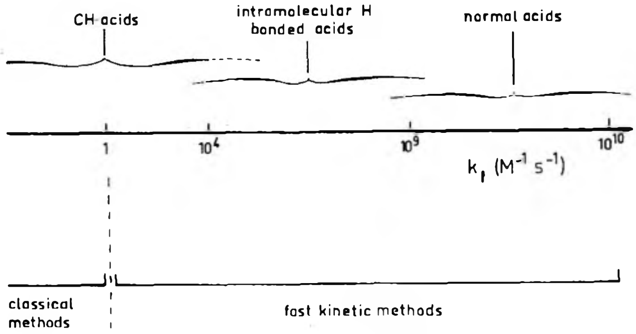


Figure 1. Types of acids according to their rates of ionization, k_f (OH^- as base).

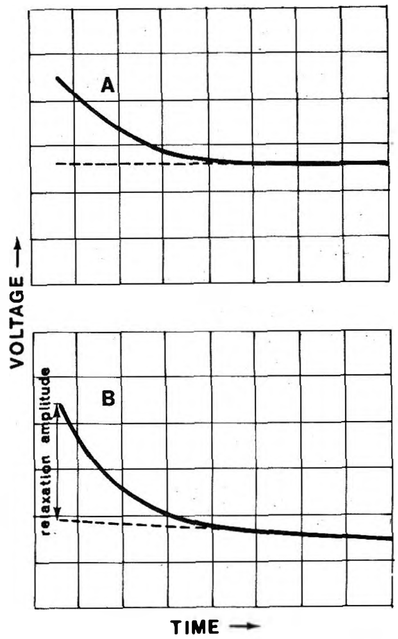


Figure 2. Slow relaxation time (compound III): A, scope 50×10^{-3} V and 0.2 sec, pH 12.27; B, scope 20×10^{-3} V and 0.2 sec, pH 12.70.

For each kinetic run the pH was adjusted to the desired value by injecting with a microsyringe a predetermined amount of a 1 *N* alkali solution. The pH was measured with a Beckman Research type pH meter at 25°. The alkaline glass electrode used operates in the range 0–14 without correction. All solutions were 0.1 *M* in $NaClO_4$. In this way relaxation times have been determined at different ionic strength varying from about 0.1 (pH lower than 12) to about 0.2 (pH near 13). The effect of this ionic strength variation on the rate constant was experimentally found to be extremely weak and to lie within the experimental error.

The solution to be investigated was then transferred into the T-jump cell. In order to prevent any carboxylation the cell was hermetically sealed by use of a plastic film.

After the T-jump experiment, the final pH was checked again directly in the cell. pH variations during the relaxation experiment did not exceed 0.05 pH unit.

Relaxation experiments were carried out using a commercial T-jump apparatus[7] (Messanlagen Studiengesellschaft, Göttingen, Germany). Unexpected oscillations due to the light source instability (Osram lamps XBO and HBO) were suppressed by using a second photomultiplier between the cell and the monochromator. Satisfactory reproducibility was obtained in the millisecond range. The final temperature after the T-jump was 25°. The kinetic analysis was performed at a wavelength corresponding to the maximum absorption of the enolate ion, 280 nm. The given relaxation times represent the average of five to six values.

At high pH (pH > 12.5), the decomposition of the keto ester was observed in competition with the slow chemical relaxation time. This produces a continuous decrease of the enolate ion absorbance. The hydroxide ion concentration does not vary, since the overall β-keto ester concentration is much smaller. The calculation of the relaxation time takes account of this by a graphical method shown in Figure 2B. In this way the measured relaxation times and the rate constants are not affected by the decomposition.

Equilibrium Constant Measurement. The enol content was determined by the enol reactivity toward bromine. This method is based on the assumption that bromination is much more rapid than the keto–enol transformation. The bromine concentration was electrochemically measured by means of a couloamperometric apparatus described elsewhere.[8] Experiments were performed at 25°, in acidic aqueous solution at a 0.1 constant ionic strength by use of NaBr. The experimental error reaches 10%, essentially owing to the imprecise determination of the titration end point.

Spectroscopic Data. Nuclear magnetic resonance spectra of the pure liquids were recorded, at 27°, on a JEOL JNM PS 100 spectrometer. The high sensitivity of this apparatus allowed the detailed analysis of the enol signal. Tetramethylsilane was used as internal standard.

Calculation of Relaxation Times

The keto–enol transformation catalyzed by the hydroxide ion is shown in the following equation.

$$\underset{1}{\text{Enol}} + \text{OH}^- \underset{k_{21}}{\overset{k_{12}}{\rightleftharpoons}} \underset{2}{\text{Carbanion–Enolate}} + \text{H}_2\text{O} \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} \underset{3}{\text{Ketone}} + \text{OH}^- \qquad (6)$$

Equation 6 is generally characterized by two relaxation times, τ_{12} and τ_{32}.[7] If one of these equilibria is much more rapid than the other, a simple analytical expression can be derived for τ_{12} and τ_{32} from the kinetic and equilibrium data.

If the enol content is very small, the acidity of the enol form is much stronger than that of the keto form and eq 3 and 4 reduce to

$$\text{p}K_{\text{EH}} \ll \text{p}K_{\text{g}} \text{ and } \text{p}K_{\text{CH}} \cong \text{p}K_{\text{g}} \qquad (7)$$

Thus the relaxation time τ_{12} is related to the fast enol–enolate equilibrium.

$$\tau_{12}^{-1} = k_{21} + k_{12}([\overline{\text{OH}^-}] + [\overline{\text{EH}}]) \qquad (8)$$

This classical result means that the rapid equilibrium is not disturbed by the slow one.

τ_{32} is given by considering the rate equation of the keto form CH.

$$\frac{\text{d[CH]}}{\text{d}t} = -k_{32}[\text{CH}][\text{OH}^-] + k_{23}[\text{E}] \qquad (9)$$

Instantaneous concentrations are expressed by

$$[\text{CH}] = [\overline{\text{CH}}] + \delta[\text{CH}] \qquad (10)$$

$$[\text{E}] = [\overline{\text{E}}] + \delta[\text{E}] \qquad (11)$$

$$[\text{OH}^-] = [\overline{\text{OH}^-}] + \delta[\text{OH}^-] \qquad (12)$$

$[\overline{\text{CH}}]$, $[\overline{\text{E}}]$, and $[\overline{\text{OH}^-}]$ being equilibrium concentrations.

Equation 9 becomes

$$\frac{\text{d}\delta[\text{CH}]}{\text{d}t} = -k_{32}([\overline{\text{CH}}] + \delta[\text{CH}])([\overline{\text{OH}^-}] + \delta[\text{OH}^-]) + k_{23}([\text{E}] + \delta[\text{E}]) \qquad (13)$$

By considering the fast equilibrium constant K_1 from eq 6, one obtains for eq 13

$$\frac{\text{d}\delta[\text{CH}]}{\text{d}t} = -\delta[\text{CH}][k_{32}([\overline{\text{OH}^-}] + \alpha[\overline{\text{CH}}]) + k_{23}\alpha] \qquad (14)$$

$$\alpha = \frac{K_1[\text{OH}^-]}{1 + K_1([\overline{\text{EH}}] + [\overline{\text{OH}^-}])}$$

In eq 14, the term between brackets corresponds to the relaxation time τ_{32}.

$$\tau_{32}^{-1} = k_{23}\alpha + k_{32}([\overline{\text{OH}^-}] + \alpha[\overline{\text{CH}}]) \qquad (15)$$

α takes into account the influence of the fast equilibrium. Typical experimental data concerning compound II allow the determination of α.

$$[\overline{\text{OH}^-}] = 2 \times 10^{-2}\,M \quad [\overline{\text{EH}}] = 4 \times 10^{-7}\,M \quad [\overline{\text{E}}] = 7 \times 10^{-5}\,M$$

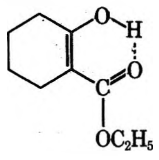
$$\alpha = 0.995$$

Taking α equal to 1, with an approximation better than 1%, eq 15 becomes eq 16.

$$\tau_{32}^{-1} = k_{23} + k_{32}([\overline{\text{CH}}] + [\overline{\text{OH}^-}]) \qquad (16)$$

This unexpected result leads to the interesting conclusion that both relaxation times are dependent solely on the corresponding equilibrium.

Unfortunately, the observation of the rapid phenomenon is extremely difficult when compounds have a low enol content. In this series τ_{12} could only be measured for acetoacetic ester.[9] We also obtained τ_{12} for a β-keto ester showing a highly analogous enolic structure: ethyl 2-hydroxycyclohexenecarboxylate (enol content about 2%).[10]



Rate constants were obtained by plotting τ_{32}^{-1} (or τ_{12}^{-1}) *vs.* hydroxide ion concentration. The slope gives k_{32} (or k_{12}) and the intercept k_{23} (or k_{21}). Experimental error is of the order of 10% for k_{12} and k_{32} and 20% for k_{21} and k_{23}.

Results

A typical example of the slow relaxation curve is shown in Figure 2A. In strong alkaline solutions the enolate ion and the ketone concentrations decrease continuously because of decomposition. This phenomenon is accompanied by a decrease of the total amplitude of the relaxation curve. For instance, after a delay of about 10 min, decomposition of compound III is so important that observation of the relaxation curve is no longer possible. Rate constants are shown in Table I.

For compounds VI and VII, the observed relaxation times show poor sensitivity to hydroxide ion concentration. In fact, by varying this concentration by a factor of 10, τ_{32}^{-1} decreases from 9.35 to 8.35 sec^{-1} (VI) and from 4.35 to 3.30 sec^{-1} (VII). This is related to a continuous decrease of the difference between k_{32} and k_{23} which makes k_{23} no longer negligible with respect to k_{32}.

The keto form acidity (pK_{CH}) is given by

$$K_{\text{CH}} = 10^{-14}\frac{k_{32}}{k_{23}} \qquad (17)$$

This equation is derived by setting

$$\frac{k_{32}}{k_{23}} = \frac{[\text{E}]}{[\text{CH}][\text{OH}^-]} = \frac{a_{\text{E}}a_{\text{H}^+}}{[\text{CH}]}\frac{1}{[\text{OH}^-][\text{H}^+]\gamma_{\text{E}}\gamma_{\text{H}^+}}$$

where a_{E} and $a_{\text{H}+}$ are activities and γ_{E} and $\gamma_{\text{H}+}$ are the corresponding activity coefficients. By assuming $\gamma_{\text{E}} = \gamma_{\text{OH}-}$, which is a very good approximation, one obtains $[\text{OH}^-][\text{H}^+]\gamma_{\text{E}}\gamma_{\text{H}+} = 10^{-14}$ at 25°.

The values obtained here are reported in Table I together with the literature data. Rumpf[3] has pointed out the difficulty of measuring this acidity by conventional techniques because of the rapid hydrolysis of the ester function in alkaline solution. These studies are so difficult that the determination is quite impossible for secondary R substituents. Thus it appears that the high instability of the chemical systems studied requires a fast observation time technique, such as T-jump relaxation.

The enol content obtained for dilute aqueous solution is presented in Table II. Each value has been averaged from at

Table II
Determination of the Enol Content (K_T) by Bromination. Enol Acidity

Compd	Expt	$[Br_2]$, $\times 10^7$, M^{-1}	[β-keto ester] $\times 10^5$, M^{-1}	$K_T \times 10^2$	pK_{EH}
I				0.39[a]	8.24
II	1	4.02	2.43		
	2	4.13	3.01		
	3	2.27	1.69		
	4	4.40	3.79	0.29	9.70
	5	2.08	2.38		
	6	2.91	2.95		
III	1	2.04	1.93		
	2	2.14	2.85		
	3	1.99	1.85	0.17	9.70
	4	2.12	2.65		
	5	4.07	3.68		
IV	1	3.45	2.95		
	2	3.45	3.65		
	3	5.70	5.45		
	4	3.42	2.86	0.13	9.60
	5	3.62	4.07		
	6	4.33	4.05		
	7	5.8	5.05		
V	1	3.62	4.53		
	2	3.73	4.88		
	3	5.9	8.7		
	4	3.72	4.83	0.09	9.65
	5	3.65	5.25		
	6	6.15	8.96		
	7	6.28	10.10		
VI	1	2.24	0.675		
	2	4.22	1.69		
	3	4.45	2.48		
	4	2.26	0.68	0.05	10.20
	5	2.23	0.905		
	6	4.30	1.78		
	7	4.38	2.35		
VII	1	1.68	4.50		
	2	1.64	6.6		
	3	3.08	11.1		
	4	3.22	13.8	0.04	9.70
	5	1.63	4.34		
	6	3.06	8.5		

[a] See ref 2.

Table III
Chemical Shifts and Coupling Constants of the Enolic Protons

	$\delta_{O(H)}$, ppm		Coupling
	Measured	Literature[a]	constant, Hz
I	12.16	12.17	0.6
II	12.70	12.63	0.6
III	12.70	12.73	0.6
IV	12.80	12.80	0.6
V	12.75	12.85	
VI	12.97	12.98	
VII	13.09	13.1[b]	

[a] J. L. Burdett and M. T. Rogers, *J. Amer. Chem. Soc.*, **86**, 2105 (1964). [b] S. T. Ioffe, E. I. Fedin, P. V. Petrovskii, and M. I. Kabachnik, *Tetrahedron Lett.*, 2661 (1966).

least five experimental runs. The calculated enol acidity constants (pK_{EH}) are tabulated in the same table.

The chemical shifts and coupling constants of the enolic proton are presented in Table III. The value of the chemical shift expresses the strength of the intramolecular H bond,[11] which appears to be weaker than for the symmetric β-diketones $CH_3COCHRCOCH_3$.[9] Compounds I–IV present a sufficiently high enol content to allow a fine structure analysis of the enolic peak (Figure 3). It exhibits a quartet with a single coupling constant of 0.6 Hz.

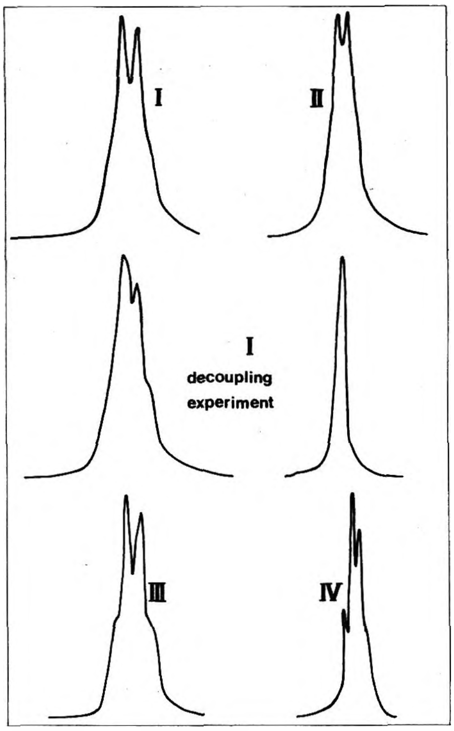
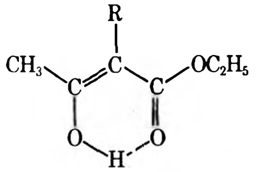


Figure 3. Nuclear magnetic resonance spectra of the enolic proton.

The possibility of coupling with the vinylic proton has been proposed by Burdett.[12] However, it should result in a doublet and not in a quartet. Moreover, for R ≠ H this coupling should disappear. From a decoupling experiment (Figure 3), it is seen that coupling takes place with the methyl group. This coupling shows that the enolic proton is closer to the carbonyl oxygen than to the ester oxygen, whereas for the above-mentioned β-diketones it is equidistant from these two oxygen atoms.[13] This result leads us to propose the following structure for the enolic forms of our β-keto esters.



Discussion

It is generally accepted that the carbanion–enolate anion is an intermediate species in the base-catalyzed keto–enol transformation. This anion is at the same time the conjugate base of both the ketone and the enol, and is produced by the abstraction of the acidic proton by a base in the reacting medium. Equation 6 represents catalysis by the hydroxide ion occurring in our kinetic experiments. If now the medium is slightly acidic (in order to avoid any protonation of the carbonyl function), the concentration of the carbanion–enolate intermediate will decrease and become very low compared with that of the un-ionized species. This is the case for the water-catalyzed transformation occurring in our equilibrium constant determinations.[14]

Enol–Enolate Equilibrium. Some 30 years ago, Schwarzenbach and Felder measured the acidity of both tautomers of acetoacetic ester.[2] They observed a higher acidity for the enol than for the keto form. Our results show that the introduction of R = alkyl leads to a significant constant decrease in the enol acidity. All the substituted keto esters present a pK_{EH} value of about 9.7, without

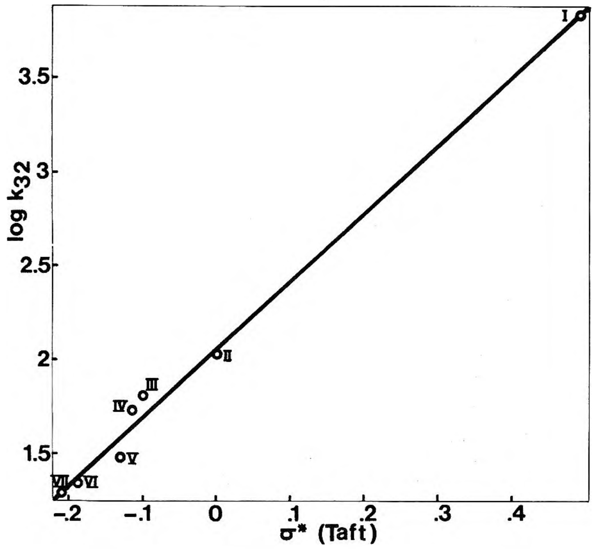


Figure 4. The relationship between the σ^* constants and the deprotonation rate constants k_{32} of the keto form.

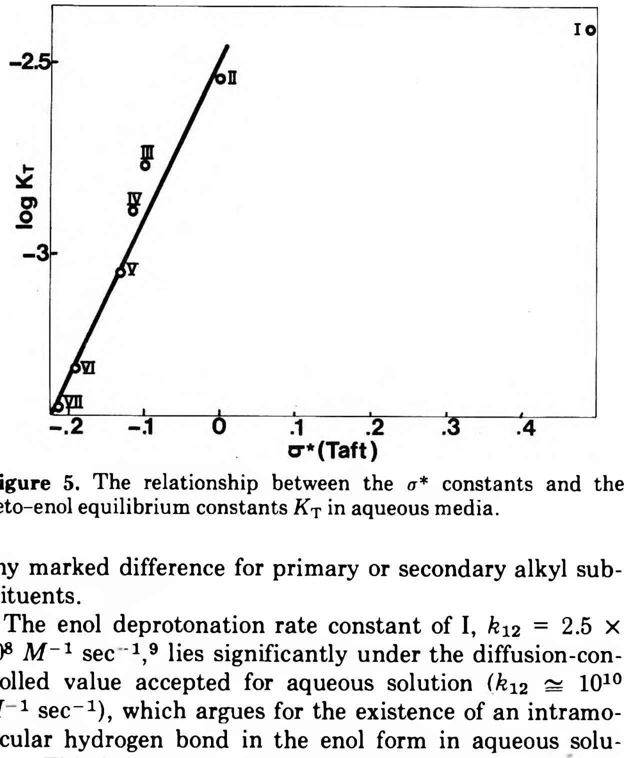
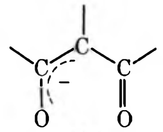


Figure 5. The relationship between the σ^* constants and the keto-enol equilibrium constants K_T in aqueous media.

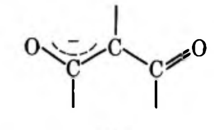
any marked difference for primary or secondary alkyl substituents.

The enol deprotonation rate constant of I, $k_{12} = 2.5 \times 10^8\ M^{-1}\ \text{sec}^{-1}$,[9] lies significantly under the diffusion-controlled value accepted for aqueous solution ($k_{12} \cong 10^{10}\ M^{-1}\ \text{sec}^{-1}$), which argues for the existence of an intramolecular hydrogen bond in the enol form in aqueous solution. *This hydrogen bonding is essentially responsible for the stability of the enol and any modification of its conformation should result in a variation of* k_{12} *and enol content.* k_{12} being unknown for compounds II–VII, we investigated the deprotonation rate of ethyl 2-hydroxycyclohexenecarboxylate, which may be taken as a model for alkyl-substituted β-keto esters. The rate constant obtained, $k_{12} = 2.4 \times 10^8\ M^{-1}\ \text{sec}^{-1}$, is very close to that of I. For the chemical shift of the enolic proton of this compound, we obtained 12.24 ppm, a value extremely close to that found for ethyl acetoacetate (12.16 ppm). Thus k_{12} and δ_{OH} appear to be two independent estimates of the intensity of intramolecular hydrogen bonding. Considering the larger chemical shift for compounds II–VII (~12.8 ppm) it would appear that representative value of k_{12} is slightly less than $2.4 \times 10^8\ M^{-1}\ \text{sec}^{-1}$. This has been demonstrated directly for β-dicarbonyl compounds of the form $CH_3COCHRCOCH_3$.[9] This result tends to show that the hydrogen bond is only slightly modified by R substitution.

A possible explanation is that our results can be accommodated within the currently accepted framework that alkyl structural effects are exerted on the enol form.[3,15] According to this view, if one assumes that there is no difference in the steric requirements of the enol and enolate (a reasonable assumption, since they are both flat), then a lack of variation of pK_{EH} with alkyl subtitution is expected. The lower pK_{EH} for R = H would be the consequence of an inductive effect. This hypothesis assumes that the nature of the effect is necessarily steric. In our opinion the fact that the two forms are planar does not require that the steric effect be identical in each case; a more complete knowledge of their structures is necessary. The geometry of the enol form is quite well known (cyclic planar structure, enolization toward the carbonyl) but that of the enolate is less evident. There are two possibilities which may be drawn as follows.



A



B

If structure A corresponds to the real situation a similarity of steric effects between enol and enolate appears quite probable, while this is not the case if structure B is operating. From an analysis of the infrared and Raman spectra of the anion corresponding to penta-2,4-dione, Ernstbrunner[16] has shown that in organic solvents structure A prevails while in aqueous solution B is by far the more important. Thus one can reasonably assume this same structure for the anion of ethyl acetoacetate, and consequently reject the hypothesis that steric effects are equally important for the enol and enolate forms. Moreover, a destabilization of the enol form seems incompatible with the invariable intensity of hydrogen bonding, considering that this bonding is probably the most important factor determining enol stability. It seems to us that the hypothesis of a very weak effect on the ionization equilibrium of the enol is more consistent with the factors we have just discussed.

Ketone–Enolate Equilibrium. The ketone acidity is more sensitive to structural effects than the enol acidity. It decreases significantly as the number of carbon atoms increases for primary alkyl substituents, and as the degree of branching of a substituent increases. Barlin and Perrin[17] showed for these β-keto esters the existence of a linear free energy relationship between the overall acidity, which may be identified with the ketone acidity in view of the very weak enol content, and the Taft σ^* constants: $pK_{CH} = 12.59 - 3.44\sigma^*$.

In order to carry out a more accurate analysis of the structural effect on the equilibration step $2 \rightleftharpoons 3$ from eq 6, we shall examine the rate constants k_{23} and k_{32}. We find that, while k_{23} is remarkably constant, k_{32} varies, by a factor of 350, in the same direction as pK_{CH}. Thus α-alkyl substitution affects the ketone reactivity tremendously. A thorough investigation of the k_{32} variation in relation to the structure shows a linear relationship between log k_{32} and the Taft σ^* constants (Figure 4). Furthermore, the same analysis on the keto-enol equilibrium constant K_T shows a similar relationship between log K_T and σ^* (Figure 5), with the exception of the point corresponding to R = H, which is ruled out without any doubt.[18] Consequently there exists, for alkyl groups, a linear free energy relationship between the rate constant of ketone deprotonation and the enol content. In a strictly formal sense, this is compatible with the two limiting hypotheses under discussion: a steric effect on the enol or an electronic effect on the ketone. We will now consider the arguments in favor of the first hypothesis. The increase of pK_{CH} with the degree of branching is expected since the enolate has greater steric requirements than the ketone. The constancy of k_{23} and the variation of k_{32} with pK_{CH} are explicable if the steric requirements of the enolate are the same as those of the transition state. This is expected, since only a flat transition state will allow conjugation with the carbonyl oxygens. Unfortunately, we have practically no knowledge of the structure of the keto form (all we know is that the dipole moment is greater for the ketone than for the enol) and it does not seem certain to us that the effect, if it is steric, would be more important on the enolate than on the ketone. Moreover, the probability of an isosteric effect on the enol, enolate, and ketonic transition state appears difficult to accept; the condition of simultaneous coplanarity is not sufficient to reach such a conclusion. The following considerations lead us to believe that an electronic effect operating principally on the keto form is the most probable.

(1) The correlations pK_{CH}, log K_T, and log k_{32} = f(σ^*) do not support a steric effect interpretation.

(2) Ingold,[19] quoting Hughes, concludes that the +I effect of alkyl groups would lead to an increase in the thermodynamic stability of the ketone.

(3) The coupling constant between the methyl and acidic protons is not affected by alkyl substitution, probably indicating a constant planar geometry for the enol form.

(4) The variation of the enol content with respect to R = H corresponds to a decrease for electron-donating substituents and an increase for electron-withdrawing substituents.

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Registry No.—I, 141-97-9; II, 609-14-3; III, 607-97-6; IV, 1540-28-9; V, 1540-29-0; VI, 1522-46-9; VII, 1540-31-4.

References and Notes

(1) This work is taken from the Doctoral Thesis of R. Brouillard, Université Paris VII.

(2) G. Schwarzenbach and E. Felder, *Helv. Chim. Acta*, **27**, 1701 (1944).

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A Study of Acetate Participation in Acyclic Epoxide Systems. Acid-Catalyzed Rearrangements of *trans*- and *cis*-1-Acetoxy-3,4-epoxypentanes, -4,5-epoxyhexanes, and -5,6-epoxyheptanes

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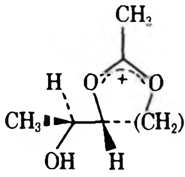
Acid-catalyzed rearrangements of *trans*- and *cis*-1-acetoxy-3,4-expoypentanes gave, respectively, *cis*- and *trans*-2-methyl-3-acetoxytetrahydrofuran. Similar reaction of *cis*- and *trans*-1-acetoxy-4,5-epoxyhexane gave *threo*- and *erythro*-2-(1-acetoxyethyl)tetrahydrofuran. In the course of these rearrangements the configuration at the epoxide carbons is retained. The mechanism of these rearrangements, elucidated by ^{18}O-labeling experiments, is consistent with the intermediacy of ortho esters. When the ester group is further removed from the epoxide moiety no participation is observed.

The present investigation, as part of a general study of the chemistry of epoxides, was prompted by the possibility of forming bicyclic ortho esters **2** by intramolecular hydroxyl attack on 1,3-dioxolenium ions **1**.

Neighboring-group participation by ester groups to give 1,3-dioxolenium ions is now well established.[1] In 1942 Winstein and Buckles[2] found that solvolysis of 2-acetoxy-3-bromobutanes in dry acetic acid–silver acetate takes place with retention of configuration, threo bromo acetate giving the *dl* diacetate and the erythro bromo acetate giving meso diacetate. The postulated 1,3-dioxolenium ion intermediate **4** was later observed[3] by nmr spectroscopy whan 3-acetoxy-2-chloro-2,3-dimethylbutane (**3**) was dissolved in SbF_5–SO_2 or SbF_5–FSO_3H–SO_2 at −60°. Meer-



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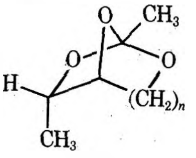

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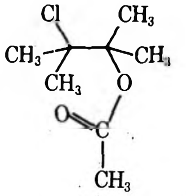
wein, *et al.*,[4] were able to prepare stable 1,3-dioxolenium salts **6** by reaction of fluoro esters **5** with boron trifluoride.



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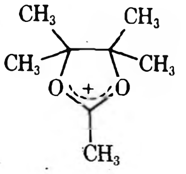

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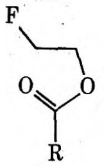

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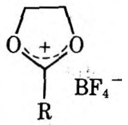

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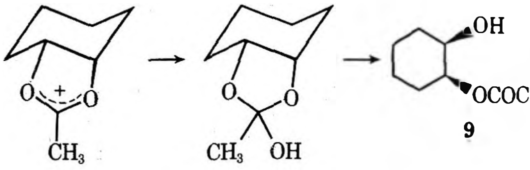
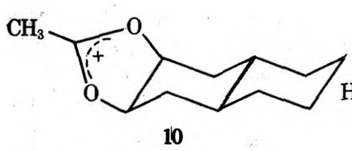
1,3-Dioxolenium ions react with anionic nucleophiles and with water or alcohols. For reaction with water, ring opening occurs *via* an ortho ester **8** rather than attack by water at a C–C carbon.[5] This is demonstrated by reaction of acetonium ion **7** with water to give the cis alcohol ester **9**.



7 8 9

Ring opening of ortho esters takes place with remarkable stereospecificity.[6] The 1,3-dioxolenium ion **10** in moist acetic acid gives the thermodynamically less stable acetoxy alcohol **11**.



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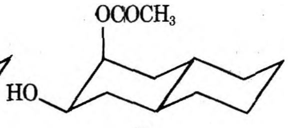

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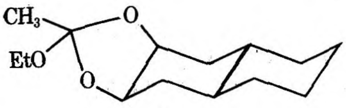

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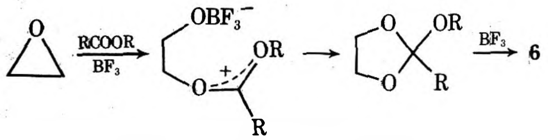


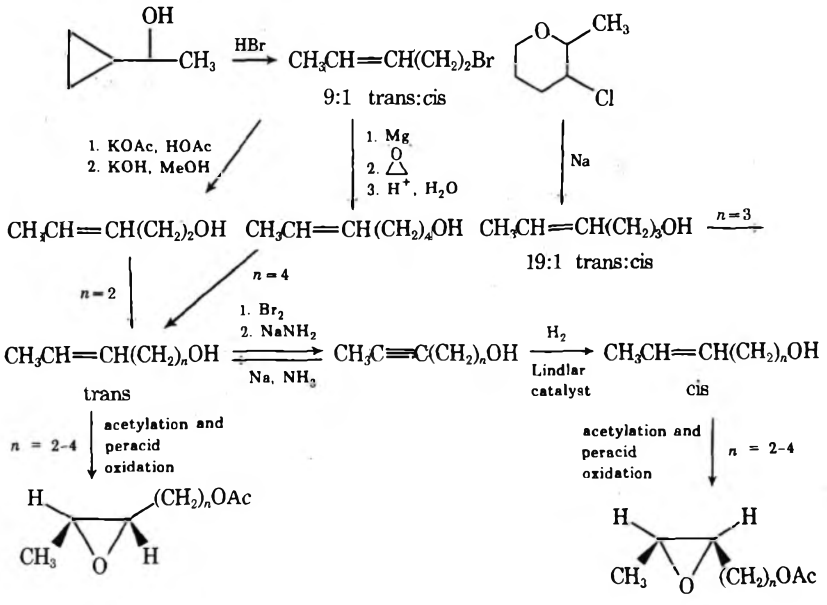
Partial hydrolysis of the ortho ester **12** under mild conditions gives almost exclusively axial ester **11**. Ortho esters can be prepared by reaction of 1,3-dioxolenium ions with alcohols or by reaction of epoxides with carboxylic esters in the presence of catalytic amounts of BF_3. In the presence of greater amounts of BF_3 only the 1,3-dioxolenium salt **6** is observed.

Results

We now report the preparation (Scheme I) and acid-catalyzed reactions of *cis-* and *trans*-1-acetoxy-3,4-epoxypentanes (**13** and **15**), -1-acetoxy-4,5-epoxyhexanes (**17** and **21**), and -1-acetoxy-5,6-epoxyheptanes (**25** and **28**).

The common intermediate to the synthesis of *trans*-pent-3-en-1-ol, -hex-4-en-1-ol, and -hept-5-en-1-ol, precursors to the required trans epoxides, was *trans*-1-bromopent-3-ene.[7] A 1:9 mixtures of *cis-* and *trans*-1-bromopent-3-ene was prepared by reaction of cyclopropylcarbinol with hydrogen bromide. The pure *trans*-1-bromopent-3-ene could not be separated from this mixture by distillation. The 1-acetoxypent-3-enes prepared by reaction of the mixed 1-bromopent-3-enes with potassium acetate in glacial acetic acid were similarly inseparable. After alkaline hydrolysis *trans*-pent-3-en-1-ol could be purified by distillation. The required *trans*-1-acetoxy-3,4-epoxypentane was prepared by oxidation of *trans*-1-acetoxypent-3-ene with monoperoxyphthalic acid. The acetoxy olefin was prepared by acetylation of the corresponding hydroxy olefin. The *cis*-pent-3-en-1-ol was prepared from the mixed pent-3-en-1-ols by bromination and dehydrobromination with sodium amide to give pent-3-yn-1-ol.[8] The yield was low (13%) and extensive variation of reaction conditions failed to improve the yield. Hydrogenation of pent-3-yn-1-ol to *cis*-pent-3-en-ol was carried out over Lindlar cata-

Scheme I

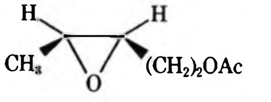


lyst. The *cis*-pent-3-en-1-ol was acetylated with acetic anhydride–pyridine and epoxidized with monoperoxyphthalic acid to give *cis*-1-acetoxy-3,4-epoxypentane (13).

A mixture of *cis*- and *trans*-hex-4-en-1-ol was prepared by addition of formaldehyde to the Grignard reagent formed from *cis*- and *trans*-1-bromopent-3-enes. The reaction was, however, inefficient and the mixture of alcohols could not be separated by preparative glc. An alternative reaction pathway[9] involving reaction of 3-chloro-2-methyltetrahydropyran with sodium afforded a 1:19 mixture of *cis*- and *trans*-hex-4-en-1-ol. The mixed hydroxy alkenes were brominated and dehydrobrominated to give hex-4-yn-1-ol in good yield. Reduction of hex-4-yn-1-ol with sodium in liquid ammonia afforded pure *trans*-hex-4-en-1-ol, which after acetylation followed by epoxidation with monoperoxyphthalic acid gave *trans*-1-acetoxy-4,5-epoxyhexane (21). Hydrogenation of hex-4-yn-1-ol over Lindlar catalyst gave *cis*-hex-4-en-1-ol. The alkene was converted into *cis*-1-acetoxy-4,5-epoxyhexene (17) in the usual manner.

A 1:9 mixture of *cis*- and *trans*-hept-5-en-1-ols was prepared by reaction of the Grignard reagent prepared from the *cis*- and *trans*-1-bromopent-3-ene mixture with ethylene oxide.[10] The *cis*- and *trans*-hept-5-en-1-ols could not be separated by preparative glc and were prepared in a similar manner to the hexenols.

Rearrangements of Epoxy Acetates. Reaction of *cis*-1-acetoxy-3,4-epoxypentane (13) with boron trifluoride etherate in ether as solvent gave *trans*-3-acetoxy-2-methyltetrahydrofuran (14) in 40% yield. The identity of this product follows from the nmr spectra and from its identity after hydrolysis with the major product from reduction of dihydro-2-methylfuran-3(2*H*)-one with sodium in moist ether. Reduction of dihydro-2-methylfuran-3(2*H*)-one under these reaction conditions favors the formation of the thermodynamically more stable trans isomer. Reaction of *trans*-1-acetoxy-3,4-epoxypentane (15) with boron trifluoride etherate in ether gave the isomeric furan, *cis*-3-acetoxy-2-methyltetrahydrofuran (16), but in higher yield (68%). Reduction with $LiAlH_4$ gave *cis*-2-methyltetrahydrofuran-3-ol, identical with the minor product obtained with sodium–moist ether reduction of dihydro-2-methylfuran-3(2*H*)-one. The configuration of the 2-methyltetrahydrofuran-3-ols was further established in that the methyl group for the cis isomer was deshielded (δ 1.25) in the nmr spectra relative to the trans isomer (δ 1.18), consistent with the proximity of the methyl and hydroxyl groups in the former compound.[11] The *cis*- and *trans*-1-acetoxy-3,4-epoxypentanes (13 and 14) also gave the corresponding *trans*- and *cis*-3-acetoxy-2-methyltetrahydrofurans (14 and 16) when the reaction was carried out using *p*-toluenesulfonic acid or trifluoroacetic acid in ether. The formation of the rearranged furans in the *p*-toluenesulfonic acid and trifluoroacetic acid reactions excludes the possible intermediacy of fluorohydrins in the analogous reaction using boron trifluoride etherate. On reaction with *p*-toluenesulfonic acid the cis epoxide 13 gave a mixture of trans (14, 64%) and cis furans (16, 24%)[12] and two unidentified products. In the presence of trifluoroacetic acid, the major product detected by glc was trans furan (14, 97%). Only a trace of the cis furan 16 could be detected. Similar reaction of trans epoxide 15 with *p*-toluenesulfonic acid or trifluoroacetic acid gave mixtures containing 10% trans furan 14 and 80% cis furan 16 and 5% trans furan 14 and 95% cis furan 16, respectively.



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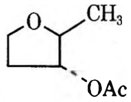

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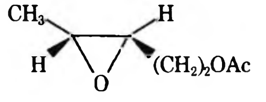

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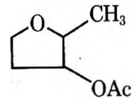
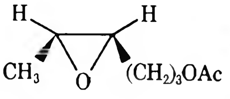


16

Reaction of *cis*- and *trans*-1-acetoxy-4,5-epoxyhexane (17) with boron trifluoride etherate in ether was slower than reaction of the corresponding epoxypentanes and gave from the cis epoxide 17 *erythro*-2-(1-acetoxyethyl)tetrahydrofuran (18, 30%), *threo*-1-acetoxy-5-fluorohexan-4-ol (19, 14%), *threo*-1-acetoxy-4-fluorohexan-5-ol (20, 7%), 1-acetoxyhexan-5-one (14%), and 1-acetoxyhexan-4-one (30%); and from the trans epoxide 21 *threo*-2-(1-acetoxyethyl)tetrahydrofuran (22, 62%), *erythro*-1-acetoxy-5-fluorohexan-4-ol (23, 17%), *erythro*-1-acetoxy-4-fluorohexan-5-ol (24, 13%), 1-acetoxyhexan-5-one (trace), and 1-acetoxyhexan-4-one (3%). The structures of the 2-(1-acetoxyethyl)tetrahydrofurans (18 and 22) were established from the nmr spectra and from the conversion of the acetates into known threo and erythro alcohols by reaction with $LiAlH_4$. Solution infrared spectra of these alcohols established the configuration, intramolecular hydrogen bonding being less favored for the erythro isomer than for the threo isomer.[13] The configuration of the fluorohydrins follows from the known preference for opening of epoxides with inversion[14] of configuration at the site of nucleophilic attack and from reaction with KO-*t*-Bu-*t*-BuOH.[15]



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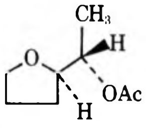

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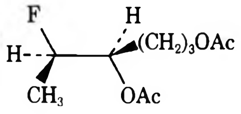

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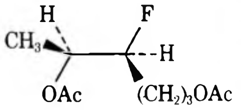

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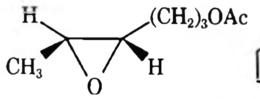

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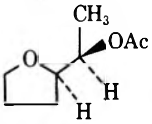

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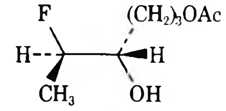

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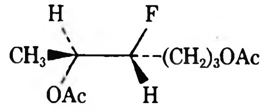

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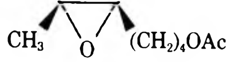
Reaction of *cis*- and *trans*-1-acetoxy-5,6-epoxyheptanes (25 and 28) with boron trifluoride etherate in ether is slow and gives from the cis epoxide 25 1-acetoxyheptan-5-one (35%), 1-acetoxyheptan-6-one (25%), *threo*-1-acetoxy-6-fluoroheptan-5-ol (26, 13%), and *threo*-1-acetoxy-5-fluoroheptan-6-ol (27, 10%); and from the trans epoxide 28 5-acetoxy-2-methylpentan-1-al (29, 5%), 1-acetoxyheptan-



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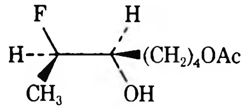

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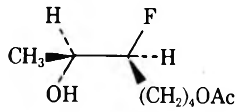

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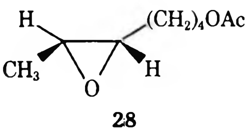

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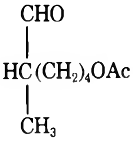

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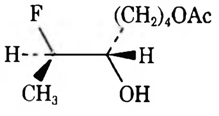

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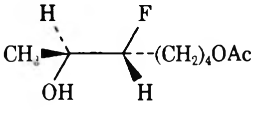

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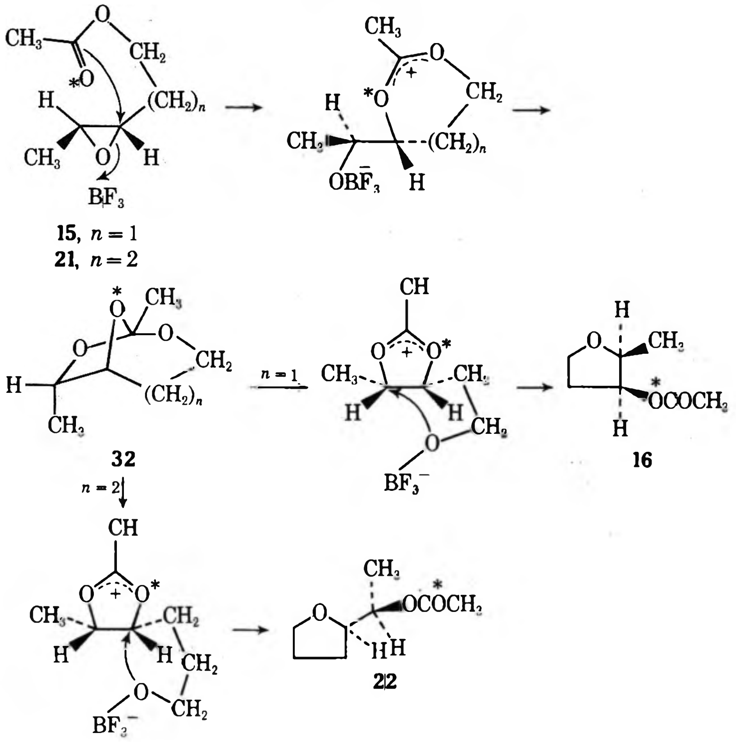
Scheme II



5-one (11%), 1-acetoxyheptan-6-one (8%), *erythro*-1-acetoxy-6-fluoroheptan-5-ol (**30**, 36%), and *erythro*-5-fluoroheptan-6-ol (**33**, 35%).

Discussion

The acid-catalyzed reactions of *trans*- and *cis*-1-acetoxy-3,4-epoxypentanes and -1-acetoxy-4,5-epoxyhexanes gave products that can only arise from intramolecular acetate participation with epoxide C–O bond cleavage. The reaction of *cis*- and *trans*-1-acetoxy-5,6-epoxyheptanes (**17**, and **21**) with boron trifluoride etherate is, however, dominated by two reaction processes which do not involve intramolecular ester participation. Attack by a fluoride-containing nucleophile occurs with consequent fluorohydrin formation and hydride migration occurs with rearrangement to ketone products. For both the *cis*- and *trans*-1-acetoxy-5,6-epoxyheptanes little discrimination is observed between the epoxide carbons for the site of nucleophilic attack. Attack by fluoride is the dominant reaction path for the trans epoxide; however ketone formation predominates from the cis epoxide. The fluorohydrin products were shown by separate experiment to be stable under the reaction conditions and are therefore not intermediates in the formation of ketone products.

The same features of reaction were observed for reaction of *cis*- and *trans*-1-acetoxy-4,5-epoxyhexanes (**17** and **21**) with boron trifluoride etherate. Fluorohydrin formation was favored from the trans epoxide **21** and hydride migration was favored from the cis epoxide **17**. The most notable feature[16] of the reaction of the hexane epoxides was the stereoselective formation of *threo*- and *erythro*-2-(1-acetoxyethyl)tetrahydrofuran (**22** and **18**). Products analogous to these furans were isolated from the reaction of *cis*- and *trans*-1-acetoxy-3,4-epoxypentane (**13** and **15**).

The formation of these furans **14** and **16** from epoxides **13** and **15** and **18** and **22** from epoxides **17** and **21** can be accounted for as shown in Scheme II for the trans epoxides. Participation by the terminal acetate with cleavage of the epoxide C–O bond results in formation of a dioxolenium ion which by attack with the OBF_3^- moiety gives the ortho ester **32**. The ortho ester can rearrange intramolecularly to give, when $n = 1$, the furan **16** and, when $n = 2$, furan **22**.

The validity of the reaction scheme was demonstrated by ^{18}O-labeling experiments. Rearrangement of *trans*-1-acetoxy-3,4-epoxypentane (**15**), ^{18}O enriched at the acetate carbonyl, gave *cis*-3-acetoxy-2-methyltetrahydrofuran (**16**, 21.5% ^{18}O) which on hydrolysis to the alcohol showed no significant loss of oxygen label (20% ^{18}O). The carbonyl oxygen of the starting acetate must therefore be present as the ether or hydroxyl oxygen in the product. Reaction of *trans*-1-acetoxy-4,5-epoxyhexane (**21**) labeled at the carbonyl oxygen with ^{18}O gave labeled *threo*-2-(1-acetoxyethyl)tetrahydrofuran (**22**, 21% ^{18}O) which on hydrolysis gave *threo*-2-(1-hydroxyethyl)tetrahydrofuran with complete loss of oxygen label.

Experimental Section

***trans*-1-Bromopent-3-ene.** The procedure of Julia, *et al.*,[7] was used in the preparation of this material. A mixture of 32.5 g of α-methylcyclopropanemethanol and 150 ml of 48% hydrobromic acid was stirred rapidly for 10 min. The reaction mixture was extracted with light petroleum ether, neutralized with sodium bicarbonate solution, and dried with sodium sulfate. The solvent was removed to give a 1:9 mixture of *cis*- and *trans*-1-bromopent-3-ene: bp 125°; ν_{max} 970 cm^{-1}; nmr δ 5.45 ($W_{1/2}$ = 60 Hz, C^3 H, C^4 H), 3.30 (apparent t, J = 7 Hz, –CH$_2$Br), 2.83–2.25 (C^2 H$_2$), 1.65 (d, J = 4.5 Hz, C^5 H$_3$).

***trans*-1-Acetoxypent-3-ene.** The method of Julia *et al.*,[7] was used. A solution of 70 g of *cis*- and *trans*-1-bromopent-3-ene and 146 g of potassium acetate in 300 ml of acetic acid was heated under reflux for 12 hr. The product was extracted into ether, washed with aqueous sodium bicarbonate, and dried with anhydrous sodium carbonate. After removal of solvent, distillation gave a 1:9 mixture of *cis*- and *trans*-1-acetoxypent-3-ene (53 g): bp 92° (100 mm); ν_{max} 1745, 1360, 1345, and 965 cm^{-1}; nmr δ 5.46 ($W_{1/2}$ = 48 Hz, C^3 H, C^4 H), 4.05 (apparent t, J = 7 Hz, –CH$_2$OAc), 2.50–2.10 (C^2 H$_2$), 2.02 (–COCH$_3$), 1.63 (d, J = 4.5 Hz, C^5 H$_3$).

***trans*-Pent-3-en-5-ol.** A solution of 42 g (1:9) of *cis*- and *trans*-1-acetoxypent-3-ene and 56 g of potassium hydroxide in 200 ml of methanol was heated under reflux for 1 hr. The hydroxy olefin was extracted into ether washed with water and dried. After removal of solvent the mixture was carefully distilled through an annular teflon spinning band distillation column to give *trans*-pent-3-en-1-ol free of the cis isomer: bp 78–79° (88 mm); ν_{max}

3375 and 965 cm^{-1}; nmr δ 5.50 ($W_{1/2}$ = 48 Hz, C^3 H, C^4 H), 3.60 (apparent t, J = 6.5 Hz, $-CH_2OH$), 2.47–2.05 (C^2 H_2), 1.67 (d, J = 4.5 Hz, C^5 H_3). Acetylation of *trans*-pent-3-en-1-ol in acetic anhydride–pyridine gave *trans*-1-acetoxypent-3-ene.

***trans*-Acetoxy-3,4-epoxypentane (15).** A solution of 1.28 g of *trans*-1-acetoxypent-3-ene in 50 ml of a 0.35 *M* monoperoxyphthalic acid–ether solution was kept at 5° for 1 week. Excess anhydrous potassium carbonate was added and the mixture was filtered. After the ether was removed by distillation, preparative glc gave *trans*-1-acetoxy-3,4-epoxypentane (**15**, 0.86 g): ν_{max} 1745, 1360, 1350 cm^{-1}; nmr δ 4.18 (apparent t, J = 6 Hz, $-CH_2OAc$), 2.93–2.58 (C^3 H, C^4 H), 2.12–1.65 (C^2 H_2), 2.03 ($-COCH_3$), 1.28 (d, J = 5 Hz, C^5 H_3).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.3; H, 8.4. Found: C, 57.8; H, 8.4.

Pent-3-yn-1-ol. The procedure of Crombie and Harper[8] was used in the preparation of this material. To a solution of 30 g of *trans*-pent-3-en-1-ol in 100 ml of ether was added 1 molar equiv of bromine. After removal of ether the dibromo alcohol was added to a solution prepared by the addition of 50 g of sodium to 1.5 l. of ammonia liquid to which 0.25 g of ferric chloride had been added. After 30 min ammonium chloride was added and the ammonia was allowed to evaporate. The product was extracted into ether, washed with water, and dried. After removal of solvent, pent-3-yn-1-ol was isolated by preparative glc. The maximum yield of product that could be isolated was 13%: bp 154–157°; ν_{max} 3375 cm^{-1}; nmr δ 3.67 (apparent t, J = 6 Hz, $-CH_2OH$), 2.55–2.20 (C^2 H_2), 1.78 (t, J = 2.5 Hz, C^5 H_3).

***cis*-Pent-3-en-1-ol.** The method of Crombie and Harper[8] was used. A mixture of pent-3-yn-1-ol and 50 mg of Lindlar catalyst was stirred in a hydrogen atmosphere until 1 mol of hydrogen had been adsorbed. The reaction was slow and the catalyst was changed several times. After filtration to remove the catalyst and evaporation of the solvent, *cis*-pent-3-en-1-ol was isolated by preparative glc: ν_{max} 3350 and 710 cm^{-1}; nmr δ 5.54 ($W_{1/2}$ = 48 Hz, C^3 H, C^4 H), 3.60 (apparent t, J = 6 Hz, $-CH_2OH$), 2.55–2.11 (C^2 H_2), 1.63 (d, J = 5 Hz, C^5 H_3).

***cis*-1-Acetoxy-3,4-epoxypentane (13).** A solution of 0.5 g of *cis*-pent-3-en-1-ol in 2.5 ml of pyridine and 0.6 ml of acetic anhydride was kept at room temperature overnight. Ether was added and the pyridine was removed by washing with dilute aqueous acid. After removal of solvent the residue was epoxidized with monoperoxyphthalic acid in the usual manner. The product, *cis*-1-acetoxy-3,4-epoxypentane (**13**, 0.49 g) was obtained pure by preparative glc: ν_{max} 1740, 1370, and 1360 cm^{-1}; nmr δ 4.22 (apparent t, J = 6 Hz, $-CH_2OAc$), 3.27–2.83 (C^3 H, C^4 H), 2.05 ($-OCOCH_3$), 1.92 (m, $J_{1,2}$ = $J_{2,3}$ $\cong$ 6 Hz, C^2 H_2), 1.28 (d, J = 5.5 Hz, C^5 H_3).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.3; H, 8.4. Found: C, 58.1; H, 8.4.

***trans*-Hex-4-en-1-ol.** The method of Crombie and Harper[9] was used. A solution of 2440 g of *cis*- and *trans*-3-chloro-3-methyltetrahydropyran in 1 l. of ether was treated with 92 g of sodium. After all the sodium had reacted the mixture was washed with water and the solvent was removed by distillation. After distillation of 1:9 mixture of *cis*- and *trans*-hex-4-en-1-ol was obtained: bp 68° (15 mm); ν_{max} 3350 and 960 cm^{-1}; nmr δ 5.44 ($W_{1/2}$ = 16 Hz, C^4 H, C^5 H), 3.60 (apparent t, J = 6 Hz, $-CH_2OH$), 2.27–1.85 (C^3 H_2), 1.85–1.30 (C^2 H_2), 1.63 (d, J = 5.5 Hz, C^6 H_3).

***trans*-1-Acetoxy-4,5-epoxyhexane (21).** A solution of 2 g of mixed *cis*- and *trans*-hex-4-en-1-ols in 10 ml of pyridine and 2 ml of acetic anhydride was kept at room temperature overnight. The product was isolated and epoxidized with monoperoxyphthalic acid. Preparative glc gave 1.9 g of pure *trans*-1-acetoxy-4,5-epoxyhexane (**21**): ν_{max} 1725, 1370, and 1360 cm^{-1}; nmr δ 4.10 (apparent t, J = 6 Hz, $-CH_2OAc$), 2.92–2.52 (C^4 H, C^5 H), 2.02 ($-OCOCH_3$), 1.97–1.40 (C^2 H_2, C^3 H_2), 1.28 (d, J = Hz, C^6 H_3).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.7, H, 8.9.

***cis*-Hex-4-en-1-ol.** To a solution of 30 g of *trans*-hex-4-en-1-ol in 100 ml of ether was added 1 molar equiv of bromine. After removal of excess bromine the dibromo alcohol was added to a solution prepared by addition of 50 g of sodium to 1.5 l. of liquid ammonia to which 0.25 g of ferric chloride had been added. The product hex-4-yn-1-ol was purified and then hydrogenated over Lindlar catalyst. The reaction product was purified by preparative glc to give 3.9 g of *cis*-hex-4-en-1-ol: ν_{max} 3350 and 710 cm^{-1}; nmr δ 5.45 ($W_{1/2}$ = 40 Hz, C^4 H, C^5 H), 3.63 (apparent t, J = 6 Hz, $-CH_2OH$), 2.38–1.86 (C^3 H_2), 1.86–1.35 (C^2 H_2), 1.62 (d, J = 5 Hz, C^6 H_3).

***cis*-1-Acetoxy-4,5-epoxyhexane (17).** A solution of 1 g of *cis*-hex-4-en-1-ol in 50 ml of pyridine and 1 ml of acetic anhydride was kept at room temperature overnight. The product was isolated in the usual manner and epoxidized with monoperoxyphthalic acid. The reaction product was purified by preparative glc to give 0.95 g of *cis*-1-acetoxy-4,5-epoxyhexane (**17**): ν_{max} 1740, 1375, and 1350 cm^{-1}; nmr δ 4.13 (apparent t, J = 6 Hz, $-CH_2OAc$), 3.27–2.75 (C^4 H, C^5 H), 2.03 ($OCOCH_3$), 2.00–1.38 (C^2 H_2, C^3 H_2), 1.27 (d, J = 5 Hz, C^6 H_3).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.7; H, 8.9.

***trans*-Hept-5-en-1-ol.** The procedure of Dreger[10] was used in the preparation of this compound. The magnesium derivative of 27.5 g of a 1:9 mixture of *cis*- and *trans*-1-bromopent-3-ene was prepared in 90 ml of ether and allowed to react with an excess of ethylene oxide. The product was isolated in the usual manner and distillation on a spinning band column gave 20 g of a 1:9 mixture of *cis*- and *trans*-hept-5-en-1-ol: ν_{max} 3340 and 960 cm^{-1}; nmr δ 5.37 ($W_{1/2}$ = 15 Hz, C^5 H, C^6 H), 3.50 (apparent t, J = 6 Hz, $-CH_2OH$), 2.20–1.77 (C^4 H_2), 1.77–1.17 (m, C^3 H_2, C^4 H_2, C^7 H_3).

***trans*-1-Acetoxy-5,6-epoxyheptane (28).** A solution of 2 g of a 1:9 mixture of *cis*- and *trans*-hept-5-en-1-ols in 10 ml of pyridine and 2 ml of acetic anhydride was kept at room temperature overnight. The product was isolated in the usual manner and epoxidized with monoperophthalic acid. The reaction product was purified by preparative glc to remove the cis isomer and gave 1.8 g of *trans*-1-acetoxy-5,6-epoxyheptane (**28**): ν_{max} 1740, 1370, and 1355 cm^{-1}; nmr δ 4.07 (apparent t, J = 6 Hz, $-CH_2OAc$), 2.94–2.50 (C^5 H, C^6 H), 2.05 ($-OCOCH_3$), 1.83–1.43 (C^2 H_2, C^3 H_2, C^4 H_2), 1.28 (d, J = 5 Hz, C^7 H_3).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.8; H, 9.4. Found: C, 62.9; H, 9.3.

***cis*-Hept-5-en-1-ol.** To a solution of 30 g of a 1:9 mixture of *cis*- and *trans*-hept-5-en-1-ols in 100 ml of ether was added 1 molar equiv of bromine. After removal of excess bromine the dibromo alcohol was added to a solution prepared by addition of 50 g of sodium to 1.5 l. of ammonia in the presence of catalytic amounts of ferric chloride. The product hept-5-yn-1-ol was purified by preparative glc and then hydrogenated over Lindlar catalyst to give 5.8 g of *cis*-hept-5-en-1-ol: ν_{max} 3350 and 710 cm^{-1}; nmr δ 5.42 ($W_{1/2}$ = 30 Hz, C^5 H, C^6 H), 3.65 (apparent t, J = 6 Hz, $-CH_2OH$), 2.42–1.86 (C^4 H_2), 1.77–1.10 (C^2 H_2, C^3 H_2), 1.62 (d, J = 5 Hz, C^7 H_3).

***cis*-1-Acetoxy-5,6-epoxyheptane (25).** *cis*-Hept-5-en-1-ol (1 g) was acetylated and epoxidized with monoperoxyphthalic acid in the usual manner. The final reaction product was purified by preparative glc to give 0.90 g of *cis*-1-acetoxy-5,6-epoxyheptane (**25**): ν_{max} 1740, 1380, and 1365 cm^{-1}; nmr δ 4.09 (apparent t, J = 6 Hz, $-CH_2OAc$), 3.23–2.73 (C^5 H, C^6 H), 2.03 ($-OCOCH_3$), 1.97–1.40 (C^2 H_2, C^3 H_2, C^4 H_2), 1.27 (d, J = 5 Hz, C^7 H_3).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.8; H, 9.4. Found: C, 62.8; H, 9.3.

Rearrangement of *cis*-1-Acetoxy-3,4-epoxypentane (13) with Boron Trifluoride Etherate in Ether. A solution of 120.1 mg of *cis*-1-acetoxy-3,4-epoxypentane in 120 ml of sodium-dried ether was stirred and 430 mg of boron trifluoride etherate was added. After 2.5 hr at room temperature the reaction was quenched by adding 0.5 ml of a saturated potassium carbonate solution. After the mixture was stirred for 15 min, 118.2 mg of tetrahydrofurfuryl acetate was added as an internal standard for glc analysis. Anhydrous potassium carbonate was added to remove the water and the mixture was filtered. The crude reaction product was shown by glc to contain 40% *trans*-3-acetoxy-2-methyltetrahydrofuran and traces of two compounds that had retention times characteristic of ketone products. No other low-boiling compounds or fluorohydrins were found. The reaction was carried out in duplicate.

trans-3-Acetoxy-2-methyltetrahydrofuran (**14**) was isolated by preparative glc from a reaction carried out using 0.5 g of epoxide **15**: ν_{max} 1735, 1365, and 1350 cm^{-1}; nmr δ 4.86 (m, $J_{3,4}$ = 3, $J_{3,2}$ = 6 Hz, C^3 H), 4.15–3.70 (C^2 H, C^5 H_2), 2.57–1.50 (C^4 H_2), 2.03 ($-OCOCH_3$), 1.22 (d, J = 6 Hz, C^2 CH_3).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.3; H, 8.4. Found: C, 58.1; H, 8.3.

Rearrangement of *trans*-1-Acetoxy-3,4-epoxypentane (15) with Boron Trifluoride Etherate in Ether. Rearrangement of *trans*-1-acetoxy-3,4-epoxypentane (**15**) was carried out as above for the cis isomer. The crude reaction product was shown by glc using tetrahydrofurfuryl acetate as internal standard to contain *cis*-3-acetoxy-2-methyltetrahydrofuran (**16**) in 68% yield and traces of three compounds that had retention times characteristic of ketone products. The latter of these compounds had the same retention time as one of the trace products from rearrangement of cis epoxide. No products with retention times characteristic of fluorohydrins were found.

cis-3-Acetoxy-2-methyltetrahydrofuran (16) was isolated by preparative glc from a reaction carried out on 1 g of *trans*-1-acetoxy-3,4-epoxypentane: ν_{max} 1740 and 1360 cm^{-1}; nmr δ 5.27 (m, J = 5.5, 2.2, 3.7 Hz, C^3 H), 4.25–3.52 (C^2 H, C^5 H_2), 2.67–1.67 (C^4 H_2), 2.07 ($-OCOCH_3$), 1.20 (d, J = 6 Hz, C^2 CH_3).

Anal. Calcd for $C_7H_{12}O_3$: C, 58.3; H, 8.4. Found; C, 58.2; H, 8.3.

Rearrangement of *cis*-1-Acetoxy-3,4-epoxypentane (13) with *p*-Toluenesulfonic Acid and Trifluoroacetic Acid in Ether. The reaction was carried out as for the boron trifluoride etherate catalyzed reaction but using an equivalent amount of an azeotropically dried solution of 4.7 g of *p*-toluenesulfonic acid in 1 l. of ether. The reaction product was isolated in the usual manner and shown by glc to be a mixture of *trans*-3-acetoxy-2-methyltetrahydrofuran (14, 64%), *cis*-3-acetoxy-2-methyltetrahydrofuran (16, 24%), and two unknown products (6% each). The reaction was carried out in the usual manner but with an equivalent amount of a solution of trifluoroacetic acid in ether as the acid catalyst. The reaction product, volatile to glc, contained *trans*-3-acetoxy-2-methyltetrahydrofuran (14, 97%) and a trace of *cis*-3-acetoxy-2-methyltetrahydrofuran (16).

Rearrangement of *trans*-1-Acetoxy-3,4-epoxypentane (15) with *p*-Toluenesulfonic Acid and Trifluoroacetic Acid in Ether. The reaction was carried out as above but with *p*-toluenesulfonic acid as catalyst. The crude reaction product was shown by glc to contain *trans*-3-acetoxy-2-methyltetrahydrofuran (14, 10%), *cis*-3-acetoxy-2-methyltetrahydrofuran (16, 80%), and two unidentified compounds (6 and 4%). When trifluoroacetic acid was used as catalyst, the reaction product was *cis*-3-acetoxy-2-methyltetrahydrofuran (16, 95%) and *trans*-3-acetoxy-2-methyltetrahydrofuran (14, 5%).

Rearrangement of *cis*-1-Acetoxy-4,5-epoxyhexane (17) with Boron Trifluoride Etherate in Ether. The reaction of *cis*-1-acetoxy-4,5-epoxyhexane (17) with boron trifluoride etherate in ether was carried out as for *cis*-1-acetoxy-3,4-epoxypentane above. Cyclohexanol was used as the internal standard for glc analysis. The crude reaction product was shown to contain *erythro*-2-(1-acetoxyethyl)tetrahydrofuran (18, 30%), 1-acetoxyhexan-4-one (30%), 1-acetoxyhexan-5-one (14%), *threo*-1-acetoxy-5-fluoro-4-hydroxyhexane (19, 14%), and *threo*-1-acetoxy-4-fluoro-5-hydroxyhexane (20, 7%). The fluorohydrins were unstable to preparative glc and were converted by reaction with acetyl chloride in pyridine to the corresponding fluoro diacetates. The components were separated by preparative glc. *erythro*-2-(1-Acetoxyethyl)tetrahydrofuran (18) had ν_{max} 1740 and 1350 cm^{-1}; nmr δ 4.90 (m, $J_{Me,H}$ = 6, $J_{H,C2H}$ = 4.5 Hz, CHOAc), 4.70–3.60 (C^5 H_2), 2.13–1.53 (C^3 H_2, C^4 H_2), 2.03 ($-OOCOCH_3$), 1.22 [d, J = 6 Hz, $-CH(OAc)CH_3$]. Hydrolysis by $LiAlH_4$ gave *erythro*-2-(1-hydroxyethyl)tetrahydrofuran: ν_{max} (CCl_4) 3560 and 3588 cm^{-1}; nmr δ 4.12–2.50 (C^2 H, CHOH, C^5 H_2), 2.03–1.67 (C^3 H_2, C^4 H_2), 1.13 [d, $J_{CH,Me}$ = 6 Hz, $CH(OH)CH_3$].

1-Acetoxyhexan-4-one had ν_{max} 1740, 1718, and 1350 cm^{-1}; nmr δ 4.07 (apparent t, J = 6 Hz, $-CH_2OAc$), 2.50 (t, $J_{2,3}$ = 6 Hz, C^3 H_2), 2.45 (q, $J_{5,6}$ = 7 Hz, C^5 H_2), 2.2–1.5 (C^2 H_2), 2.03 ($-OCOCH_3$), 1.05 (t, $J_{5,6}$ = 7 Hz, C^6 H_3).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.8; H, 8.9. Found: C, 60.8; H, 8.8.

1-Acetoxyhexan-5-one had ν_{max} 1740, 1720, and 1350 cm^{-1}; nmr δ 4.07 (apparent t, $J_{1,2}$ = 6 Hz, $-CH_2OAc$), 2.48 ($W_{1/2}$ = 15 Hz, C^4 H_2), 2.13 ($COCH_3$), 2.03 ($-OCOCH_3$), 1.77–1.48 (C^2 H_2, C^3 H_2).

Anal. Calcd for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.8; H, 8.9.

threo-1-4,Diacetoxy-5-fluorohexane (19) had ν_{max} 1740 and 1350 cm^{-1}; nmr δ 4.95 (m, $J_{4,F} \cong 17$, $J_{4,5} \cong 4$ Hz, $J_{4,3}$ not determined, C^4 H), 4.65 (m, $J_{5,F} \cong 49$, $J_{5,6}$ = 6, $J_{5,4} \cong 4$ Hz, C^5 H), 4.08 (apparent t, $J_{1,2}$ = 6 Hz, $-CH_2OAc$), 2.10 (C^4 $OCOCH_3$), 2.03 (C^1 $OCOCH_3$), 1.92–1.10 (C^2 H_2, C^3 H_2), 1.30 (d of d, $J_{6,F}$ = 24, $J_{6,5}$ = 6 Hz, C^6 H_3).

Anal. Calcd for $C_{10}H_{17}FO_4$: C, 54.5; H, 7.8; F, 8.6. Found: C, 54.1; H, 7.9; F, 8.8.

threo-1,5-Diacetoxy-4-fluorohexane (20) had ν_{max} 1740 and 1350 cm^{-1}; nmr δ 5.02 (m, $J_{5,F} \cong 22$, $J_{5,6}$ = 6, $J_{5,4} \cong 4$ Hz, C^5 H), 4.35 (m, $J_{4,F} \cong 47$, $J_{4,5} \cong 4$ Hz, $J_{4,3}$ not determined, C^4 H), 4.10 (apparent t, $J_{1,2}$ = 6 Hz, $-CH_2OAc$), 2.07 (C^5 $OCOCH_3$), 2.03 (C^1 $OCOCH_3$), 2.00–1.10 (C^2 H_2, C^3 H_2), 1.27 (d, J = 6 Hz, C^6 H_3).

Anal. Calcd for $C_{10}H_{17}FO_4$: C, 54.5; H, 7.8; F, 8.6. Found: C, 54.1; H, 8.0; F, 9.1.

Rearrangement of *trans*-1-Acetoxy-4,5-epoxyhexane (21) with Boron Trifluoride Etherate in Ether. The reaction of *trans*-1-acetoxy-4,5-epoxyhexane (21) with boron trifluoride etherate in ether was carried out under similar reaction conditions to that of the cis isomer. Cyclohexanol was used as the internal standard for glc analysis. The crude reaction product was shown to contain *threo*-2-(1-acetoxyethyl)tetrahydrofuran (22, 62%), 1-acetoxyhexan-4-one (3%), 1-acetoxyhexan-5-one (trace), *erythro*-1-acetoxy-5-fluorohexan-4-ol (23, 17%), and *erythro*-1-acetoxy-4-fluorohexan-5-ol (24, 13%). The fluorohydrins were unstable to preparative glc and were converted, by reaction with acetyl chloride in pyridine, to the corresponding fluoro diacetates. The products were then separated by preparative glc.

threo-2-(1-Acetoxyethyl)tetrahydrofuran (22) had ν_{max} 1735 and 1350 cm^{-1}; nmr δ 4.85 [m, $J_{H,2}$ = 6, $J_{H,Me}$ = 6 Hz, $-CH(CH_3)OAc$], 4.05–3.58 (C^2 H, C^5 H_2), 2.25–1.50 (C^3 H_2, C^4 H_2), 2.05 ($-OCOCH_3$), 1.20 [d, J = 6 Hz, $-CH(OAc)CH_3$]. Hydrolysis by reaction with $LiAlH_4$ gave *threo*-2-(1-hydroxyethyl)tetrahydrofuran: ν_{max} (CCl_4) 3578 cm^{-1}; nmr δ 4.23–2.87 (C^2 H, CHOH, C^6 H_2), 2.05–1.23 (C^3 H_2, C^4 H_2, C^5 H_2), 1.12 [d, $J_{CH,Me}$ = 6 Hz, $-CH(OH)CH_3$].

erythro-1,4-Diacetoxy-5-fluorohexane (24) had ν_{max} 1742, 1736, and 1355 cm^{-1}; nmr δ 4.95 (m, $J_{5,F}$ = 19, $J_{5,6}$ = 6, $J_{5,4} \cong 4$ Hz, C^5 H), 4.45 (m, $J_{4,F}$ = 49, $J_{4,5} \cong 4$, Hz, $J_{4,3}$ not determined, C^4 H), 4.10 (apparent t, $J_{1,2}$ = 6 Hz, $-CH_2OAc$), 2.07 (C^5 $OCOCH_3$), 2.03 (C^1 $OCOCH_3$), 1.97–0.92 (C^2 H_2, C^3 H_2), 1.25 (m, $J_{6,5}$ = 6, $J_{6,F}$ = 1.2 Hz, C^6 H_3).

Anal. Calcd for $C_{10}H_{17}FO_4$: C, 54.5; H, 7.8; F, 8.6. Found: C, 55.0; H, 8.0; F, 9.0.

The ketones 1-acetoxyhexan-4-one and 1-acetoxyhexan-5-one were identical with samples isolated from rearrangement of cis epoxide 17.

Rearrangement of *cis*-1-Acetoxy-5,6-epoxyheptane (25) with Boron Trifluoride Etherate in Ether. A solution of 120.2 mg of *cis*-1-acetoxy-5,6-epoxyheptane (25) in 120 ml of sodium-dried ether was stirred and 960 mg of boron trifluoride etherate was added in three equal amounts over a period of 2 hr. The reaction was kept at room temperature for 24 hr. The boron trifluoride etherate was quenched by the addition of 1 ml of a saturated potassium carbonate solution. The product was isolated in the usual manner and shown by glc using tetrahydrofurfuryl acetate as standard to contain 1-acetoxyheptan-5-one (35%), 1-acetoxyheptan-6-one (25%), *threo*-1-acetoxy-6-fluoroheptan-5-ol (26, 13%), and *threo*-1-acetoxy-5-fluoroheptan-6-ol (27, 10%) The products were isolated from a reaction using 1 g of epoxide. The acetoxyfluoro alcohols decompose on preparative glc and so the reaction mixture was acetylated with acetyl chloride–pyridine before chromatography.

1-Acetoxyheptan-5-one had ν_{max} 1740, 1718, and 1350 cm^{-1}; nmr δ 4.05 (apparent t, $J_{2,1}$ = 6 Hz, $-CH_2OAc$), 2.65–2.22 (C^4 H_2, C^6 H_2), 2.03 ($OCOCH_3$), 1.78–1.45 (C^2 H_2, C^3 H_2), 1.05 (t, $J_{6,7}$ = 7 Hz, C^7 H_3).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.8; H, 9.4. Found: C, 62.7; H, 9.3.

1-Acetoxyheptan-6-one had ν_{max} 1740, 1718, and 1350 cm^{-1}; nmr δ 4.03 (apparent t, $J_{2,1}$ = 6 Hz, $-CH_2OAc$), 2.43 (*ca.* t, $J_{5,4}$ = 6 Hz, C^5 H_2), 2.13 ($COCH_3$), 2.03 (C^1 $OCOCH_3$), 1.90–1.17 (C^2 H_2, C^3 H_2, C^4 H_2).

Anal. Calcd for $C_9H_{16}O_3$: C, 62.8; H, 9.4. Found: C, 62.8; H, 9.3.

threo-1,5-Diacetoxy-6-fluoroheptane had ν_{max} 1740 and 1355 cm^{-1}; nmr δ 4.93 (m, $J_{5,F} \cong 17$, $J_{5,6} \cong 4$ Hz, $J_{5,4}$ not determined, C^5 H), 4.67 (m, $J_{6,F}$ = 49, $J_{6,7}$ = 6, $J_{6,5} \cong 4$ Hz, C^6 H), 4.05 (apparent t, $J_{1,2}$ = 6 Hz, CH_2OAc), 2.10 (C^5 $OCOCH_3$), 2.02 (C^1 $OCOCH_3$), 1.92–1.10 (C^2 H_2, C^3 H_2, C^4 H_2), 1.28 (m, $J_{7,F}$ = 24, $J_{7,6}$ = 6 Hz, C^7 H_3).

Anal. Calcd for $C_{11}H_{19}FO_4$: C, 56.4; H, 8.2; F, 8.1. Found: C, 56.1; H, 8.2; F, 8.6.

threo-1,6-Diacetoxy-5-fluoroheptane had ν_{max} 1740 and 1355 cm^{-1}; nmr δ 5.00 (m, $J_{6,F}$ = 22, $J_{6,7}$ = 6, $J_{6,5}$ = 4 Hz, C^6 H), 4.37 (m, $J_{5,F} \cong 47$, $J_{5,6} \cong 4$ Hz, C^5 H), 4.05 (apparent t, $J_{1,2}$ = 6 Hz, CH_2OAc), 2.07 (C^6 $OCOCH_3$), 2.03 (C^1 $OCOCH_3$), 1.95–1.10 (C^2 H_2, C^3 H_2, C^4 H_2), 1.25 (m, $J_{6,7}$ = 6, $J_{7,F}$ = 0.8 Hz, C^7 H_3).

Anal. Calcd for $C_{11}H_{19}FO_4$: C, 56.4; H, 8.2; F, 8.1. Found: C, 56.0; H, 8.1; F, 8.5.

Rearrangement of *trans*-1-Acetoxy-5,6-epoxyheptane (28) with Boron Trifluoride Etherate in Ether. The reaction of *trans*-1-acetoxy-5,6-epoxyheptane (28) with boron trifluoride etherate was carried out in duplicate under the same reaction conditions as those of the cis isomer. Tetrahydrofurfuryl acetate was used as the internal standard for glc analysis. The crude reaction product was shown to contain 5-acetoxy-2-methylpentan-1-al (29, 5%), 1-acetoxyheptan-5-one (11%), 1-acetoxyheptan-6-one (8%), *erythro*-1-acetoxy-6-fluoroheptan-5-ol (**30**, 36%), and *erythro*-1-acetoxy-5-fluoroheptan-6-ol (**33**, 35%). The products were separated by preparative glc.

5-Acetoxy-2-methylpentan-1-al (**29**) had δ 9.60 (d, J = 2 Hz, CHCHO), 4.05 (apparent t, $J_{5,4}$ = 6 Hz, CH_2OAc), 2.67–2.17 (C^2 H), 2.03 ($OCOCH_3$), 1.85–1.05 (C^2 H_2, C^3 H_2, C^4 H_2), 1.10 (d, $J_{H,Me}$ = 6.5 Hz, $CHOH_3$). The aldehyde decomposed rapidly on storage.

1-Acetoxyheptan-5-one and 1-acetoxyheptan-6-one were identical in all respects with the same ketones obtained from rearrangement of the cis epoxide.

erythro-1-Acetoxy-6-fluoroheptan-5-ol (**30**) had ν_{max} 3475, 1740, 1370, and 1350 cm^{-1}; nmr δ 4.55 (m, $J_{6,F} \cong 49$, $J_{6,7} = 6$, $J_{6,5} = 4$ Hz, C^6 H), 4.08 (apparent t, $J_{1,2}$ = 6 Hz, CH_2OAc), 3.93–3.50 (m, C^5 H), 2.03 ($OCOCH_3$), 1.83–1.22 (C^2 H_2, C^3 H_2, C^4 H_2), 1.30 (m, $J_{7,F} = 25$, $J_{7,6} = 6$ Hz, C^7 H_3).

Anal. Calcd for $C_9H_{17}FO_3$: C, 56.2; H, 8.9; F, 9.9. Found: C, 56.2; H, 8.9, F, 10.6.

erythro-1-Acetoxy-5-fluoroheptan-6-ol (**31**) had ν_{max} 3475, 1740, 1370, and 1350 cm^{-1}; nmr δ 4.33 (m, $J_{5,F} = 49$, $J_{5,6} \cong 5$, $J_{5,4} \cong 6$ Hz, C^5 H), 4.07 (apparent t, $J_{1,2}$ = 6 Hz, CH_2OAc), 3.87 (m, $J_{6,F} \cong 22$, $J_{6,7} = 6$, $J_{6,5} \cong 4$ Hz, C^6 H), 2.03 ($OCOCH_3$), 2.10–1.00 (C^2 H_2, C^3 H_2, C^4 H_2), 1.20 (m, $J_{7,6} = 6$, $J_{7,F} = 1.2$ Hz, C^7 H_3).

Anal. Calcd for $C_9H_{17}FO_3$: C, 56.2; H, 8.9; F, 9.9. Found: C, 55.9; H, 8.8; F, 10.3.

Synthesis and Rearrangement of C=^{18}O *trans*-1-Acetoxy-3,4-epoxypentane (15). To a solution of *trans*-1-hydroxy-3,4-epoxypentane in 2 ml of pyridine was added 230 mg of acetyl chloride containing 21% ^{18}O label. The mixture was kept at room temperature for 16 hr. The product was isolated by means of ether and the pyridine was removed by washing with dilute acid. The solvent was removed by careful distillation and the crude acetoxy olefin was treated with 20 ml of 0.35 *M* monoperoxyphthalic acid at 5° for 9 days. Anhydrous potassium carbonate was added and the mixture was stirred overnight. The organic phase was removed by filtration and the ether was removed by careful distillation. The product, C=^{18}O *trans*-1-acetoxy-3,4-epoxypentane (**15**), was allowed to react with boron trifluoride etherate in ether in the usual manner and the product *cis*-3-acetoxy-2-methyltetrahydrofuran (**16**) was purified by preparative glc. The percentage of oxygen label was determined from the ratio of M/(M + 2) and (M − M)/ (M + 2 − Me) peaks in the mass spectrum to be 21.5%. Reaction of *cis*-3-acetoxy-2-methyltetrahydrofuran (**16**) with $LiAlH_4$ in ether gave *cis*-2-methyltetrahydrofuran-3-ol. The mass spectra showed 20% incorporation of ^{18}O label in this furanol.

Synthesis and Rearrangement of C=^{18}O *trans*-1-Acetoxy-4,5-epoxyhexane (21). Synthesis of *trans*-1-acetoxy-4,5-epoxyhexane (**21**) from *trans*-4,5-epoxyhexan-1-ol was carried out in a similar manner to above.

Rearrangement of C=^{18}O labeled *trans*-1-acetoxy-4,5-epoxyhexane with boron trifluoride etherate in ether gave *threo*-2-(1-acetoxyethyl)tetrahydrofuran (**22**) containing 21% ^{18}O label. Reduction of *threo*-2-(1-acetoxyethyl)tetrahydrofuran (**22**) with $LiAlH_4$ in ether gave *threo*-2-(1-hydroxyethyl)tetrahydrofuran containing no detectable ^{18}O label.

Acknowledgments. The authors thank Professor R. Hodges, Massey University, and Dr. G. J. Wright, University of Canterbury, for determination of mass spectra. Financial support from the Research Committee of the New Zealand Grants Committee is gratefully acknowledged.

Registry No.—**13**, 41763-95-5; **14**, 41763-96-6; **15**, 41763-93-3; **16**, 41763-94-4; **17**, 41763-97-7; 18, 33964-67-9; **19**, 50273-74-0; **20**, 50273-75-1; **21**, 41763-98-8; **22**, 33964-66-8; **24**, 50273-78-4; **25**, 50273-79-5; **28**, 50273-80-8; **29**, 50273-81-9; **30**, 50273-82-0; **31**, 50273-83-1; *cis*-1-bromopent-3-ene, 50273-84-2; *trans*-1-bromopent-3-ene, 7515-62-0; *cis*-1-acetoxypent-3-ene, 42125-19-9; *trans*-1-acetoxypent-3-ene, 42125-35-9; *trans*-pent-3-en-5-ol, 1576-96-1; pent-3-yn-1-ol, 10229-10-4; *cis*-pent-3-en-1-ol, 764-38-5; *cis*-3-chloro-2-methyltetrahydropyran, 50273-91-1; *trans*-3-chloro-2-methyltetrahydropyran, 50273-92-2; *cis*-hex-4-en-1-ol, 928-91-6; *trans*-hex-4-en-1-ol, 928-92-7; *cis*-hept-5-en-1-ol, 50273-95-5; *trans*-hept-5-en-1-ol, 25143-94-6; *erythro*-2-(1-hydroxyethyl)tetrahydrofuran, 16765-39-2; 1-acetoxyhexan-4-one, 13777-63-4; 1-acetoxyhexan-5-one, 4305-26-4; *threo*-2-(1-hydroxyethyl)tetrahydrofuran, 16765-41-6; 1-acetoxyheptan-5-one, 50274-01-6; 1-acetoxyheptan-6-one, 5070-61-1; *threo*-1,5-diacetoxy-6-fluoroheptane, 50274-03-8; *threo*-1,6-diacetoxy-5-fluoroheptane, 50546-28-6.

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(15) The epoxide that would be formed by reaction of base on a 1,2-fluorohydrin was not isolated. The products isolated were the same as isolated from reaction of the corresponding epoxy alcohols under the same reaction conditions. A full report on this work will be published separately. See W. H. Swallow, Ph.D. Thesis, University of Canterbury, 1972.

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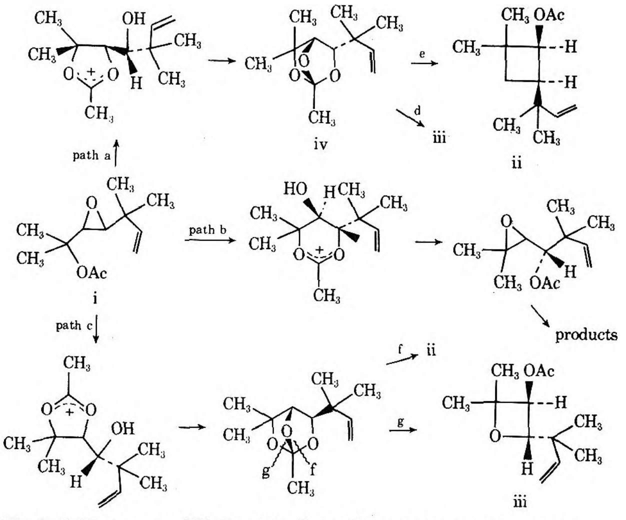

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Synthesis of Isopentenylated Chrysins

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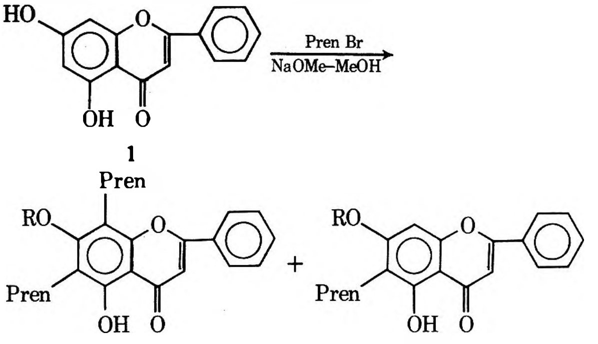
Received September 17, 1973

Chrysin (1) when heated with prenyl bromide in the presence of methanolic methoxide gives 6-prenyl (3) and 6,8-diprenyl (2) derivatives, but with 2-hydroxy-2-methyl-3-butene in the presence of boron trifluoride etherate affords, besides the above two compounds, the 8-prenyl derivative (11). Their structures have been established by nmr spectra of themselves, their acetates, and partial methyl ethers and by acid cyclization of the hydroxy compounds and their partial methyl ethers. Cyclodehydrogenation of the three prenyl compounds (3, 11, and 2) has been accomplished by DDQ in benzene; the first two formed chromenes 10 and 14, respectively, and the last one yielded 3-deoxy derivatives of sericetin (16) and isosericetin (15).

Thirteen isopentenylated flavones have been isolated from species of the two genera *Artocarpus* and *Morus* by Venkataraman, *et al.*[2] They are artocarpesin,[3] cycloartocarpesin,[4] oxydihydroartocarpesin,[4] artocarpin,[5] norartocarpin,[5] cycloartocarpin,[6] heterophyllin,[7] cycloheterophyllin,[7] chaplashin,[8] mulberrin,[9] mulberrochromene,[9] cyclomulberrin,[9] and cyclomulberrochromene.[9] They are either 5,7,2′,4′-tetra- or 5,7,2′,4′,5′-pentaoxygenated flavones having isopentenylation at either C-6 or C-8 or C-3 and C-6, or C-3, C-6, and C-8. The isopentenyl unit is either γ,γ-dimethylallyl (prenyl), 3-methyl-1-butenyl, a condensed 2,2-dimethylpyran ring, 2-(2-methyl-2-propenyl)-pyran, or exepine ring. Besides the above flavones, 8-prenylluteolin[10,11] and laceolatin A[12] have been isolated from other plant families. The last named compound is unique in having an unusual C_5 moiety, *viz.* a 3-hydroxy-3-methyl-1-butenyl unit in the 8 position. Although the constitutions of all the above 15 flavones have been established on the basis of their spectral data and degradation, none of them has been synthesized so far. As a model experiment, the simplest flavone, chrysin (1), has been subjected to nuclear prenylation under two different conditions in order to see which positions are affected. Further oxidative cyclization of the resulting o-prenyl phenols has been accomplished to get the corresponding chromenes.

Chrysin[13] (1) when refluxed with prenyl bromide in the presence of methanolic methoxide gave two products separable by column chromatography (reaction 1). The first eluate analyzed for a diprenyl derivative and formed a monomethyl ether (nmr δ 3.80, s, 3 H, OCH_3) with 1 mol of dimethyl sulfate in the presence of potassium carbonate and acetone. The positive ferric reaction of both the hydroxy compound and the partial methyl ether indicated that both hydroxyl groups were free. This was confirmed by the formation of a diacetate (nmr δ 2.34, 2.45, 2 s, 6 H, $OCOCH_3$). Further, both prenyl units were found to be in the nuclear positions of ring A by the nmr signals of H-3 and the protons of intact side phenyl ring but not of ring A. The nmr spectra also showed the signals of two benzylic methylene groups, two methine protons, and four olefinic methyl groups (see Experimental Section). Hence the first prenylation product could be assigned formula 2 (5,7-dihydroxy-6,8-diprenylflavone) which was further confirmed by preparing its bisdihydropyran derivative (6) on heating with formic acid (reaction 2). The structure of 6 was confirmed by its nmr spectrum.

The second prenylation product also showed a positive ferric reaction and formed a diacetate [nmr δ 2.34, 2.46 (2 s, 6 H, $-OCOCH_3$)] and a 7-methyl ether [nmr δ 3.92 (s, 3 H, OCH_3)]. The nmr spectra of the diacetate and the 7-methyl ether show the presence of only one prenyl unit and one aromatic H of ring A. Hence, it could be either a 6-prenyl or a 8-prenyl derivative. The precise location of the prenyl unit was established by studying the cyclization of the hydroxy compound and its 7-methyl ether with formic acid. The latter gave 7 (reaction 3), which had a negative ferric reaction and exhibited two characteristic triplets of methylene protons in its nmr spectrum at δ 1.78 and 2.65 (J = 7 Hz). The formation of a dihydropyran is possible only when the prenyl group is in the 6 position.



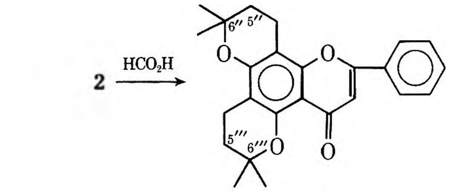
1

2, R = H
4, R = Me

3, R = H
5, R = Me

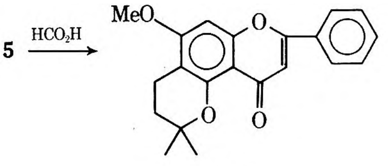
(1)

Pren = $Me_2C{=}CHCH_2$-



6

(2)



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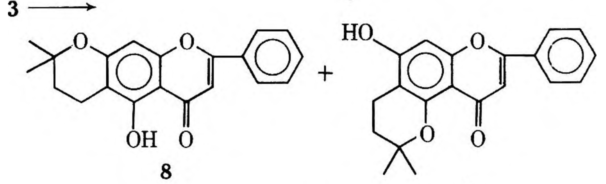
(3)



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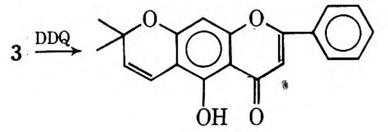
(4)



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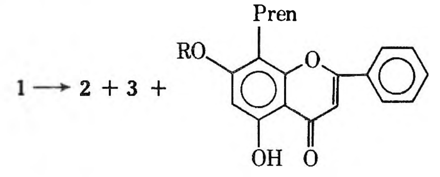
(5)

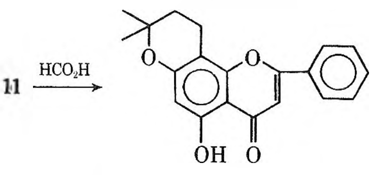
The same conclusion was reached on acid cyclization of the dihydroxy compound (**3**), which yielded two dihydropyrans (reaction 4). One dihydropyran derivative, mp 180°, which gave a positive ferric reaction and has two characteristic triplets of methylene protons in its nmr spectrum at δ 1.85 and 2.77 (J = 7 Hz) was assigned structure **8**. Since the other dihydropyran of mp 296° gave no ferric reaction and was isomeric with **8**, it was assigned structure **9**. Cyclodehydrogenation of **3** with DDQ provided further confirmation for its structure by yielding the **10** (reaction 5), which was identical in melting point with the chromene obtained by Hlubucek, *et al.*,[14] on heating chrysin with 3-chloro-2-methyl-1-butyne.

In the second method of prenylation, treatment of chrysin with 2-hydroxy-2-methyl-3-butene, in the presence of boron trifluoride etherate, gave three compounds which were separated by column chromatography (reaction 6). The first eluate was **2** and the second eluate **3**. The third eluate was a new monoprenyl derivative, which gave a positive ferric reaction and formed a diacetate [nmr δ 2.36, 2.40 (2 s, 6 H, $-OCOCH_3$)] and a partial methyl ether [nmr δ 3.99 (s, 3 H, $-OCH_3$)], still showing a positive ferric reaction. Hence both of the hydroxyls were free. The nmr spectra of both the diacetate and the partial methyl ether showed the presence of one prenyl unit in ring A. Thus these were signals of protons of the intact phenyl ring, a proton in position 3, one aromatic proton of ring A, one benzylic methylene, one methine, and two methyl groups at the unsaturated center (see Experimental Section). Since the prenyl in the product was different from **3**, it was assumed to be 8-prenyl chrysin (**11**). This was established as follows. While the partial methyl ether **12** did not undergo any cyclization with formic acid, the dihydroxy compound **11** could be cyclized to afford 5-hydroxy-6″,6″-dimethyl-4″,5″-dihydropyrano[2″,3″:7,8]flavone (**13**) (reaction 7) as shown by a positive ferric reaction and the characteristic two nmr triplets at δ 1.88 and 2.80 ppm (J = 7 Hz). Further **11** gave the angular chromene, 5-hydroxy-6″,6″-dimethylpyrano[2″,3″:7,8]flavone (**14**) on treatment with DDQ, identical with the one obtained by Hlubucek, *et al.*,[14] (reaction 8).



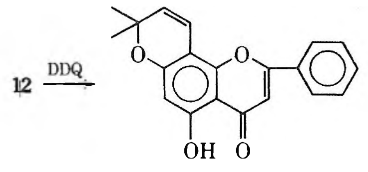
(6)

11, R = H
12, R = Me



(7)

13



(8)

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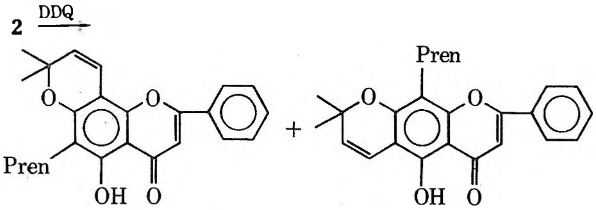
The above results indicate that only the 6 and 8 positions are affected by prenylation of chrysin and that the 3 position remains unaffected. Hence flavones having prenyl groups in ring A can be synthesized in this manner and those having a prenyl group in position 3 by using some active substrate like a 1,3 diketone.

Mulberrochromene[9] has free prenyl unit and a fused pyran system in the ring A of flavonoids. An analogous example in the flavonol series is sericetin which was isolated from the roots of *Mundulea sericea*[15] and identified as 8-prenyl-6″,6″-dimethylpyrano[2″,3″:7,6]galangin. It is therefore likely that analogous derivatives of chrysin may also be isolated from nature. In view of this possibility, cyclodehydrogenation of 6,8-diprenylchrysin with DDQ has been studied (reaction 9). A mixture of two isomeric products was obtained which was separated first by column chromatography and then by fractional crystallization. The major product, mp 156°, was identified as the angular chromene, 5-hydroxy-6-prenyl-6″,6″-dimethylpyrano[2″,3″:7,8]flavone [3-deoxyisosericetin (**15**)] on the basis of its nmr and mass spectra. Thus the nmr spectrum showed signals of one prenyl unit, a condensed 2,2-dimethylpyran unit, a proton in 3 position, and a phenyl group (see Experimental Section). The mass spectrum showed characteristic (M − 56) mass fragments at m/e 332 (63%) which establishes its angular nature.[16] The minor products, mp 166°, was therefore the linear isomer[16] (3-deoxysericetin). The structure was confirmed by nmr and mass spectra. The mass spectrum showed the characteristic (M − 55) fragment at m/e 333 (73%), which establishes its linear nature.[16]



(9)

15 **16**

Experimental Section[17]

Nuclear Prenylation of Chrysin (1) Using Prenyl Bromide. To a solution of chrysin[13] (4 g) in anhydrous methanol (125 ml) was added a methanolic solution of sodium methoxide, *i.e.* 5.6 g of Na/60 ml of methanol. The mixture was cooled, treated with prenyl bromide (7.6 ml) in one lot, and refluxed for 3 hr. After removal of the solvent, the mixture was treated with ice and acidified in cold with dilute HCl. The solid product was examined on tlc using solvent system B which showed the presence of two compounds. It was therefore subjected to column chromatography and the column eluted successively with (1) light petroleum-benzene (8:2) and (2) benzene, giving the following fractions A and B.

Fraction A was crystallized from the benzene-light petroleum mixture yielding 5,7-dihydroxy-6,8-di-*CC*-prenylflavone (**2**) as shining yellow needles (1 g): mp 196°; soluble in aqueous Na_2CO_3; intense green ferric reaction; R_f 0.42 (solvent A); nmr δ 1,80, 1.84 [2 d, 12, J = 4 and 1.5 Hz, $(CH_3)_2C{=}$], 3.47, 3.65 (2 d, 4, J = 6 Hz, $ArCH_2$), 5.36 (broad m, 2, $-CH{=}$), 6.72 (s, 1 H in position 3), 7.58 (m, 3 H in positions 3′, 4′, and 5′), and 7.96 (m, 2 H in positions 2′ and 6′).

Anal. Calcd for $C_{25}H_{26}O_4$: C, 76.9; H, 6.7. Found: C, 76.9; H, 6.8.

The diacetate, prepared from **2** by the acetic anhydride-pyridine method, was crystallized from ethyl acetate-light petroleum mixture as colorless needles: mp 176°; R_f 0.50 (solvent D); negative ferric reaction; nmr δ 1.72, 1.74 [2 s, 12, $(CH_3)_2C{=}$], 2.34, 2.45 (2 s, 6, $OCOCH_3$), 3.29, 3.57 (2 d, 4, J = 6 Hz, CH_2), 5.18 (m, 2, $-CH{=}$), 6.68 (s, 1 H in position 3), 7.51 (m, 3 H in positions 3′, 4′, and 5′) and 7.85 (m, 2 H in positions 2′ and 6′).

Anal. Calcd for $C_{29}H_{30}O_6$: C, 73.4; H, 6.3. Found: C, 73.4; H, 6.4.

Fraction B was crystallized from the ethyl acetate-light petroleum mixture to give 5,7-dihydroxy-6-prenylflavone (**3**) as yellow plates [0.5 g): mp 216°; R_f 0.69 (solvent C); soluble in aqueous Na_2CO_3; green ferric reaction.

Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6. Found: C, 74.5; H, 6.0.

The diacetate prepared from **3** by the acetic anhydride-pyridine method was crystallized from methanol as shining needles: mp 116°; R_f 0.41 (solvent D); negative ferric reaction; nmr δ 1.69, 1.74 [2 s, 6, $(CH_3)_2C{=}$], 2.34, 2.46 (2 s, 6, $-OCOCH_3$), 3.30 (d, 2, J = 6 Hz, $ArCH_2$), 5.03 (m, 1, $-CH{=}$), 6.68 (s, 1 H in position 3), 7.36 (s, 1 H in position 8), 7.54 (m, 3 H in positions 3′, 4′, and 5′), and 7.86 (m, 2 H in positions 2′ and 6′).

Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.9; H, 5.5. Found: C, 70.9; H, 5.6.

5-Hydroxy-7-methoxy-6,8-diprenylflavone (4). A solution of 5,7-dihydroxy-6,8-diprenylflavone (**2**, 100 mg) in acetone (20 ml) was refluxed with dimethyl sulfate (0.03 ml) and K_2CO_3 (500 mg) for 3 hr. Acetone was distilled off and water added to the residue. The solid thus obtained was purified by column chromatography and crystallized from the ethyl acetate-light petroleum mixture; 5-hydroxy-7-methoxy-6,8-diprenylflavone (**4**) was obtained as long yellow needles (80 mg): mp 128°; R_f 0.80 (solvent B); intense green ferric reaction; nmr δ 1.70, 1.83 [2 s, 12, $(CH_3)_2C{=}$], 3.43, 3.60 (2 d, 4, J = 6 Hz, $ArCH_2$), 3.80 (s, 3, OCH_3), 5.29 (m, 2, $-CH{=}$), 6.70 (s, 1 H in position 3), 7.57 (m, 3 H in positions 3′, 4′, and 5′) and 7.94 (m, 2 H in positions 2′ and 6′).

Anal. Calcd for $C_{26}H_{28}O_4$: C, 77.2; H, 7.0. Found: C, 76.8; H, 7.2.

6′′,6′′,6′′′,6′′′-Tetramethyl-4′′,5′′:4′′′,5′′′-bis(dihydropyrano)[2′′,3′′:7,8;2′′′,3′′′:5,6]flavone (6). A solution of **2** (300 mg) in formic acid (20 ml) was heated on a steam bath for 2 hr and then poured over ice. The solid thus obtained was purified by column chromatography. Elution with benzene gave **6**, which was crystallized from benzene-light petroleum mixture as yellow prisms (100 mg): mp 186°; R_f 0.40 (solvent C); negative ferric reaction; nmr δ 1.38, 1.43 [2 s, 12, $(CH_3)_2C<$], 1.86 (m, 4, $-CH_2-$), 2.64, 2.96 (2 t, 4, J = 6 Hz, $-CH_2-$), 6.64 (s, 1 H in position 3), 7.47 (m, 3 H in positions 3′, 4′, and 5′) and 7.88 (m, 2 H in positions 2′ and 6′).

Anal. Calcd for $C_{25}H_{26}O_4$: C, 76.9; H, 6.7. Found: C, 77.3; H, 7.2.

5-Hydroxy-7-methoxy-6-prenylflavone (5). A solution of **3** (100 mg) in acetone (18 ml) was refluxed with dimethyl sulfate (0.025 ml) and K_2CO_3 (500 mg) for 3 hr. The product was crystallized from ethyl acetate-light petroleum mixture to afford **5** (70 mg) as glistening light yellow crystals: mp 162-63°; R_f 0.80 (solvent C); green ferric reaction; nmr δ 1.70, 1.83 [2 s, 6, $(CH_3)_2C{=}$], 3.39 (d, 2, J = 6 Hz, $ArCH_2$), 3.92 (s, 3, OCH_3), 5.29 (m, 1, $-CH{=}$), 6.52 (s, 1 H in position 3), 6.68 (s, 1 H in position 8), 7.57 (m, 3 H in positions 3′, 4′, and 5′), and 7.90 (m, 2 H in positions 2′ and 6′).

Anal. Calcd for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0 Found: C, 75.4; H, 6.3.

7-Methoxy-6′′,6′′-dimethyl-4′′,5′′-dihydropyrano[2′′,3′′:5,6]flavone (7). **5** upon treatment with formic acid gave **7** which was crystallized from methanol as light yellow needles: mp 250°; R_f 0.50 (solvent D); negative ferric reaction; nmr δ 1.42 [s, 6, $(CH_3)_2C<$], 1.78, 2.65 (2 t, 4, J = 7 Hz, $-CH_2-$), 3.90 (s, 3, OCH_3), 6.47 (s, 1 H in position 8), 6.58 (s, 1 H in position 3), 7.47 (m, 3 H in 3′, 4′, and 5′ positions), and 7.82 (m, 2 H in positions 2′ and 6′).

Anal. Calcd for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0. Found: C, 74.5; H, 6.5.

Reaction of 5,7-Dihydroxy-6-prenylflavone (3) with formic acid. A solution of **3** (400 mg) in formic acid (30 ml) was kept at room temperature for 1 hr, water added and the whole mixture extracted with $CHCl_3$. The product in $CHCl_3$ showed two spots on tlc, one showing positive ferric reaction and the other negative. It was separated by column chromatography. Elution with benzene-light petroleum (1:1) gave 5-hydroxy-6′′,6′′-dimethyl-4′′,5′′-dihydropyrano[2′′,3′′:7,6]flavone (**8**), which was crystallized from methanol as yellow needles (200 mg): mp 180°; R_f 0.78 (solvent C); bluish green ferric reaction; nmr δ 1.39 [s, 6, $(CH_3)_2C<$], 1.85, 2.77 (2 t, 4, J = 7 Hz, $-CH_2-$), 6.47 (s, 1 H in position 8), 6.66 (s, 1 H in position 3), 7.54 (m, 3 H in positions 3′, 4′, and 5′). and 7.91 (m, 2 H in positions 2′ and 6′).

Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6. Found: C, 74.8; H, 6.0.

Further elution with benzene-ethyl acetate (7:3) gave a compound which was crystallized from ethyl acetate to give 7-hydroxy-6′′,6′′-dimethyl-4′′,5′′-dihydropyrano[2′′,3′′:5,6]flavone (**9**) as yellow hexagonal plates (50 mg): mp 296°; R_f 0.36 (solvent D); negative ferric reaction.

Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6. Found: C, 74.9; H, 5.2.

5-Hydroxy-6′′,6′′-dimethylpyrano[2′′,3′′:7,6]flavone (10). **3** (100 mg) was dissolved in dry benzene (20 ml), and the solution was refluxed for 35 min; colorless hydroquinone separated out. It was filtered and purified by column chromatography. When the column was eluted with benzene-light petroleum (5:95) and the eluate crystallized from methanol, **10** was obtained as pale yellow needles: mp 188° (lit.[14] mp 187-188°); R_f 0.56 (solvent B); bluish green ferric reaction; nmr δ 1.47 (s, 6, $(CH_3)_2C{=}$), 5.60, 6.71 (2d, 2, J = 10 Hz, two olefinic H of pyran ring), 6.50 (s, 1 H in position 8), 6.60 (s, 1 H in position 3), 7.50 (m, 3 H in positions 3′, 4′, and 5′), and 7.90 (m, 2 H in positions 2′ and 6′).

Anal. Calcd for $C_{20}H_{16}O_4$: C, 75.0; H, 5.0. Found: C, 75.1; H, 5.0.

Nuclear Prenylation of Chrysin (1) using 2-Hydroxy-2-methyl-3-butene. To a stirred solution of chyrsin (6 g) in dry dioxane (140 ml) was added gradually boron trifluoride etherate (3.5 ml) at room temperature during a course of 30 min, and the solution acquired a pink-red color. To this was added a solution of 2-hydroxy-2-methyl-3-butene (3 ml) in dry dioxane (20 ml), and the whole solution was stirred for 4 hr and kept at room temperature overnight. After dilution with moist ether (300 ml), the ethereal solution was washed with water (6 × 100 ml), whereby the color of the solution discharged. It was then extracted with 1% aqueous Na_2CO_3 (3 × 100 ml) to remove unreacted chrysin (3 g); the remaining ethereal solution on examination by tlc (solvent B) showed the presence of three compounds. Hence it was subjected to column chromatography and column eluted successively with (1) benzene-light petroleum (2:8), (2) benzene, and (3) benzene-ethyl acetate (9:1) giving the following three distinct fractions A, B, and C.

Fraction A was crystallized from the benzene-light petroleum mixture affording **2** (240 mg), identical in melting point, mixture melting point, and R_f with the sample prepared earlier.

Fraction B was crystallized from the ethyl acetate-light petroleum mixture yielding **3** (480 mg), identical in melting point, mixture melting point, and R_f with the sample prepared earlier.

Fraction C was crystallized from benzene to give **11** (1 g) as yellow needles: mp 206°; soluble in aqueous Na_2CO_3; intense green ferric reaction; R_f 0.60 (solvent C).

Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6. Found: C, 75.0; H, 5.7.

The diacetate prepared from **11** by acetic anhydride-pyridine method was crystallized from methanol as colorless needles: mp 173°; R_f 0.40 (solvent C); negative ferric reaction; nmr δ 1.72 (1 broad s, 6, $(CH_3)_2C{=}$), 2.36, 2.40 (2 s, 6, $OCOCH_3$), 3.60 (d, 2, J = 7 Hz, $ArCH_2$), 5.22 (m, 1, $-CH{=}$), 6.98 (s, 1 H in position 3), 7.30 (s, 1 H in position 6), 7.53 (m, 3 H in positions 3′, 4′, and 5′), and 7.95 (m, 2 H in positions 2′ and 6′).

Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.9; H, 5.5 Found: C, 70.7; H, 5.9.

5-Hydroxy-7-methoxy-8-prenylflavone (12). It was prepared from **11** as the 6-prenyl isomer and was crystallized from ethyl acetate-light petroleum mixture. It formed glistening yellow crystals: mp 156°; R_f 0.87 (solvent C); intense green ferric reaction; nmr δ 1.72, 1.82 (2 broad s, 6, $(CH_3)_2C{=}$), 3.43 (d, 2, J = 7 Hz, $ArCH_2$), 3.99 (s, 3, OCH_3), 5.24 (m, 1, $-CH{=}$), 6.60 (s, 1 H in position 3), 7.35 (s, 1 H in position 6), 7.49 (m, 3 H in positions 3′, 4′, and 5′), and 7.99 (m, 2 H in positions 2′ and 6′).

Anal. Calcd for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0. Found: C, 75.2; H, 6.4.

It was recovered unchanged when heated with formic acid.

5-Hydroxy-6′′,6′′-dimethyl-4′′,5′′-dihydropyrano[2′′,3′′:7,8]flavone (13). **11** upon treatment with formic acid and subsequent crystallization of the product from ethyl acetate-light petroleum mixture gave **13** as light yellow needles: mp 210°; R_f 0.74 (solvent C); light green ferric reaction; nmr δ 1.37 [s, 6, $(CH_3)_2C<$], 1.88, 2.80 (2 t, 4, J = 7 Hz, $-CH_2-$), 6.70 (s, 1 H in position 3), 7.36 (s, 1 H in position 6), 7.59 (m, 3 H in positions 3′, 4′, and 5′), and 7.86 (m, 2 H in positions 2′ and 6′).

Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.5; H, 5.6. Found: C, 74.2; H, 6.0.

5-Hydroxy-6′′,6′′-dimethylpyrano[2′′,3′′:7,8]flavone (14). **11** (100 mg) was refluxed with DDQ (70 mg) in dry benzene (20 ml) for 35 min and the product purified by column chromatography. Elution with benzene-light petroleum (9:1) gave angular chromene **14** (60 mg) which was crystallized from ethyl acetate-light petroleum mixture as yellow prisms: mp 178° (lit.[14] mp 176-177°); R_f 0.50 (solvent B); intense green ferric reaction; nmr δ 1.49 [s, 6, $(CH_3)_2C{=}$], 5.65, 6.76 (2 d, 2, J = 10 Hz, two olefinic H of pyran ring), 6.48 (s, 1 H in position 3), 7.45 (s, 1 H in position 6), 7.56 (m, 3 H in positions 3′, 4′, and 5′), and 7.96 (m, 2 H in positions 2′ and 6′).

Anal. Calcd for $C_{20}H_{16}O_4$: C, 75.0; H, 5.0. Found: C, 75.0; H, 5.0.

3-Deoxysericetin (16) and 3-Deoxyisosericetin (15). To a solution of 2 (500 mg) in dry benzene (40 ml) was added DDQ (300 mg) and the whole solution refluxed for 1 hr. It was filtered while hot, benzene distilled off, and the residue subjected to column chromatography. Elution with benzene–light petroleum (2:8) gave a solid which again proved to be a mixture. Fractional crystallization with light petroleum (mother liquor A) yielded the sparingly soluble solid which on recrystallization from ethyl acetate–light petroleum mixture afforded 5-hydroxy-6-prenyl-6′′,6′′-dimethylpyrano[2′′,3′′:7,8]flavone [3-deoxyisosericetin (15)] (120 mg): mp 156°; R_f 0.78 (solvent A); light green ferric reaction; nmr δ 1.50 [s, 6, $(CH_3)_2C<$], 1.70, 1.83 [2 broad s, 6, $(CH_3)_2C=$], 3.41 (d, 2, J = 7 Hz, $ArCH_2$), 5.33 (m, 1, $-CH=$), 5.67 6.88 (2 d, 2, J = 10 Hz, two olefinic H of pyran ring), 6.70 (s, 1 H in position 3), 7.59 (m, 3 H in positions 3′, 4′, and 5′) and 7.93 (m, 2 H in positions 2′ and 6′); mass spectrum (70 eV) *m/e* (rel intensity) 388 (85), 373 (100), 345 (57), 332 (63), 317 (11), 215 (17), 165 (11), 105 (11), 77 (10).

Anal. Calcd for $C_{25}H_{24}O_4$: C, 77.3; H, 6.2. Found: C, 76.8; H, 5.9.

The mother liquor A yielded a solid which after crystallization twice from methanol yielded 5-hydroxy-8-prenyl-6′′,6′′-dimethylpyrano[2′′,3′′:7,6]flavone [3-deoxysericetin (16)] (80 mg) as pale yellow needles: mp 166°; R_f 0.74 (solvent A); intense green ferric reaction; nmr δ 1.50 [s, 6, $(CH_3)_2C<$], 1.72, 1.79 [2d, 6, J = 2 Hz, $(CH_3)_2C=$], 3.56 (d, 2, J = 7 Hz, $ArCH_2$), 5.26 (m, 1, $-CH=$), 5.66, 6.81 (2 d, 2, J = 10 Hz, two olefinic H of pyran ring), 6.71 (s, 1 H in position 3), 7.59 (m, 3 H in positions 3′, 4′, and 5′), and 7.96 (m, 2 H in positions 2′ and 6′); mass spectrum (70 eV) *m/e* (rel intensity) 388 (82), 373 (100), 345 (68), 333 (73), 215 (28), 165 (14), 105 (27), 85 (36), 77 (22), 71 (55), 55 (46).

Anal. Calcd for $C_{25}H_{24}O_4$: C, 77.3; H, 6.2. Found: C, 76.8; H, 5.9.

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Registry No.—1, 480-40-0; 2, 50678-89-2; 2 diacetate, 50678-90-5; 3, 50678-91-6; 3 diacetate, 50678-92-7; 4, 50678-93-8; 5, 50678-94-9; 6, 50678-95-0; 7, 50678-96-1; 8, 50830-97-2; 9, 50678-97-2; 10, 34187-26-3; 11, 34125-75-2; 11 diacetate, 50678-98-3; 12, 50678-99-4; 13, 50679-00-0; 14, 34187-25-2; 15, 50679-01-1; 16, 50679-02-2; prenyl bromide, 870-63-3; 2-hydroxy-2-methyl-3-butene, 115-18-4.

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(17) All melting points were taken on Buchi melting point apparatus and are uncorrected. Tlc was carried out on plates coated with silica gel supplied by NCL, Poona. Spraying reagent was generally 10% aqueous sulfuric acid, but 10% alcoholic ferric chloride was also used for such compounds which gave positive ferric reaction. Tlc was carried out using one of the following solvent systems: (A) benzene, (B) benzene–ethyl acetate (9:1), (C) benzene–ethyl acetate (75:25), (D) benzene–ethyl acetate (1:1). Column chromatography was carried out using silica gel supplied by NCL, Poona. Nuclear magnetic resonance spectra were determined in $CDCl_3$ using 60 MHz spectrophotometer. Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane as internal standard. Mass spectra were determined on samples introduced through the heated inlet system using MS 72 spectrometer, 70 eV ionizing voltage, 900 × 10 trap current, and 2.0 kV accelerating voltage.

1,8 Interactions in Naphthalene Derivatives. An X-Ray Structure Determination and Nuclear Magnetic Resonance Studies of 1,8-Di(bromomethyl)naphthalene[1]

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The conformation of 1,8-di(bromomethyl)naphthalene has been determined in the crystalline state and it has been found that the molecule has essentially twofold symmetry about the C-9–C-10 bond with the bromines located above and below the plane of the ring. The carbon–bromine bonds are inclined toward one another about 10° from planes perpendicular to the naphthalene ring which contain the C-1–C-11 and C-8–C12 bonds. This conformation has formally nonbonded H···Br distances of 2.85 Å which are substantially less than the sum of the van der Waals radii and could well indicate some degree of electrostatic binding. The strain in the molecule is largely relieved both by in-plane and out-of-plane bending of the C-1–C-11 and the C-8–C-12 bonds as well as some skeletal distortion of the ring. Low-temperature proton nmr studies of 1,8-di(bromomethyl)naphthalene and some related compounds showed no evidence of barriers to rotation about the C-1–C-11 and C-8–C-12 bonds large enough to be detectable.

Alkyl or aryl substituents at the 1,8 positions (the peri positions) of naphthalene are in close proximity to one another and provide many interesting opportunities for study of conformations and barriers to rotation about the extracyclic bonds, C-1–C-11 and C-8–C-12.[3,4] Relatively few other simple molecules have the special feature of having the substituents close to one another and attached to a relatively rigid framework by essentially parallel bonds. Because of the importance of knowing just what conformations are, in fact, favored for molecules of this type, we have determined the structure of 1,8-di(bromomethyl)naphthalene (1) by X-ray diffraction. On the as-

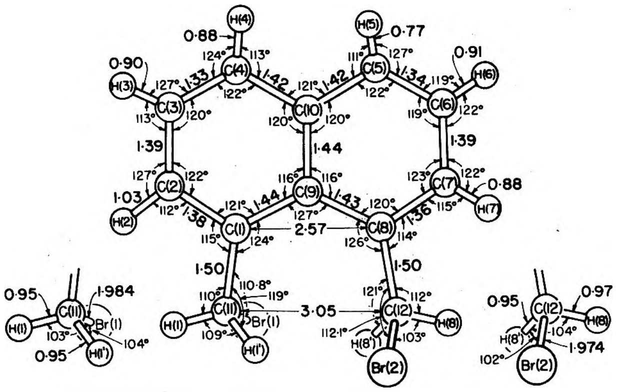
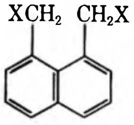


Figure 1. Bond angles and bond distances found for 1 in the crystal. Estimated standard deviations in the bond distances are about 0.006 Å for C–Br, 0.01 Å for C–C, and 0.06 Å for C–H.

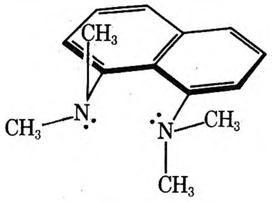
sumption that the conformation observed for the solid state might also be important in solution, we have investigated the proton nmr spectra of 1 and of several related compounds (2–4) at low temperatures.



1, X = Br
2, X = H
3, X = Cl
4, X = OH

Most of the 1,8-disubstituted naphthalenes bearing substituents at the 1,8 positions whose structures have been investigated by X-ray diffraction have been halogen derivatives. These substances have no complications of extracyclic conformations but do show substantial nonplanarity, both of the halogens with respect to the rings and of the naphthalene rings themselves.[5] Relief of steric strain is normally most easily achieved by bond bending, but for 1,8-disubstituted naphthalenes there is a buttressing effect exerted by the 2,7 hydrogens which tends to favor out-of-plane distortions. This type of interaction for dihalonaphthalenes reaches an extreme with 1,8-diiodonaphthalene.[6]

The crystallographic investigations of substances where conformational properties should be important include 3-bromo-1,8-dimethyl-[7] and octamethylnaphthalenes,[8] but in these two studies the methyl hydrogens were not located; 1,8-dinitronaphthalene,[9] where the planes of the nitro groups are twisted about 43° from the plane of the ring; 1,4,5,8-tetranitronaphthalene[10] with similar conformations of the nitro groups; 1,8-diphenylnaphthalene,[4a] where the phenyl rings are face-to-face but substantially splayed outward and inclined to approximately 45° from the plane of the naphthalene ring; 1,4,5,8-tetraphenylnaphthalene,[11] which is similarly disposed; the conjugate acid of 1,8-bis(dimethylamino)naphthalene,[12] which has the added proton in the plane of the ring shared between the two nitrogen lone pairs; the methyl groups are above and below the plane; and 1,8-bis(dimethylamino)naphthalene,[13] the only case really comparable to the present one in that it involves saturated substituents. 1,8-Bis(dimethylamino)naphthalene assumes what appears to be a compromise conformation (5), with the methyl groups not in the most favorable location to avoid the hydrogens on C-2 and C-7, with the unshared pairs not face-to-face, and possibly with some degree of lone-pair delocalization in the ring (which, of course, would be particularly favored with the methyl groups in the plane of the ring).



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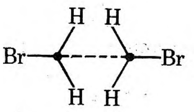
Some of the more symmetrical, possible conformations of 1 are 6–8, which represent end-on views at C-11 and C-12 and are chosen to avoid close proximity of bromines with the respective opposite carbons C-11 and C-12, or other obvious steric conflicts between substituents on these atoms. Of these, 6 would be expected to be the least favorable because of the eclipsing of the hydrogens and the interactions of the bromines with the hydrogens at C-2 and C-7. Arrangements 7 and 8 relieve these interactions at the cost of creating new nonbonded hydrogen–hydrogen (and, for 8, hydrogen–bromine) interactions. Clearly, the mode by which the molecule resolves these conflicts is of substantial interest.



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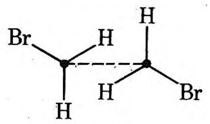

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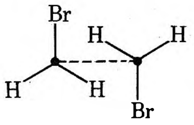

8

Experimental Section

1,8-Di(bromomethyl)naphthalene (1) was prepared as described[14] and recrystallized from ether. Preliminary Weissenberg and precession photographs indicated the monoclinic space group C2/c (systematic absences: *hkl* for $(h + k)$ odd; *h0l* for *l* odd). Unit-cell dimensions were derived from a least-squares fit to 20 values for 15 medium- to high-angle reflections centered on a diffractometer; they are $a = 23.500 \pm 0.004$ Å, $b = 7.662 \pm 0.002$ Å, $c = 12.543 \pm 0.006$ Å, $\beta = 95.73 \pm 0.02°$.[15] The density calculated for eight molecules in the unit cell is 1.856 g cm^{-3}, in satisfactory agreement with the value 1.850 ± 0.002 g cm^{-3} measured by flotation.

The crystal used for collection of intensity data was an approximate cube, 0.2 mm on an edge, mounted along the *c* axis. Intensities were measured using a Datex-automated General Electric three-circle diffractometer equipped with a copper-target X-ray tube, Ni filter, scintillation counter, and pulse-height analyzer.

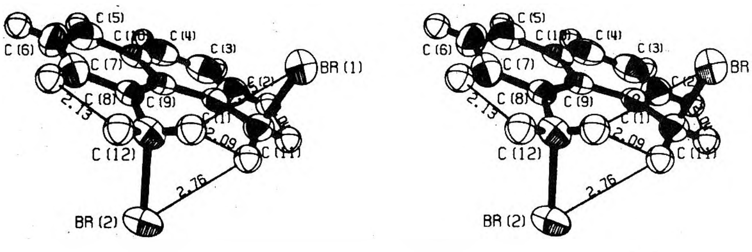

Figure 2. Stereoview of 1,8-di(bromomethyl)naphthalene (1) as it exists in the crystal.

Table I
Atomic Coordinates As Determined by X-Ray Diffraction[a]

	x	*y*	*z*
Br (1)	0.15221 (3)	−0.29088 (8)	0.00417 (5)
Br (2)	0.09420 (3)	0.16626 (9)	−0.24065 (5)
C (1)	0.1777 (2)	0.0748 (7)	0.0346 (4)
C (2)	0.2267 (3)	0.1128 (10)	0.1000 (5)
C (3)	0.2270 (4)	0.2348 (11)	0.1820 (6)
C (4)	0.1785 (4)	0.3152 (10)	0.2002 (5)
C (5)	0.0752 (4)	0.3690 (8)	0.1591 (5)
C (6)	0.0258 (3)	0.3454 (9)	0.0981 (6)
C (7)	0.0251 (3)	0.2396 (8)	0.0079 (5)
C (8)	0.0719 (2)	0.1498 (7)	−0.0182 (4)
C (9)	0.1251 (2)	0.1657 (6)	0.0470 (4)
C (10)	0.1261 (3)	0.2834 (7)	0.1365 (4)
C (11)	0.1838 (3)	−0.0682 (9)	−0.0452 (5)
C (12)	0.0623 (3)	0.0475 (8)	−0.1202 (4)
H (1)	0.223 (2)	−0.095 (7)	−0.048 (4)
H (1′)	0.166 (2)	−0.055 (7)	−0.116 (4)
H (2)	0.261 (2)	0.039 (7)	0.081 (4)
H (3)	0.262 (2)	0.254 (7)	0.216 (4)
H (4)	0.176 (2)	0.396 (7)	0.250 (4)
H (5)	0.081 (2)	0.431 (7)	0.208 (4)
H (6)	−0.006 (2)	0.404 (7)	0.114 (4)
H (7)	−0.006 (2)	0.227 (7)	−0.037 (4)
H (8)	0.022 (2)	0.038 (7)	−0.145 (4)
H (8′)	0.077 (2)	−0.067 (7)	−0.125 (4)

[a] Values in parentheses are standard deviations in the last digit.

All reflections with 2θ <120° were recorded using a θ–2θ scan mode at a scan rate of 1° (in 2θ)/min; the scan width varied from 2.0° at $2\theta = 0°$ to 2.9° at $2\theta = 120°$. A 20-sec background count was recorded at each scan extremum. Three check reflections (10, 2, 2; 10, 0, 6; 0, 2, 4) were recorded periodically; they showed steady but somewhat unequal drops in intensity, averaging about 10% over the 5-day period. The recorded intensities were corrected for this average decay, and for Lorentz and polarization effects; no absorption corrections were applied ($\mu r \approx 1.0$). Assigned variances $\sigma^2(F_o{}^2)$ were based on counting statistics plus the term $(0.02S)^2$, where S is the scan count. Of the 1675 independent reflections that were recorded, 1551 had net intensities greater than zero.

The structure was derived by standard heavy-atom techniques beginning with a three-dimensional Patterson map.[16] Two cycles of least-squares refinement of the heavy-atom coordinates (C and Br) gave an R value of 0.17. During the remaining eight least-squares cycles, additional parameters were added until they totaled 158: coordinates and anisotropic temperature factors for the 14 heavy atoms, coordinates for the 10 hydrogen atoms (which were initially assigned on geometric grounds), a scale factor, and a secondary-extinction parameter.[17] The hydrogen atoms were assigned fixed, isotropic temperature factors with $B = 5.0$ Å^2. During the final refinement cycle, the largest shift in a heavy-atom parameter was 0.5σ and, in a hydrogen-atom coordinate, 0.9σ. The goodness-of-fit, $[\Sigma w(F_o{}^2 - F_c{}^2)^2/(N - P)]^{1/2}$ for N = 1675 reflections and P = 158 parameters, was 1.36; the R index, $\Sigma||F_o| - |F_c||/\Sigma|F_o|$, was 0.056 for the 1551 reflections with net intensities greater than zero.

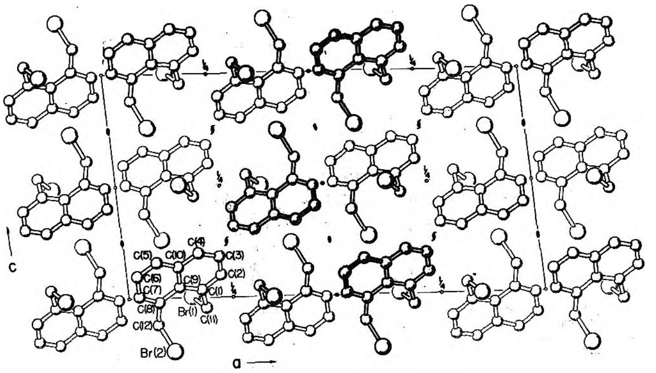

Figure 3. Arrangement of molecules of 1 in the crystal.

Results and Discussion

The final atomic coordinates are given in Table I and the anisotropic temperature parameters in Table II. Bond distances and angles are shown in Figure 1, a stereoptic view of the molecule in Figure 2, and the arrangement of the molecules in Figure 3.

Bond distances in the naphthalene ring are in excellent agreement with values found in 1,8-bis(dimethylamino)-naphthalene, the only other 1,8-disubstituted naphthalene derivative to have been studied with comparable accuracy. Once again we note that the four ring C–C bonds involving C-1 and C-8 are appreciably longer—by an average of 0.025 Å in the present case—than the corresponding bonds involving C-4 and C-5. In the case of 1,8-bis(dimethylamino)naphthalene[13] the effect was somewhat larger, 0.035 Å, and was attributed in part to the electron-withdrawing ability of the substituent nitrogen atoms, and in part to overcrowding of the peri groups. In the present case, the substituent -CH_2Br groups should have little electronic influence on the ring bonds, so that the distortion must be blamed almost entirely on overcrowding. A comparison of bond distances with those found for naphthalene[18] and perdeuterionaphthalene[19] suggests that this overcrowding leads to a redistribution of bonding electrons within the naphthalene nucleus, the bonds involving C-4 and C-5 being shortened by about the same amount that those involving C-1 and C-8 are lengthened.

Overcrowding between the peri -CH_2Br groups is relieved in two additional ways: in-plane bending of the C-1-C-11 and C-8-C-12 bonds, and out-of-plane distortions involving the entire molecule. Deviations of the individual

Table II
Anisotropic Temperature Parameters[a]

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Br (1)	6.06 (4)	4.59 (3)	5.27 (4)	1.41 (3)	1.22 (3)	0.72 (3)
Br(2)	6.08 (4)	5.77 (4)	3.40 (3)	−0.16 (3)	0.02 (2)	1.24 (3)
C (1)	3.7 (3)	4.1 (3)	3.4 (2)	0.0 (2)	0.3 (2)	1.1 (2)
C (2)	4.2 (3)	6.9 (4)	4.5 (3)	0.2 (3)	−0.2 (3)	0.9 (3)
C (3)	5.5 (4)	7.3 (5)	5.0 (4)	−1.6 (4)	−1.4 (3)	1.4 (3)
C (4)	8.7 (5)	5.2 (4)	3.8 (3)	−2.0 (4)	0.0 (3)	0.0 (3)
C (5)	8.9 (5)	3.4 (3)	4.6 (3)	−0.2 (3)	2.3 (4)	−0.9 (2)
C (6)	5.6 (4)	4.7 (3)	7.3 (4)	1.1 (3)	2.4 (4)	0.4 (3)
C (7)	4.7 (3)	4.7 (3)	4.9 (4)	0.6 (3)	0.2 (3)	0.3 (3)
C (8)	4.2 (3)	3.1 (2)	3.3 (2)	0.1 (2)	0.7 (2)	0.8 (2)
C (9)	4.2 (3)	3.1 (2)	2.8 (2)	−0.5 (2)	0.5 (2)	0.7 (2)
C (10)	5.8 (3)	3.2 (3)	3.1 (3)	−0.9 (3)	0.4 (2)	0.4 (2)
C (11)	4.0 (3)	5.8 (3)	3.6 (3)	1.1 (3)	0.7 (2)	1.1 (3)
C (12)	4.1 (3)	3.9 (3)	3.5 (3)	−0.1 (2)	−0.3 (2)	0.5 (2)

[a] Values in parentheses are standard deviations in the last digit. The temperature factors have the general form exp $-\frac{1}{4}(B_{11}h^2a^{*2} \cdots + 2B_{23}klb^*c^*)$.

Table III
Deviations from the Least-Squares Plane of the Naphthalene Ring[a]

Atom	Deviation, Å	Atom	Deviation, Å
C (1)	−0.068	C (8)	0.051
C (2)	−0.020	C (7)	0.045
C (3)	0.047	C (6)	−0.041
C (4)	0.037	C (5)	−0.041
C (9)	0.000	C (10)	−0.010
C (11)	−0.229	C (12)	0.188
Br (1)	−2.110	Br (2)	2.024

[a] The plane was passed through atoms C-1–C-10, all weighted equally. The direction cosines of the plane relative to *a*, *b*, and *c* are 0.2911, 0.7511, and −0.6186, and the origin-to-plane distance is 1.445 Å.

Table IV
Ring-Proton Coupling Constants and Chemical-Shift Differences for 1,8-Di(bromomethyl)naphthalene (1), 1,8-Dimethylnaphthalene (2), 1,8-Di(chloromethyl)naphthalene (3), and 1,8-Di(hydroxymethyl)naphthalene (4)

Compd	Solvent	J_{23}, Hz	J_{24}, Hz	J_{34}, Hz	δ_{43}, ppm	δ_{42}, ppm
1	CCl_4	7.5	1.6	8.5	0.28	0.43
2	CCl_4	7.0	1.8	7.4	0.38	0.42
3	CCl_4	7.5	1.4	8.9	0.30	0.44
4	DMSO[a]	7.5	1.5	8.6	0.23	0.42

[a] Dimethyl sulfoxide.

atoms from the mean plane of the naphthalene ring are given in Table III. These deviations are smaller than in the dimethylamino compound,[13] while the in-plane splaying of the C-CH_2Br bonds is larger; presumably the double-bond character in the C-1-N and C-8-N bonds of the dimethylamino compound makes bond bending a less attractive mechanism for relieving strain than in the present case.

The puckering of the naphthalene system is accomplished primarily by a twist about the central C-9-C-10 bond by about 4° in the present compound and 9° in the dimethylamino compound. This twist apparently results in a redistribution of electrons in the ring system, for in both compounds (as well as in other peri compounds[7-13] the C-9-C-10 bond is significantly longer than in naphthalene and perdeuterionaphthalene while the C-2-C-3 and C-6-C-7 bonds are marginally shorter.

The C-1-C-11 and C-8-C-12 bonds are sufficiently nonparallel as to result in a C-11···C-12 distance of 3.05 Å compared to 2.57 Å for C-1···C-8. This C-11···C-12 distance is substantially larger than the corresponding distance in 3-bromo-1,8-dimethylnaphthalene, 2.92 Å.[7] The conformations about the C-CH_2Br bonds are such that the bromine atoms are directed to opposite sides of the molecular plane: the torsion angles C-2-C-1-C-11-Br-1 and C-7-C-8-C-12-Br-2 are 101.1 and 101.8°. A number of the nonbonded distances (Figure 2) are less than the sums of the van der Waals radii as given by Pauling[20] or Bondi.[21] The most uncomfortable interactions appear to be the Br-1···H-8′ (2.85 Å) and Br-2···H-1′ (2.76 Å) contacts; however, it is possible that these interactions include electrostatic attraction effects of the type postulated to account for the unusual stability of axial halogens on cyclohexane rings in the presence of polar groups.[22]

Nmr Studies. The arrangement and general tightness of the bromomethyl groups of **1** as shown in Figure 2 suggest that the hydrogens on the methylene groups should be nonequivalent and that there might be a significant barrier to rotation, a process which would, of course, make the methylene hydrogens on the average equivalent. For this reason, some variable-temperature nmr studies were made of **1** and some related compounds, **2**, **3**, and **4**. At room temperature, the proton interactions on the ring carbons of **1–4** were analyzed[23] as independent ABC spin systems on the assumption that the couplings between the hydrogens on opposite sides of the molecule were small, as they are in other naphthalene derivatives.[24] The results of these analyses are shown in Table IV and they accord generally with the work of others.[24,25]

For compounds **1–4**, the methylene proton signals were single sharp lines at room temperature in carbon tetrachloride, while with **4** in dimethyl sulfoxide, hydroxyl exchange was slowed sufficiently so that the methylene signal was split into a doublet corresponding to a J_{HCOH} coupling of 5.3 Hz.

The singlets observed for the methylene protons at room temperature remained unchanged for **1** in vinyl chloride down to −130°, for **2** in the same solvent to −140°, for **3** in dimethyl ether to −130°, and for **4** in carbon disulfide to −40°. Although these results are perhaps not too surprising in view of what has been reported recently,[4c] at the time the experiments were carried out, we considered some possible explanations of the results which did not require that the barrier to rotation be small, especially for **1**. Briefly, these were (1) that the conformation of **1** in the crystal is dictated not by intramolecular but rather by intermolecular forces so that the stable conformation in solution is, in fact, **6**; and (2) that the methylene protons might coincidentally have the same shifts even for **8**. The arguments against the first proposition are that the crystal structure shows no unusual intermolecular interactions which would favor **8** over **6**, although this argument is weakened by not having crystals of **6** and knowing what their structure would be like, and also that **6** would be expected to have very substantial H-2···Br-1 and H-7···Br-2 interactions. The possibility that the chemical shifts would be coincident seems highly unlikely on the basis of a crude ring-current effect calculation which suggests that there should be perhaps 0.15 ppm difference in shift between them. There will also be a substantial influence produced by the bromines on the immediately adjacent hydrogens, of Br-1 on H-8′ and of Br-2 on H-1′. Qualitatively, one would expect that these influences on the close protons would be in the same direction (downfield) as the ring-current effect. For this reason, it seems quite unlikely that accidentally coincident chemical shifts are involved, and we conclude that rapid rotation is the correct explanation for the variable-temperature spectra. For **1–3**, the free energies of activation for rotation are probably less than 8 kcal/mol.

Registry No.—**1**, 2025-95-8; **2**, 569-41-5; **3**, 50585-29-0; **4**, 2026-08-6.

References and Notes

(1) Supported by the National Science Foundation and the Public Health Service through Research Training Grant 5T01 GM-01262-09-13CH to J. S. S.

(2) Centre D'Etudes Nucléaires de Grenoble, France.

(3) A very valuable review of the literature on this subject up to 1965 has been prepared by V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

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Notes

Kinetics of Hydrolysis of *o*-Tolunitrile in Moderately Concentrated Perchloric Acid Solutions[1]

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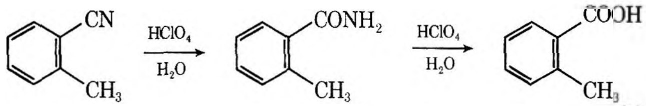
A kinetic study of the hydrolysis of benzonitrile was recently published by Hyland and O'Connor.[3] This prompts us to report a set of data obtained some years ago[4] concerning rates of hydrolysis of o-tolunitrile in $HClO_4$ solutions at 133.5°.

The hydrolysis reaction is represented in eq 1. An analytical technique was chosen that reveals only destruction of the nitrile and is insensitive to further hydrolysis of amide to acid. The data obtained in 1.5–6 *M* $HClO_4$ solutions are listed in Table I.



(1)

These data are correlated quite well by the linear free energy relationship (LFER) of eq 2, in which H_0 is the Hammett acidity function, k_ψ is the measured pseudo-first-order rate constant at any acid concentration, and k_2^0 is the second-order rate constant (first order in substrate, first order in H^+) at infinite dilution in water as reference state.[5] The correlation and the resulting parameters are summarized in Table II. The slope (ϕ value) is +0.61.

$$\log k_\psi + H_0 = \phi(H_0 + \log[H^+]) + \log k_2^0 \qquad (2)$$

Correlation of log k_ψ + H_0 with log a_w,[6] where a_w is the activity of water, was also attempted. That correlation is also summarized in Table II. The slope (w value) is +3.33. As revealed particularly by the standard deviations of points from the linear regression lines, σ_y, the correlation with log a_w is less satisfactory than with (H_0 + log [H^+]). A plot of the correlation with log a_w shows slight but persistent curvature, whereas the LFER plot is straight except for small random deviations most likely due to experimental error.

Table I
Kinetics of Hydrolysis of *o*-Tolunitrile in Aqueous Perchloric Acid at 133.5°

[HClO4], *M*	$10^5 k_\psi$, sec^{-1} [a]	H_0	$H_0 + \log [H^+]$
1.47	2.12 ± 0.06	−0.59	−0.41
3.01	6.42 ± 0.43	−1.33	−0.86
4.00	12.5 ± 0.55	−1.79	−1.18
4.51	16.0 ± 0.35	−2.02	−1.38
4.99	19.8 ± 0.53	−2.28	−1.58
5.50	32.0[b]	−2.59	−1.85
6.02	38.3 ± 1.15	−2.90	−2.12

[a] Standard deviations are shown. [b] Average of 31.7 ± 0.7 and 32.3 ± 1.4.

Table II
Summary of Rate Correlations

Correlation	Slope	Intercept	σ_y[a]	σ_{sl}[b]	r[c]
(log k_ψ + H_0) *vs.* (H_0 + log [H^+])	+0.61[d]	−4.99	0.03	0.02	0.997
(log k_ψ + H_0) *vs.* log a_w	+3.33[e]	*f*	0.04	0.16	0.994
log k_ψ *vs.* $-H_0$	+0.55	*f*	0.05	0.03	0.994

[a] Standard deviation of points, in the y direction, from the linear regression line. [b] Standard deviation of slope. [c] Correlation coefficient. [d] ϕ value. [e] w value. [f] Not listed; has no fundamental significance.

Correlation of log k_ψ with $-H_0$[7] was also attempted, and the correlation is summarized in Table II. The σ_y values show that this correlation gives the least satisfactory fit of experimental points to a straight line. The slope is 0.55.

The H_0 values[8] and log a_w values[6] employed in these correlations are for 25° or thereabouts, while the reactions were conducted at 133.5°. Also, acid concentrations were not corrected for thermal expansion of the reaction solutions from room to reaction temperature. The magnitudes of the slopes and intercepts may therefore be somewhat affected. The ϕ parameters measured by Hyland and

O'Connor[3] for benzonitrile hydrolysis diminish from +0.64 at 70° to +0.48 at 111° and crudely extrapolate to about +0.38 at 133.5°. The ϕ parameter we obtain for o-tolunitrile hydrolysis at 133.5°, namely +0.61, is considerably higher than +0.38.

From Arrhenius extrapolation of the log k_2^0 values of Hyland and O'Connor to 133.5°, we reckon k_2^0 for benzonitrile hydrolysis at that temperature to be 5.3×10^{-6} M^{-1} sec^{-1}. This compares with 1.1×10^{-5} M^{-1} sec^{-1} for o-tolunitrile from our data. The ortho methyl group approximately doubles the hydrolysis rate. This augmentation probably is to be attributed to a favorable effect of o-methyl on equilibrium protonation of the nitrile. It also suggests that there is minimal steric hindrance by o-methyl to attack of water at carbon of the protonated nitrile.

For hydrolysis of a weakly basic substrate, the ϕ parameter is composite, being the sum of ϕ_e for equilibrium protonation of the substrate and ϕ_r for the step(s) in which the protonated substrate progresses to transition state and thence to products.[5] Inasmuch as only the ϕ_r value could be related to reaction mechanism and there are no data available from which to calculate the ϕ_e value for nitrile protonation, we eschew attempting to draw mechanistic conclusions from our kinetic data.

Experimental Section

A small amount of o-tolunitrile was dissolved in a standardized solution of $HClO_4$ in distilled water. Aliquots were sealed in glass ampoules which were immersed, all at once, in a thermostat at 133.5 ± 0.2°. At measured times ampoules were removed, plunged into cold water, and opened, and 2-ml portions transferred by pipet into 10-ml volumetric flasks containing 3 ml of 6 M aqueous NaOH. The flasks were diluted to the mark with distilled water and the absorbances of the resulting solutions were immediately measured at 231 nm by means of a Beckman Model DU spectrophotometer. (Independent measurements showed that in alkaline solution o-toluamide and o-toluate ion have equal extinction coefficients at 231 nm.) Plots of ln ($A_t - A_\infty$) were linear, and the negatives of their slopes (calculated by linear regression analysis) were taken as k_ψ.

Registry No.—o-Tolunitrile, 529-19-1; perchloric acid, 7601-90-3.

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(1) Research supported in part by the National Science Foundation and the Army Research Office (Durham).
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Nitration of the Acridizinium Ion and Its 6,11-Dihydro Derivative[1]

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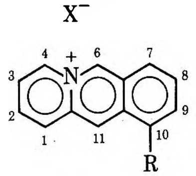
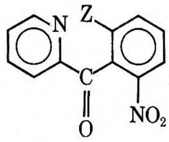
To date, the only clear-cut electrophilic substitution reaction carried out with the unsubstituted acridizinium ion 1 has been sulfonation,[2] which occurs at position 10 of the cation. The mechanism of the halogenation reaction is obscure. It was suggested[3] that at least some of the products were formed by an addition-elimination mechanism. To date, there has been no report of the nitration of the acridizinium ion.



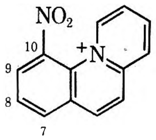
1, R = H
2, R = NO_2



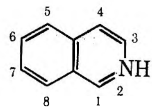
3, Z = COOH
4, Z = H

Earlier experiments showed that, when acridizinium salts are heated with nitric acid, the product is a compound formed by oxidation[4] as well as nitration. When a mixture of concentrated nitric and sulfuric acids at below −5° is used, a mononitro acridizinium salt is obtained in good yield. The product is so susceptible to nucleophilic attack that it can be crystallized satisfactorily only if acid is present. Oxidation of the new nitroacridizinium salt at 100° in concentrated nitric acid afforded a 2-(2-carboxynitrobenzoyl)pyridine which, on decarboxylation, yielded the known[5] 2-(2-nitrobenzoyl)pyridine (4). From this, it follows that the acid is 3 and the original nitration product is the 10-nitro derivative (2).

The 10 position, like the 8 position, does not bear a positive charge in any of the canonical forms contributing to the resonance hybrid. It is probable that nitration and sulfonation occur predominantly at position 10 (rather than 8) because of the greater reactivity of α positions in polycyclic systems. The observation parallels exactly that of the nitration of the benzo[c]quinolizinium ion[6] (yielding 5) in that the nitration occurs in the ring most remote from the positive charge and at that α position which does not bear a positive charge in any of the canonical forms contributing to the resonance hybrid. Another interesting parallel is the nitration of isoquinoline. In mixed acid, in which it exists as its conjugate acid 6, it affords the 5-nitro derivative in 90% yield.[7] This orientation is explicable on the same basis as that of the two benzoquinolizinium systems (2 and 5). Reduction of the nitro group of 2 is accompanied by reduction of the quinolizinium system.

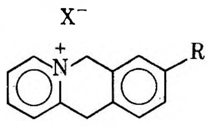


5

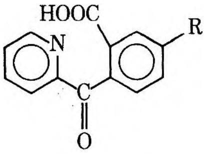


6

As was reported earlier,[8] acridizinium salts can be reduced over a palladium catalyst to yield the 6,11-dihydro product (7). Nitration of 7 afforded a 70% yield of 8-nitro-6,11-dihydroacridizinium salt (8), the identity of which was established by oxidation to the known[4] 2-(2-carboxy-4-nitrobenzoyl)pyridine (10). The discovery that this oxidation could be carried out by the use of permanganate prompted a reinvestigation of the oxidation of acridizinium bromide. In the first paper[9] dealing with acridizinium salts, the statement was made that the crude permanganate oxidation product, obtained in 81% yield, was impure phthalic acid. This statement, based only on a



7, R = H
8, R = NO_2



9, R = H
10, R = NO_2

melting point and on sublimation experiments which were discontinued after a few milligrams of phthalic anhydride was obtained, is obviously in error. Oxidation of acridizinium bromide with potassium permanganate has now been found to afford a 36% yield of 2-(2-carboxybenzoyl)pyridine (**9**).

Our nitration experiments make it clear that, in the oxidative nitration which converts the acridizinium ion into 2-(2-carboxy-4-nitrobenzoyl)pyridine (**10**), oxidation must precede nitration or else the product would be **3**. It has now been shown that **9** is not an intermediate since it is recovered unchanged when subjected to the conditions of the oxidative nitration.

Experimental Section

10-Nitroacridizinium Perchlorate (2, X = ClO_4). To a mechanically stirred solution containing 50 ml of concentrated sulfuric acid and 50 ml of concentrated nitric acid, cooled to −5 to −10°, 5 g of acridizinium bromide[10] was added in small portions. After an additional 15 min, the mixture was poured into 400 ml of ice-water. The resulting solution was allowed to come to room temperature and filtered to remove some reddish solid. Addition of 100 ml of 35% perchloric acid to the filtrate and cooling gave 4.2 g of yellow needles. Recrystallization from water containing perchloric acid afforded 3.8 g (65.5%) of pure yellow needles, mp 197–198°.

Anal. Calcd for $C_{13}H_9ClN_2O_6$: C, 48.07; H, 2.77; N, 8.63. Found: C, 48.19; H, 2.70; N, 8.65.

The **bromide** was prepared by suspending 1 g of the perchlorate salt (**2**) in 25 ml of methanol which had been saturated with potassium bromide. After the slurry had been warmed and stirred for 2 hr, the potassium perchlorate was filtered off, the solution concentrated, and crystallization induced by addition of ethyl acetate. The bromide consisted of yellow platelets, mp 225–227°.

Anal. Calcd for $C_{13}H_9N_2O_2Br$: C, 48.29; H, 3.40; N, 8.67. Found: C, 48.19; H, 3.38; N, 8.79.

2-(2-Carboxy-6-nitrobenzoyl)pyridine (3). A solution of 2 g of 10-nitroacridizinium perchlorate in 20 ml of concentrated nitric acid was heated for 6 hr on a steam bath. The solution was cooled and diluted with 50 ml of water; solid sodium bicarbonate was added in small portions. At a pH ~2, 0.7 g (42%) of a colorless solid, mp 203–207°, precipitated. Recrystallization from acetic acid-water afforded a product, mp 224–225°.

Anal. Calcd for $C_{13}H_8N_2O_5$: C, 57.36; H, 2.96; N, 10.29. Found: C, 56.99; H, 3.05; N, 10.40.

2-(2-Nitrobenzoyl)pyridine (4). A mixture of 0.5 g of **3** with 0.1 g of copper powder was heated for 30 min at 180°. The solid was thoroughly extracted with boiling ethanol, and the extract filtered and concentrated, causing the crystallization of 0.25 g of tan needles, mp 117–118° (lit.[4] 117–118°).

Anal. Calcd for $C_{12}H_8N_2O_3$: C, 63.15; H, 3.53; N, 12.28. Found: C, 62.67; H, 3.52; N, 12.06.

10-Aminobenzo[*b*]quinolizidine Methiodide. A suspension of 2 g of 10-nitroacridizinium perchlorate (**2**) with 0.2 g of platinum oxide in 100 ml of ethanol was hydrogenated at atmospheric pressure. After absorption of the theoretical amount of hydrogen, the catalyst was removed and the solution concentrated under reduced pressure. The salt was converted into the free base from which the methiodide was prepared. The tan solid was recrystallized from methanol-ethyl acetate to give 0.7 g (32%) of tan needles, mp 254–256°.

Anal. Calcd for $C_{14}H_{21}IN_2 \cdot \frac{1}{2}H_2O$: C, 47.60; H, 6.28; N, 7.93. Found: C, 47.94; H, 6.13; N, 7.72.

8-Nitro-6,11-dihydroacridizinium Perchlorate (8). A mixture of 15 ml of concentrated sulfuric acid and 15 ml of concentrated nitric acid was cooled to 0° and 1.5 g of 6,11-dihydroacridizinium bromide (**7**)[8] was added over a period of 15 min. After an additional 1 hr, the mixture was poured into 200 ml of ice-water. The solution was filtered and 25 ml of 35% perchloric acid added to the filtrate. The mixture was refrigerated overnight and then collected and recrystallized from water containing a few drops of perchloric acid. The yield was 1.3 g (70%) of tan needles, mp 190–193°.

Anal. Calcd for $C_{13}H_{11}ClN_2O_6$: C, 47.79; H, 3.39; N, 8.58. Found: C, 47.70; H, 3.43; N, 8.48.

2-(2-Carboxy-4-nitrobenzoyl)pyridine (10). A. By Oxidation with Nitric Acid. A 1-g sample of 8-nitro-6,11-dihydroacridizinium perchlorate (**8**) in 25 ml of concentrated nitric acid was heated overnight on a steam bath. The nitric acid was removed under reduced pressure and the residue extracted with sodium bicarbonate solution. The extract was filtered and acidified, affording the crude product. Recrystallization from acetic acid-water afforded 0.3 g (36%) of product, mp 215–217°.

B. By Oxidation with Permanganate. A 1-g sample of **8** was suspended in 25 ml of hot water on a steam bath and the solution stirred while powdered potassium permanganate was added. When the color was no longer immediately discharged, the hot solution was filtered to remove manganese dioxide and then acidified. Upon cooling, 0.3 g (36%) of product, mp 217–218°, crystallized. Both products were shown to be identical by mixture melting point and ir spectra and were shown to be identical with an authentic specimen.[4]

2-(2-Carboxybenzoyl)pyridine (9). A 1-g sample of acridizinium bromide was oxidized with permanganate essentially as in the case of **8** except that acidification of the alkaline solution with dilute hydrochloric acid was carefully done to pH 5. The product consisted of colorless needles, mp 225–227°; yield, 0.3 g (36%).

Anal. Calcd for $C_{13}H_9NO_3$: C, 68.72; H, 3.97; N, 6.17. Found: C, 68.54; H, 3.87; N, 6.13.

A sample of the keto acid (**9**), dissolved in concentrated nitric acid and heated on the steam bath for 12 hr, was recovered unchanged.

Registry No.—**1** (X = Br), 7547-88-8; **2** (X = ClO_4), 50585-79-0; **2** (X = Br), 50585-80-3; **3**, 50678-82-5; **4**, 50678-83-6; **7** (X = Br), 15757-24-1; **8** (X = ClO_4), 50585-82-5; **9**, 27693-49-8; **10**, 50585-83-6; 10-aminobenzo[*b*]quinolizidine methiodide, 50678-84-7.

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Biological Probes. I. Carbon-6-Labeled Nicotinamide

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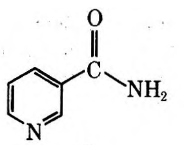
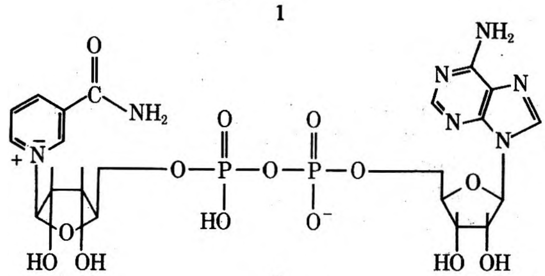
Recent interest in studies using nonradioactive labels for tracing metabolic pathways and as general biological probes has led us to develop new methods for labeling the internal ring positions of nicotinamide (**1**). The following describes an efficient method for preparing gram quantities of specifically labeled **1** containing ^{13}C at the C-6 position. The incorporation of this base into the coenzyme NAD^+ (**2**) using biosynthetic techniques can be and has been readily accomplished.[1]

The ease with which quinolines can be prepared and then oxidized to pyridinecarboxylic acids suggested that an attractive synthetic scheme could be developed incorporating these transformations as key steps. Specifically, a high yield of 2-methylquinoline-2-^{13}C (**3**) was obtained from *o*-aminobenzaldehyde and acetone-2-^{13}C under Friedlander reaction conditions, as is shown in Scheme I. Preliminary experiments had shown that the attempted direct oxidative degradation of **3** to a pyridinecarboxylic acid under a variety of conditions resulted in only partial

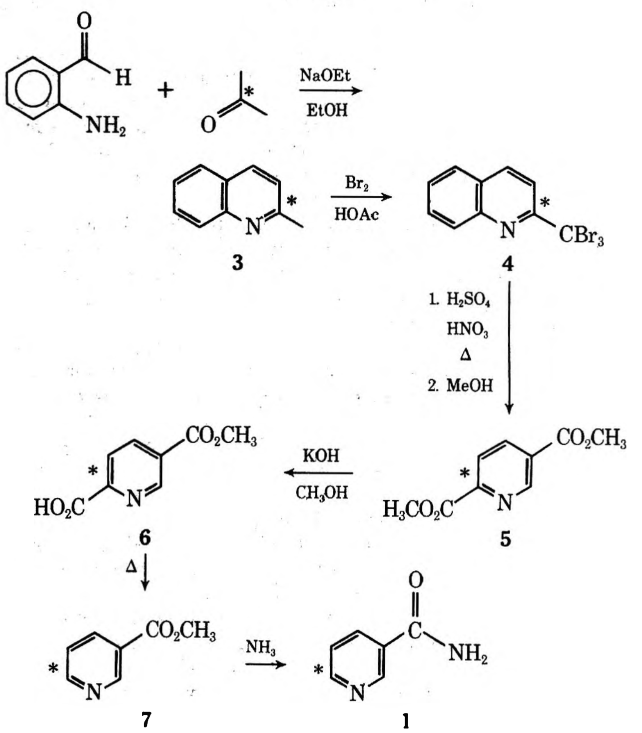


1



2

Scheme I



functionalization of the 2-methyl group. This problem was circumvented by transforming[2] **3** into its tribromomethyl derivative **4** prior to oxidation. Degradation of the benzenoid ring under vigorous oxidative conditions[3] led to pyridine-2,5-dicarboxylic acid, which was converted without isolation to its dimethyl ester **5**. Partial hydrolysis of diester **5**, according to the procedure of Isagawa and coworkers,[4] gave the monoacid **6**, which was readily decarboxylated on heating in anisole to methyl nicotinate-*6*-^{13}C (**7**) in excellent yield. Nicotinamide-*6*-^{13}C (**8**) was prepared from ester **7** following standard procedures.[5] An overall yield, based on acetone-*2*-^{13}C, of approximately 50% for the multistep sequence can be obtained if the acidic residues of the hydrolysis and decarboxylation steps (**5** → **7**) were treated with diazomethane (presumably forming **5**) and recycled as described in the Experimental Section. It should be noted, however, that the overall yield of labeled **1** was improved by only a few per cent by this recycling procedure. Other schemes for degrading quinoline and synthesizing pyridines to label C-6 of compound **1** were investigated prior to the above-cited labeling scheme. However, the method described herein was the method of choice owing to the high yields and reliability of each reaction. In addition, this series of reactions was designed so that each intermediate synthon that required purification was readily isolated by partitioning into the organic phase of a water–organic solvent extraction.[6]

Obviously this nonradioactive label is only of use as a biological probe or tracer agent by virtue of its spectroscopic properties, and accordingly the various nmr parameters such as chemical shifts (^{13}C, ^{1}H) and coupling constants (^{13}C–H) have been recorded in the Experimental Section. It is further evident that this reaction sequence could be adapted to label other internal ring positions of niacinamide (**1**). Studies are now underway to develop new techniques to specifically label additional positions of pyridine dinucleotide **2** as well as other biologically important compounds.

Experimental Section

2-Methylquinoline-*2*-^{13}C. To a stirred solution of sodium ethoxide (0.9 g of sodium in 100 ml of absolute ethanol) was added dropwise a solution of acetone-*2*-^{13}C (1.17 g, 19.8 mmol, 90% ^{13}C) with *o*-aminobenzaldehyde (2.44 g, 20.2 mmol) in 50 ml of absolute ethanol. The mixture was heated under reflux for 12 hr. The volume was reduced to 50 ml and the mixture was cautiously added to cold distilled water. After adjusting the pH to 7, the aqueous mixture was extracted with five 50-ml portions of methylene chloride. These organic extracts were combined, washed with water, and dried (MgSO$_4$). Evaporation of the volatiles afforded a residue that was distilled [bulb to bulb, 130–140° (18 mm)], giving 2.79 g (98%) of a colorless liquid: ir (neat) 3075, 1605, 820 cm^{-1}; pmr (neat) δ 2.60 (d, 3 H, $^2J_{C,H}$ = 6 Hz, CH$_3$), 6.81 (dd, 1 H, $J_{3,4}$ = 8.5, $^2J_{C,H}$ = 3.0 Hz, C$_3$H), 7.08–8.39 (m, 5 H).

2-Tribromomethylquinoline-*2*-^{13}C. To a mechanically stirred solution of 2-methylquinoline-*2*-^{13}C (2.79 g, 19.4 mmol), anhydrous sodium acetate (10 g), and glacial acetic acid (20 g) was added bromine (9.6 g, 0.12 g-atom) over a period of 15 min.

The mixture was heated at reflux for a period of 1 hr, and then cooled and poured into ice and water. The precipitate of tribromide was filtered, washed with cold water, and dried. Methylene chloride extraction (5 × 50 ml) of the combined filtrate and washing afford additional solid material upon evaporation. This material, when combined with the precipitate, afforded 6.74 g (91%) of a yellow solid (2-tribromomethylquinoline-*2*-^{13}C): mp 129–130° (lit.[2] mp 128°); ir (KBr) 760, 710 cm^{-1}; pmr (CDCl$_3$) δ 7.25–820 (m).

Dimethyl Pyridine-2,5-dicarboxylate-*2*-^{13}C. 2-Tribromomethylquinoline-*2*-^{13}C (6.74 g, 17.7 mmol) was dissolved in 11 ml of cold, concentrated sulfuric acid and heated with stirring until the vigorous evolution of bromine was observed (bath temperature approximately 140–150°). A slow stream of argon was passed over the mixture and the temperature was maintained at 150°. Bromine vapors were displaced by a continuous flow of argon. The temperature was then raised to 260° and concentrated nitric acid (11 ml) was cautiously added over a 2-hr period. Following addition, the excess nitric acid was removed by the use of a slow stream of argon. During this time the temperature rose to 275° and the solution became clear, bright yellow in color.

The mixture was cooled to room temperature and slowly added to cold methanol (200 ml). The methanolic solution was maintained at reflux for 18 hr. The volume was slowly reduced to 50 ml by periodic distillation of methanol and the resulting solution was poured onto ice and neutralized with sodium bicarbonate. The aqueous mixture was extracted five times with 125-ml portions of methylene chloride. The combined organic extracts were washed with water and dried (MgSO$_4$). Concentration of the organic solution (*in vacuo*) left 2.46 g (71%) of diester: mp 166° (lit. mp 164°); ir (CH$_2$Cl$_2$) 1730, 1270, 1130 cm^{-1}; pmr (CDCl$_3$) δ 3.98 (s, 3 H, CH$_3$), 4.03 (s, 3 H, CH$_3$), 8.14 (ddd, 1 H, $J_{3,4}$ = 8.2, $J_{3,6}$ = 0.8, $^2J_{C,H}$ = 1.5 Hz, C$_3$H), 8.42 (ddd, 1 H, $J_{3,4}$ = 8.2, $J_{4,6}$ = 2.0, $^3J_{C,H}$ = 7.0 Hz, C$_4$H), 9.25 (ddd, 1 H, $J_{3,6}$ = 0.8, $J_{4,6}$ = 2.0, $^3J_{C,H}$ = 11.5 Hz, C$_6$H); cmr (CH$_2$Cl$_2$) 151.5 ppm.

5-Carbomethoxypyridine-2-carboxylic Acid-*2*-^{13}C. Dimethyl pyridine-2,5-dicarboxylate-*2*-^{13}C (1.58 g, 81 mmol) was dissolved in 50 ml of absolute methanol and a solution of 85% potassium hydroxide (0.54 g, 82 mmol) in 15 ml of absolute methanol was added. The stirred solution was maintained at reflux for 2 hr and the solvent was removed under reduced pressure. The residue was dissolved in water and acidified to pH 2, extracted with methylene chloride (150 ml), and then subjected to continuous (methylene chloride) extraction for 48 hr. The organic extracts (continuous and separative) were combined, dried (MgSO$_4$), and concentrated under reduced pressure to give monoacid ester (1.29 g, 88%) as a white solid: mp 186–187° (lit.[4] mp 186°); ir (KBr) 1700, 1280 cm^{-1}; pmr (CF_3CO_2H) δ 4.22 (s, 3 H, CH_3), 8.76–9.70 (m, 3 H, C_3H, C_4H, and C_6H).

Methyl Nicotinate-*6-^{13}C*. A suspension of 5-carbomethoxypyridine-2-carboxylic acid-*2-^{13}C* (2.05 g, 11.3 mmol) in anisole (50 ml) was refluxed for 6 hr. The anisole solution was concentrated to 5 ml by fractional distillation (at atmospheric pressure). This mixture was then distilled at 14 mm (bulb to bulb) at 100–140°, giving a clear, colorless solution of methyl nicotinate-*6-^{13}C* in anisole.

The distillation residue (0.25 g) was dissolved in methylene chloride and treated with excess diazomethane. The dimethyl pyridine-2,5-dicarboxylate thus obtained could successfully be recycled (hydrolysis and decarboxylation), yielding additional quantities of methyl nicotinate-*2-^{13}C*.

The spectral characteristics of the anisole solution of methyl nicotinate-6-^{13}C were ir (anisole) 1725 and 1120 cm^{-1}; pmr (anisole) δ 3.57 (s, 3 H, CH_3), 6.4–7.2 (m, anisole ring protons and C_5H), 7.95 (dddd, 1 H, $J_{2,4}$ = 2.2, $J_{4,5}$ = 8.0, $J_{4,6}$ = 1.8, $^3J_{C,H}$ = 7.5 Hz, C_4H), 8.47 (ddd, 1 H, $J_{4,6}$ = 1.8, $J_{5,6}$ = 5.0, $^1J_{C,H}$ = 180 Hz), 9.14 (dd, 1 H, $^3J_{C,H}$ = 11.5, $J_{2,4}$ = 2.2 Hz, C_2H); cmr (anisole) 153.57 ppm.

Nicotinamide-6-^{13}C. The combined portions of methyl nicotinate in anisole were mixed with 150 ml of water and cooled in an ice bath. Ammonia was bubbled through the mixture for 6 hr at 3° and then for 12 hr at room temperature. Ether (50 ml) was added and the layers were separated. The etheral solution was extracted with water (25 ml). The combined aqueous portions were lyophilized, leaving 1.17 g (85%)[7] of a white solid: mp 128–130° (lit. mp 129.5–130.5°); ir (KBr) 3350, 3160, 1675, 1395 cm^{-1}; pmr (D_2O) δ 7.50 (m, 1 H, $^2J_{C,H}$ = 3.5, $J_{4,5}$ = 8.2, $J_{5,6}$ = 5.1 Hz, C_5H), 8.13 (m, 1 H, $^3J_{C,H}$ = 7, $J_{2,4}$ = 2.2, $J_{4,6}$ = 1.8, $J_{4,5}$ = 8.2 Hz, C_4H), 8.61 (ddd, 1 H, $^1J_{C,H}$ = 182. $J_{4,6}$ = 1.8, $J_{5,6}$ = 5.1 Hz, C_6H), 8.78 (dd, 1 H, $^3J_{C,H}$ = 11, $J_{2,4}$ = 2.2 Hz); cmr (D_2O) 152.64 ppm.

Acknowledgment. We gratefully acknowledge the American Cancer Society (Grant BC-111) for support of this work.

Registry No.—**1**, 50790-51-7; **3**, 50790-52-8; **4**, 50790-53-9; **5**, 50790-54-0; **6**, 50790-55-1; **7**, 50790-56-2; *o*-aminobenzaldehyde, 529-23-7; acetone-2-^{13}C, 3881-06-9.

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(7) Based on per cent conversion of 5-carbomethoxypyridine-2-carboxylic acid-2-^{13}C.

Chlorination of Phenols with Chlorine and *tert*-Butyl Hypochlorite. A Comparison

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In 1971, a review was written by Pearson and Buehler[1] on unusual electrophilic aromatic substitution reactions. A section discusses ortho enhancement, which was defined as a reaction which produces more than 66.7% ortho substitution, the statistical percentage of this position. The review states that the first successful attempts in the ortho chlorination of phenols were accomplished by *tert*-butyl hypochlorite usually in ethanol and/or carbon tetrachloride. The review also states that solvent effects and temperature have a slight influence on the ortho/para ratio but not to the extent that one would choose these factors alone to control orientation.

The statement concerning *tert*-butyl hypochlorite is derived from the work of Clark[2,3] and Ginsburg.[4,5] Clark[2,3] reported that the *tert*-butyl hypochlorite chlorination of phenol in ethanol yields 92.3% 2-chlorophenol and 87.4% 2,4-dichlorophenol, while in carbon tetrachloride it yields 57% 2-chlorophenol. Ginsburg[4,5] reported that *tert*-butyl hypochlorite reacts with 2-chlorophenol in carbon tetrachloride to yield 73% 2,6-dichlorophenol, a result which is quoted in a text on aromatic halogenation,[6] but reacts with 2-methylphenol to yield only 31% 6-chloro-2-methylphenol. Ginsburg[5] implied that alkyl hypochlorites attack phenol by a free-radical mechanism.

In 1961, Harvey and Norman[7] investigated the chlorination of various aromatic compounds, including phenols, with chlorine and *tert*-butyl hypochlorite utilizing vpc for analysis. Chlorine chlorination of molten phenol yields 39.5% 2-chlorophenol and 60.5% 4-chlorophenol. These results have been substantiated by Bing[8] and Zee.[9] Chlorination of phenol with chlorine in carbon tetrachloride yielded 74.0% 2-chlorophenol and with *tert*-butyl hypochlorite 51.0% 2-chlorophenol. From these data they concluded that *tert*-butyl hypochlorite does not give rise to high ortho/para ratios in the chlorination of phenols. Based on their observations, Harvey and Norman also proposed and gave evidence that the reaction was ionic *via* the formation of chlorine rather than free radical.

Harvey and Norman, however, did not repeat the work of Clark[2] or Ginsburg.[4] All of these authors ran their reactions at various concentrations and temperatures. For example, Harvey and Norman[7] chlorinated a 5.3% solution of phenol in carbon tetrachloride with chlorine and a 13% solution of phenol in carbon tetrachloride with *tert*-butyl hypochlorite.

One of the purposes of this work is to reexamine the chlorination of phenol in ethanol with *tert*-butyl hypochlorite. Temperature and concentration effects on the chlorination of phenol in carbon tetrachloride with chlorine and *tert*-butyl hypochlorite will be reported. Finally the results of a direct comparison of the chlorination of three phenols (phenol, 2-methylphenol, and 2-chlorophenol) with chlorine and *tert*-butyl hypochlorite, maintaining a constant temperature and concentration, will be discussed.

Results and Discussion

The claim of Clark[2] that chlorination of phenol with *tert*-butyl hypochlorite in ethanol yields 92.3% 2-chlorophenol could not be reproduced. On the contrary, *tert*-butyl hypochlorite chlorination of a 10% solution of phenol in ethanol at 15° yields 30.3% 2-chlorophenol and 65.3% 4-chlorophenol for an ortho/para ratio of 0.46. Chlorination under the same conditions except that the solvent was 95% ethanol and 5% water gave essentially the same results; *i.e.*, the maximum yield of 2-chlorophenol is 29.4% and the ortho/para ratio is 0.45. However, the addition of 2 equiv of *tert*-butyl hypochlorite to a 10% solution of phenol in ethanol at 15° did yield 86.9% 2,4-dichlorophenol, in good agreement with the 87.4% yield reported by Clark.[2]

Ethanol has been reported by Campbell and Shields[10] to be one of the solvents that favor para substitution in the chlorine chlorination of 2-methylphenol. We confirmed this report by chlorinating a 10% solution of phe-

Table I
Chlorination of Phenol in Carbon Tetrachloride

Chlorinating agent	Concentration, wt %	Temp, °C	Maximum yield of 2-chlorophenol, wt, %	Ortho/para
Cl_2	Neat	60	29	0.65[a]
Cl_2	10	78	57.7	1.6
Cl_2	5	78	68.0	2.5
Cl_2	10	18	52.8	1.3
$(CH_3)_3COCl$	10	78	53.3	1.3
$(CH_3)_3COCl$	10	15	45.8	0.92
$(CH_3)_3COCl$	33	78	47.5	1.0

[a] Reference 8.

nol in refluxing ethanol and obtained a yield of 27.5% 2-chlorophenol and 56.0% 4-chlorophenol for an ortho/para ratio of 0.49.

In their study of solvents, Campbell and Shields[10] found that the isomer ratios obtained from the chlorine chlorination of a 25% solution of 2-methylphenol in the various solvents varied owing to the hydrogen bonding between the hydroxy group and the solvent. The bound solvent molecule exerts a steric effect on the ortho position and thus leaves the para position open to attack and consequently increases the yield of the 4-chloro isomer. Thus, polar solvents that solvate the hydroxy group, such as nitrobenzene, nitromethane, acetonitrile, and sulfur dioxide, gave the highest yields of 4-chloro-2-methylphenol. Nonpolar solvents, such as carbon tetrachloride and benzene, which do not solvate the hydroxy group and actually decrease the hydrogen bonding of 2-methylphenol in solution, gave the highest yields of 6-chloro-2-methylphenol. Thus, the ortho/para ratio varied from 0.15 in nitromethane to 1.1 in carbon tetrachloride. The hydrogen bonding of 2-methylphenol in various solvents was observed in the ir.[10] For example, in carbon tetrachloride and benzene, the hydroxy group showed a sharp absorbance at 3618 cm^{-1}, indicating a "free" OH, while a solution of 2-methylphenol in nitromethane and nitrobenzene showed only a broad absorbance at 3545 and 3530 cm^{-1}, respectively, indicating a hydrogen-bonded OH. Similar observations concerning the absorption frequencies of phenols have been previously reported.[11] In regard to solvent effects, a recent article has shown a correlation between the log ortho/para ratio and the dielectric constant for the media in the chlorine chlorination of anisole.[12]

Thus, from the above discussion on hydrogen bonding, it would seem unlikely that ethanol would be a unique solvent to prepare 2-chlorophenol from the *tert*-butyl hypochlorite chlorination of phenol if the reaction is ionic. This explanation was indeed verified by our experimental observations.

Based on previous work with solvents, we decided to investigate the chlorination of phenol with chlorine and *tert*-butyl hypochlorite in carbon tetrachloride to determine what effect temperature and concentration had on the product distribution. These results are listed in Table I.

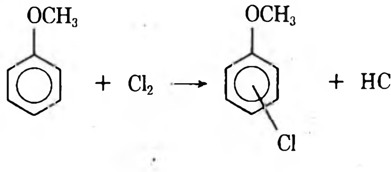
Complete analyses of all reaction products are listed in the Experimental Section. In regard to Table I, it is necessary to list both the maximum yield of 2-chlorophenol and the ortho/para ratio. The maximum yield of 2-chlorophenol is determined from the reaction profile and usually occurs very close to the disappearance of phenol when there are also dichlorophenols formed. It is not possible to determine the maximum yield of 2-chlorophenol from the ortho/para ratio alone. For example, an ortho/para ratio of 2.5 might be expected to yield 72% 2-chlorophenol but actually yields 68.0% owing to unreacted phenol and dichlorophenol present in the product. Chlorination to the extinction of phenol is important from a preparative point of view, since phenol and 2-chlorophenol have very similar boiling points, 182 and 175°, respectively, and form an azeotrope.[13]

The results in Table I show that for the chlorine chlorination of phenol, as the concentration of phenol decreases from a neat to a 5% solution in carbon tetrachloride, the ortho/para ratio increases from 0.65 to 2.5, and the maximum yield of 2-chlorophenol increases from 29 to 68.0%. As the temperature is increased from 18 to 78°, the ortho/para ratio increases from 1.3 to 1.6 and the maximum yield of 2-chlorophenol increases from 52.8 to 57.7%. Similar temperature effects were observed by Campbell and Shields[10] in all the solvent systems they studied. *tert*-Butyl hypochlorite chlorinations of phenol in carbon tetrachloride follow the same pattern. At 78°, a decrease in concentration from 33 to 10% increases the ortho/para ratio from 1.0 to 1.3 and increases the maximum yield of 2-chlorophenol from 47.5 to 53.3%. An increase in temperature from 15 to 78° increases the ortho/para ratio from 0.92 to 1.3 and the maximum yield of 2-chlorophenol from 45.8 to 53.3%. Thus, for the maximum yield of 2-chlorophenol from the chlorination of phenol with either chlorine or *tert*-butyl hypochlorite in carbon tetrachloride, high temperatures and low concentrations should be used.

The above results are consistent with the change in the ortho/para ratio being due primarily to the hydrogen bonding in phenolic solutions, since dilute solutions and high-temperature chlorinations of phenols in nonpolar solvents should shift the equilibrium from a hydrogen-bonded to a nonhydrogen-bonded species. The shift in equilibrium to nonhydrogen-bonded phenols would yield more 2-chlorophenols, since the ortho position would be more available for attack. Evidence for the above explanation can be found in the infrared spectra of phenol in carbon tetrachloride and also in the comparison of the chlorine chlorination of phenol and anisole in carbon tetrachloride.

The infrared spectrum of neat phenol in the hydroxyl stretching frequency region shows only a very broad absorbance at 3350 cm^{-1} which is characteristic of intermolecular hydrogen bonding.[11] When phenol is diluted with carbon tetrachloride to 25, 10, 5, and 1% solutions, there is an increasing appearance with dilution of a sharp absorbance characteristic of a "free" OH at 3615 cm^{-1}. In fact, there is a linear relationship between the ortho/para ratios determined from the chlorine chlorination of phenol in carbon tetrachloride and the amount of "free" or nonhydrogen-bonded phenol as determined from the infrared spectrum. This correlation is shown in Figure 1 and further supports our conclusion that the ortho/para ratio is primarily a function of the amount of hydrogen bonding of phenol in carbon tetrachloride.

Further evidence that the results shown in Table I are due to hydrogen bonding of the phenol can be observed from the chlorination of an aromatic compound, such as anisole, that is of the same reactivity as phenol, but is not capable of strong hydrogen bonding.



Results from the chlorination of anisole with chlorine with and without carbon tetrachloride as a solvent are listed in Table II. The conversions to monochloroanisoles were kept at less than 25% so that accurate para/ortho ratios could be determined. The low conversions are necessary since some of the 4-chloroanisole formed reacts further with chlorine to form 1,3,4,5,6-pentachloro-4-methoxycyclohexene.[14]

The increase in the para/ortho ratio from 4.7 to 6.0 when anisole is chlorinated neat and in a 10% carbon tetrachloride solution, respectively, is minimal when compared to the ortho/para ratio increase from 0.65 to 1.3 when phenol is chlorinated neat and in a 10% carbon tetrachloride solution, respectively. The chlorination of a 10% solution of anisole in refluxing carbon tetrachloride was attempted, but was found to be a very slow reaction, presumably owing to the low solubility of chlorine in carbon tetrachloride at 80°. The above observations further varify that the variation of the ortho/para ratio with concentration and temperature when phenols are chlorinated in nonpolar solvents is primarily due to the phenolic intermolecular hydrogen bonding, since the product distribution varies only slightly when anisole is chlorinated (Table II) but changes dramatically when phenol is chlorinated (Table I). Explanation of the changes in the isomer distribution as seen in Table I based on solvation of the chlorinating agent as noted in the chlorination of alkylbenzenes[15] cannot be operative, since it is known that chlorine does not form a complex with carbon tetrachloride.[16] However, minor changes in the product distribution could also be due to solvation of the active chlorinating species (*e.g.*, R^{-}–Cl^{+}) or solvation of the transition state.

Table II
Chlorine Chlorination of Anisole

Solvent	Concn, wt %	Temp, °C	4-Chloroanisole, %	2-Chloroanisole, %	Para/ortho
None	Neat	25	18.4	3.9	4.7
None	Neat	85	17.2	3.5	4.9
CCl_4	10	25	19.1	3.2	6.0

Based on the previous results that carbon tetrachloride was one of the best solvents for preparing 2-chlorophenols and that high temperatures and low concentrations were also necessary, a series of comparative chlorinations of 10% phenolic solutions in refluxing carbon tetrachloride were run using chlorine and *tert*-butyl hypochlorite. In Table III are listed the results of chlorinating phenol, 2-methylphenol, and 2-chlorophenol.

Table III
Chlorination with Chlorine and *tert*-Butyl Hypochlorite of a 10% Phenolic Solution in Refluxing Carbon Tetrachloride

Reactant	Product	Max yield,[a] wt %	Ortho/para	Max yield,[b] wt %	Ortho/para
Phenol	2-Chlorophenol	57.7	1.6	53.3	1.3
2-Methylphenol	6-Chloro-2-methylphenol	68.3	2.7	62.3	1.9
2-Chlorophenol	2,6-Dichlorophenol	69.0	2.7	63.7	2.2

[a] Yield with chlorine. [b] Yield with *tert*-butyl hypochlorite.

These data clearly show that *tert*-butyl hypochlorite is not a selective ortho-chlorinating reagent for phenols. In fact, chlorine gives higher yields of the ortho chloro isomer in all three examples. It can also be concluded from these results that the ortho selectivity of these reactions is not due to the chlorinating reagent but rather due primarily to the solvent effect previously discussed.

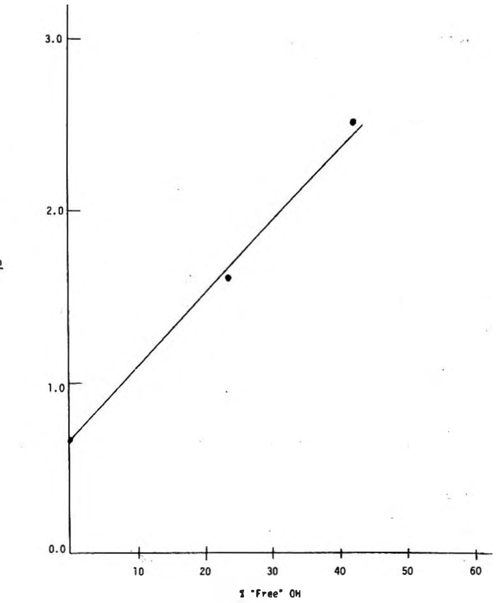


Figure 1. Correlation of ortho/para ratio in the chlorine chlorination of phenol in CCl_4 with the amount of "free" OH.

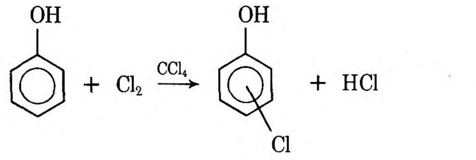
In retrospect, with the knowledge of concentration and temperature dependencies of this reaction, the results of others on the chlorination of phenols with chlorine and *tert*-butyl hypochlorite can be explained. Harvey and Norman[7] obtained an ortho/para ratio of 2.8 when chlorinating a 5.3% phenol solution in carbon tetrachloride with chlorine. Zee[9] obtained an ortho/para ratio of 1.3 when a 23% solution of phenol in carbon tetrachloride was chlorinated with chlorine and an ortho/para ratio of 2.2 with a 7.4% solution. Both chlorinations were run at 20°. Harvey and Norman[7] obtained an ortho/para ratio of 1.0 when 13% solution of phenol in carbon tetrachloride was chlorinated with *tert*-butyl hypochlorite. While there are slight discrepancies, all these results are reasonably consistent with the data in this paper.

When Campbell and Shields[10] chlorinated a 25% solution of 2-methylphenol in carbon tetrachloride at 50° with chlorine, they obtained a 47.8% yield of 6-chloro-2-methylphenol and an ortho/para ratio of 1.1, again consistent with our results. No evidence could be obtained for the product distribution described by Ginsburg[4] for the chlorination of 2-methylphenol with *tert*-butyl hypochlorite, *i.e.*, 38% 2-methylphenol, 31% 6-chloro-2-methylphenol, and 18% 4,6-dichloro-2-methylphenol. Our results show a smooth chlorination curve for this reaction, producing 62.3% 6-chloro-2-methylphenol with 1.6% unreacted 2-methylphenol and 3.1% 4,6-dichloro-2-methylphenol. From a preparative point of view, it is necessary to chlorinate to the disappearance of 2-methylphenol since it has a very similar boiling point to that of 6-chloro-2-methylphenol, 191 and 190°, respectively.

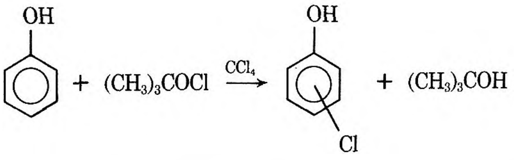
The work of Ginsburg[4] on the chlorination of a 21% solution of 2-chlorophenol in carbon tetrachloride with *tert*-butyl hypochlorite at 25° to reflux giving a 73% yield of 2,6-dichlorophenol also could not be reproduced. Duplication of Ginsburg's procedure resulted in only 51.9% 2,6-dichlorophenol and a 2,6/2,4 ratio of 1.3. One possible explanation for this discrepancy could be the similar boiling points of 2,6-dichlorophenol, 220°, and 2,4-dichlorophenol, 215°, since the mixture was purified by distillation. The dilute chlorine chlorination of 2-chlorophenol in carbon tetrachloride has recently been described in a Russian patent.[17] The patent claims the chlorination of a 7.7% solution of 2-chlorophenol in refluxing carbon tetrachloride to give product that analyzed to be 82.5% 2,6-dichlorophenol with a 2,6/2,4 ratio of 4.8. The 2,6-dichlorophenol produced could then be purified by extraction[17] or crystallization.[18] Other methods of preparing 2,6-dichlorophenol are known.[19]

The fact that different maximum yields of 2-chlorophenols and ortho/para ratios are obtained from the chlorination of the various phenols with chlorine and *tert*-butyl hypochlorite under exactly the same conditions, as shown in Table III, indicates that the two reactions differ to some extent. Recently the chlorination of toluene and *m*-xylene in nitromethane with chlorine and *tert*-butyl hypochlorite has been suggested not to involve the same chlorinating agent, and a direct reaction between the hypohalite and the aromatic was suggested, as evidenced by differences in the product distribution and the rates of reaction.[20]

Inspection of the reaction of phenol with chlorine and *tert*-butyl hypochlorite in carbon tetrachloride shows that, although the reactions can be run under identical conditions such as concentration and temperature, they are still different, since different by-products are produced.



(1)



(2)

Reaction 1 liberates hydrogen chlorine while reaction 2 liberates *tert*-butyl alcohol. The ortho/para ratio remains constant during chlorination (eq 1), implying that the hydrogen chloride has no effect on the product distribution. It is well known from the work of Campbell and Shields[10] that alcohols as solvents increase the yield of para products when compared to carbon tetrachloride. Therefore, it is possible that the *tert*-butyl alcohol that is liberated in reaction 2 is solvating with the phenol and thus decreasing the ortho/para ratio compared to reaction 1. The proposal was tested and confirmed by the simultaneous addition of 1 equiv of *tert*-butyl alcohol/equiv of chlorine in reaction 1. The results are shown in Table IV.

Table IV
Chlorination of 10% Solution of Phenol in Refluxing CCl_4

Chlorinating agent	Additive	Max yield, wt % 2-chlorophenol	Ortho/para
Cl_2		57.7	1.6
$(CH_3)_3COCl$		53.3	1.3
Cl_2	*a*	53.5	1.3

[a] 1 equiv of $(CH_3)_3COH$/1 equiv of Cl_2.

It is doubtful that chlorine would react with the *tert*-butyl alcohol to form *tert*-butyl hypochlorite under these reaction conditions,[5,21] and therefore the results from Table IV clearly show that the differences in the maximum yield of 2-chloro isomer and the ortho/para ratio for the chlorination of phenol, 2-methylphenol, and 2-chlorophenol with chlorine and *tert*-butyl hypochlorite, as shown in Table III, are due to the *tert*-butyl alcohol liberated during the reaction of the phenols with *tert*-butyl hypochlorite.

The similar product distribution shown in Table IV suggests that *tert*-butyl hypochlorite and chlorine react with phenol *via* a common reagent, *i.e.*, chlorine, by an electrophilic aromatic substitution reaction. This is consistant with the known fact that *tert*-butyl hypochlorite reacts under acidic conditions, such as with hydrogen chloride, to form *tert*-butyl alcohol and chlorine.[21]

$$(CH_3)_3COCl + HCl \longrightarrow (CH_3)_3COH + Cl_2$$

Previously, Harvey and Norman[7] had proposed that phenol was acidic enough to cause the above reaction to take place. Our results are consistent with the above.

The fact that the product distribution of the above-described reactions of phenol in carbon tetrachloride with chlorine and *tert*-butyl hypochlorite were unaffected by oxygen, light (200-W Hanovia lamp, mercury arc), and free-radical initiators such as dibenzoyl peroxide further suggests that the reactions described in this paper are ionic and not free radical.

From the data presented in this paper, it can be concluded that *tert*-butyl hypochlorite is not a selective ortho-chlorinating reagent for phenols in either ethanol or carbon tetrachloride. It is also shown that solvents can be used to change the isomer distribution from predominantly 4-chlorophenols to 2-chlorophenols. From a preparative point of view, it appears that dilute chlorine chlorination of phenols in refluxing carbon tetrachloride affords the highest yields of 2-chloro isomer.

Experimental Section

Phenol, 2-methylphenol, and 2-chlorophenol were distilled to ensure high purity (99.8%) and to azeotropically remove water. Absolute ethanol was distilled from magnesium[22] and then from calcium hydride to ensure dryness. Carbon tetrachloride was distilled in glass reagent. Chlorine (99.5%) was obtained from Matheson Corp.

The chlorinations with both chlorine and *tert*-butyl hypochlorite were run using a similar procedure. The phenol and solvent were mixed and the solution was purged with dry nitrogen both before and during the chlorinations. When *tert*-butyl hypochlorite was the chlorinating agent, the lights were turned off to prevent photolytic decomposition.[23] The chlorinating agent was added over a 1-2.5-hr period. During the reaction, small aliquots were withdrawn and after the solvent was removed the chlorophenols were analyzed by vpc. A column 10 ft × 0.125 in. packed with 20% Carbowax 20M terminated with terephthalic acid on 60/80 mesh Chromosorb W (AW-DMCS) and operated at 210° and a helium flow rate of 62 ml/min was used for analyses. In the case of chlorophenols, the elution order is 2-chlorophenol, phenol, 2,6-dichlorophenol, 2,4-dichlorophenol, 2,4,6-trichlorophenol, and 4-chlorophenol. In the case of chloro-2-methylphenols, the elution order is 6-chloro-2-methylphenol, 2-methylphenol, 4,6-dichloro-2-methylphenol, and 4-chloro-2-methylphenol. Anisole chlorination products were analyzed on a 15 ft × 0.125 in. column packed with 10% UCW-98 on 80/100m Gas-Chrom Q operated at 110° isothermally until the 2-chloroanisole eluted and then the temperature was programmed at 10°/min to a final temperature of 175°. The helium flow rate was 25 ml/min. The elution order is anisole, 4-chloroanisole, 2-chloroanisole, 2,6-dichloroanisole, 2,4-dichloroanisole, and 2,4,6-trichloroanisole. Appropriate standards were prepared to convert the analysis to weight per cent. Various samples of chlorophenols prepared with chlorine and *tert*-butyl hypochlorite were examined by mass spectrum, nmr, and ir. Only the listed aromatic products were observed. Analysis by gc using the UCW-98 column described above showed less than 0.5% 3-chlorophenol, which was the lower limit of detectability. Note that all results given in the Experimental Section and throughout this paper are in weight per cent. Details of the procedure and analysis for each experiment are given below.

Preparation of *tert*-Butyl Hypochlorite. *tert*-Butyl hypochlorite was prepared by the method of Mintz and Walling.[23] The *tert*-butyl hypochlorite was used on the day of preparation.

Chlorination of Phenol in Ethanol with *tert*-Butyl Hypochlorite. *Phenol (9.41 g, 0.100 mol) was dissolved in ethanol* (84.7 *g*), and *tert*-butyl hypochlorite (10.86 g, 0.100 mol) was added slowly over 1 hr while the temperature was maintained at 15 ± 2°. The product analyzed in weight per cent to be phenol, 1.9; 2-chlorophenol, 30.3; 4-chlorophenol, 65.3; 2,6-dichlorophenol, 0.2; and 2,4-dichlorophenol, 2.3. Another equivalent of *tert*-butyl hypochlorite (10.86 g, 100 mol) was added in 1 hr at 15 ± 2° and the product was analyzed in weight per cent to be 2-chlorophenol, 0.1; 4-chlorophenol, 0.9; 2,6-dichlorophenol, 8.0; 2,4-dichlorophenol, 86.9; and 2,4,6-trichlorophenol, 4.1.

Phenol (9.41 g, 0.100 mol) was dissolved in ethanol (80.46 g) and water (4.24 g). *tert*-Butyl hypochlorite (10.86 g, 0.100 mol) was added slowly over 1.5 hr at 17 ± 2°. The product analyzed in weight per cent to be phenol, 1.7; 2-chlorophenol, 29.4; 4-chlorophenol, 65.4; 2,6-dichlorophenol, 0.4; and 2,4-dichlorophenol, 3.1.

Chlorination of Phenol in Ethanol with Chlorine. Phenol (9.41 g, 0.100 mol) was dissolved in ethanol (84.7 g). Chlorine was sparged into the refluxing solution (79.5°) at a flow rate of 20 ml/min. After 1.75 hr, the solution analyzed in weight per cent to be phenol, 6.6; 2-chlorophenol, 27.5; 4-chlorophenol, 56.0; 2,6-dichlorophenol, 0.8; 2,4-dichlorophenol, 8.2; and 2,4,6-trichlorophenol, 0.9.

Chlorination of Phenol in Carbon Tetrachloride with Chlorine. Phenol (18.82 g, 0.200 mol) was dissolved in carbon tetrachloride (169.4 g), and chlorine gas was added to the refluxing solution (78°) at a flow rate of 41 ml/min for 1.75 hr. The product analyzed in weight per cent to be phenol, 2.9; 2-chlorophenol, 57.7; 4-chlorophenol, 35.9; 2,6-dichlorophenol, 0.2; and 2,4-dichlorophenol, 3.3.

The above procedure was repeated except that the temperature *was* 18 ± 2°. *The product analyzed in weight per cent to be phe*nol, 2.0; 2-chlorophenol, 52.8; 4-chlorophenol, 39.7; 2,6-dichlorophenol, 0.4; and 2,4-dichlorophenol, 5.1.

Phenol (9.41 g, 0.100 mol) was dissolved in carbon tetrachloride (169.4 g) and chlorine gas was added to the refluxing solution (78°) at a flow rate of 20 ml/min. After 1.8 hr, the product analyzed in weight per cent to be phenol, 2.3; 2-chlorophenol, 68.0; 4-chlorophenol, 26.7; 2,6-dichlorophenol, 0.2; and 2,4-dichlorophenol, 2.8.

Chlorination of Phenol in Carbon Tetrachloride with *tert*-Butyl Hypochlorite. Phenol (18.82 g, 0.200 mol) was dissolved in carbon tetrachloride (169.4 g) and heated to reflux (78.5°). *tert*-Butyl hypochlorite (21.72 g, 0.200 mol) was added in 2.5 hr. The product analyzed in weight per cent to be phenol, 2.2; 2-chlorophenol, 53.3; 4-chlorophenol, 40.6; 2,6-dichlorophenol, 0.6; and *2,4-dichlorophenol, 3.3.*

The above procedure was repeated except that the temperature was 15 ± 2°. The product analyzed in weight per cent to be phenol, 1.3; 2-chlorophenol, 45.8; 4-chlorophenol, 49.5; 2,6-dichlorophenol, 0.5; and 2,4-dichlorophenol, 2.9.

Phenol (9.41 g, 0.100 mol) was dissolved in carbon tetrachloride (18.8 g) and heated to reflux (78.5°). *tert*-Butyl hypochlorite (10.86 g, 0.100 mol) was added in 0.5 hr. The product analyzed in weight per cent to be phenol, 2.0; 2-chlorophenol, 47.5; 4-chlorophenol, 47.5; 2,6-dichlorophenol, 0.5; and 2,4-dichlorophenol, 2.5.

Chlorination of 2-Methylphenol in Carbon Tetrachloride with Chlorine. 2-Methylphenol (21.6 g, 0.200 mol) was dissolved in carbon tetrachloride (194.4 g), and after heating to reflux (78.5°) chlorine gas was sparged in at a flow rate of 41 ml/min. After 2 hr, the sample analyzed in weight per cent to be 2-methylphenol, 2.3; *6-chloro-2-methylphenol, 68.3; 4-chloro-2-methyl*phenol, 26.7; and 4,6-dichloro-2-methylphenol, 2.7.

Chlorination of 2-Methylphenol in Carbon Tetrachloride with *tert*-Butyl Hypochlorite. 2-Methylphenol (21.6 g, 0.200 mol) was dissolved in carbon tetrachloride (194.4 g) and the solution was heated to reflux (79°). *tert*-Butyl hypochlorite (21.72 g, 0.200 mol) was added over 2.3 hr. The product analyzed in weight per cent to be 2-methylphenol, 1.6; 6-chloro-2-methylphenol, 62.3; 4-chloro-2-methylphenol, 33.0; and 4,6-dichloro-2-methylphenol, 3.1.

Chlorination of 2-Chlorophenol in Carbon Tetrachloride with Chlorine. 2-Chlorophenol (25.72 g, 0.200 mol) was dissolved in carbon tetrachloride (231.4 g) and the solution was heated to reflux (80°). Chlorine gas was sparged in and after 2.0 hr the product analyzed in weight per cent to be 2-chlorophenol, 0.5; 2,6-dichlorophenol, 69.0; 2,4-dichlorophenol, 25.5; and 2,4,6-trichlorophenol, 5.0.

Chlorination of 2-Chlorophenol in Carbon Tetrachloride with *tert*-Butyl Hypochlorite. 2-Chlorophenol (25.72 g, 0.200 mol) was dissolved in carbon tetrachloride (231.4 g) and heated to reflux (80°). *tert*-Butyl hypochlorite (21.72 g, 0.200 mol) was added in 2.3 hr. After a slight induction period, the reaction proceeded rapidly to yield a product that analyzed in weight per cent to be 2-chlorophenol, 4.2; 2,6-dichlorophenol, 63.7; 2,4-dichlorophenol, 28.4; and 2,4,6-trichlorophenol, 3.7.

The procedure described by Ginsburg[4] was repeated. 2-Chlorophenol (25.72 g, 0.200 mol) was dissolved in carbon tetrachloride (60 ml). *tert*-Butyl hypochlorite was added over a 1.5-hr period. An induction period occurred when half of the *tert*-butyl hypochlorite was added. The temperature of the reaction rose from 25° to reflux (80°). After all the *tert*-butyl hypochlorite was added, the solution was refluxed for 2 hr. The product analyzed in weight per cent to be 2-chlorophenol, 3.9; 2,6-dichlorophenol, 51.9; 2,4-dichlorophenol, 39.9; and 2,4,6-trichlorophenol, 4.3.

Chlorination of Anisole with Chlorine. Anisole (21.6 g, 0.200 *mol) was maintained at 25° while chlorine was introduced for* 1 hr. The product analyzed in weight per cent to be anisole, 76.0; 4-chloroanisole, 18.4; 2-chloroanisole, 3.9; 2,6-dichloroanisole, 0.2; 2,4-dichloroanisole, 0.6; 2,4,6-trichloroanisole, 0.1.

The above procedure was repeated at 85°. The product analyzed in weight per cent to be anisole, 77.3; 4-chloroanisole, 17.2; 2-chloroanisole, 3.5; 2,6-dichloroanisole, 0.3; 2,4-dichloroanisole, 1.5; and 2,4,6-trichloroanisole, 0.1.

Anisole (21.6 g, 0.200 mol) was dissolved in carbon tetrachloride (194.7 g) and chlorine was introduced for 1 hr at 25°. The product analyzed in weight per cent to be anisole, 75.9; 4-chloroanisole, 19.1; 2-chloroanisole, 3.2; 2,6-dichloroanisole, 0.5; 2,4-dichloroanisole, 0.7; and 2,4,6-trichloroanisole, 0.1.

Acknowledgment. The author would like to acknowledge Mr. E. H. Kobel, who performed some of the preliminary chlorinations. The author would also like to express his deep appreciation to Drs. A. E. Young, C. G. Mitton, H. E. Hennis, and M. J. Mintz for reading and commenting on the manuscript.

Registry No.—Phenol, 108-95-2; *tert*-butyl hypochlorite, 507-40-4; chlorine, 7782-50-5; 2-methylphenol, 95-48-7; 2-chlorophenol, 95-57-8; anisole, 100-66-3.

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An Improved Synthetic Route to 11,11,12,12-Tetracyanonaphtho-2,6-quinodimethan[1a,b]

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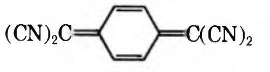
11,11,12,12-Tetracyanonaphtho-2,6-quinodimethan (TNAP, 1) is an extended conjugated analog of 7,7,8,8-tetracyanoquinodimethan (TCNQ, 2), the acceptor molecule on which the highest conductivity organic solids are based. Indeed, giant conductivity maxima, attributed to superconducting fluctuations at high (60°K) temperatures, have been observed in charge-transfer salts where the donor is based on tetrathiafulvalene (TTF, 3) and the acceptor is 2.[2]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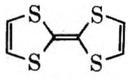
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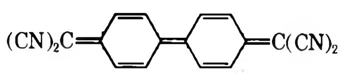

4

At the molecular level, the features of 2 which are essential for these properties are clear. In the anion-radical salts of 2 the unpaired electron is largely localized on the terminal dicyanomethylene groups. In a solid in the event of an ionic fluctuation with *two* excess electrons a *single* molecule of 2, there is a clear tendency for the two electrons to localize at opposite ends of the molecule and correlate to stay apart in order to reduce their mutual Coulomb repulsion. This correlated structure may be described by a generalized Heitler-London-type wave function

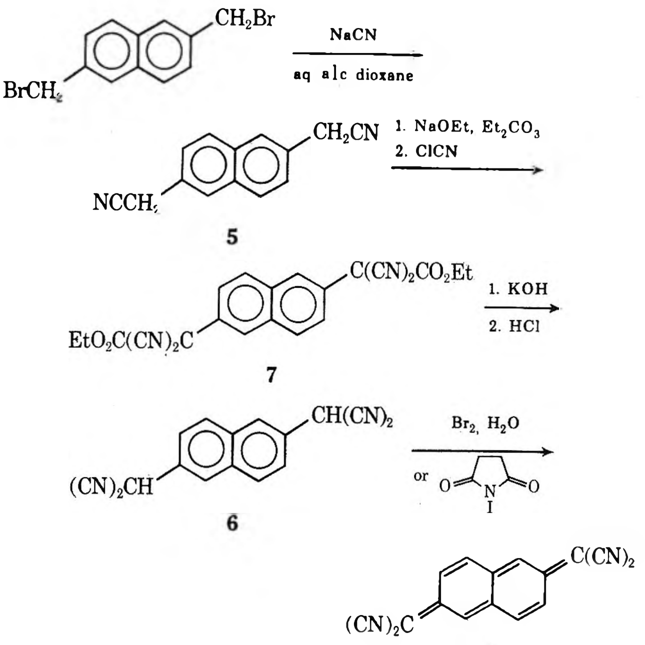
$$\psi = \frac{1}{\sqrt{2}}\left[\phi_A(1)\phi_B(2) + \phi_A(2)\phi_B(1)\right] \qquad (1)$$

where ϕ_A denotes the wave function for one dicyanomethylene group and ϕ_B denotes the wave function at the opposite group (B).[3] It is the ability of 2 to accommodate two excess electrons in the manner described above which distinguishes 2 from other types of acceptor molecules. Other molecules which allow Heitler-London-type correlation, as in 2, and which might further reduce Coulomb interactions due to their extended conjugated systems are 1 and 13,13,14,14-tetracyanodiphenoquinodimethan (TCNDQ, 4). The crucial importance of a reduced effective Coulomb interaction for achieving and maintaining a metallic state in organic systems has been discussed earlier.[3]

Given the interest cited above in acceptors such as 1 and 4, the present work was stimulated by the disadvantages found in an earlier[4,5] synthesis of 1. 2,6-Naphthalenediacetonitrile (5), the second compound in a six-step synthesis, is available in only 25% yield. 2,6-Naphthalenedimalononitrile (6), the immediate precursor to 1, was prepared from 5 *via* the classical[7] aryl malononitrile synthesis. In this synthesis diethyl 2,6-naphthalenedicyanoacetate is prepared from 5 as a mixture of diastereomers. The purification of this compound is essentially the separation of a mixture of diastereomers and the potential yield is therefore limited.

In the present work, the stereochemical problem in the earlier[4] synthesis of 1 was averted by the adoption of a novel synthesis of aryl malononitriles *via* arylenedicyanoacetates.[8] Further, a high yield preparation of 5 has been achieved.

Scheme I
Synthesis of TNAP (1)



Reaction of 2,6-bis(bromomethyl)naphthalene[4] with sodium cyanide in aqueous alcoholic dioxane at room temperature gives 5 in 70% yield. Reaction of 5 with sodium ethoxide and diethyl carbonate, followed by reaction of the resultant dianion with cyanogen chloride, leads to a 60% yield of diethyl 2,6-naphthalene $\alpha,\alpha,\alpha',\alpha'$-tetracyanodiacetate (7). Hydrolysis and decarboxylation of 7 leads to 6, and oxidation of this compound leads to a mixture of 1 and a highly insoluble substance previously described.[4] Separation and purification of 1 may be achieved by chromatography on Florisil and subsequent recrystallization from acetonitrile. The relevant chemistry is outlined in Scheme I.

In acetonitrile solution, 1 reacts with 3 to give the 1:1 complex TTF-TNAP. This complex has a resistivity (room temperature compaction) less than 0.2 ohm-cm and accordingly is the lowest resistivity TNAP complex prepared to date.[4] Although unsuccessful to date, further attempts to grow single crystals of TTF-TNAP and other TNAP salts are in progress.

Two attempts to synthesize 4 have been reported. Oxidation of *p,p'*-biphenylenedimalononitrile (8) with *N*-iodosuccinimide led to a polymer of 4,[9] and thermal or photolytic decomposition of 3-diazo-6-dicyanomethylene-1,4-cyclohexadiene also did not lead to 4.[10]

Since 8 prepared by the reported method[9] is quite difficult to purify, it was hoped that its preparation *via* the dicyanoacetate method[8] might lead to material of sufficiently improved purity[11] so as to allow isolation of 4. Accordingly, *p,p'*-bis(cyanomethyl)biphenyl[12] was converted into diethyl 1,12-biphenylene-$\alpha,\alpha,\alpha',\alpha'$-tetracyanodiacetate as described above, and this compound was used to prepare 8. However, attempted preparation of 4 *via* 8 again led to polymer.[9]

Experimental Section[13]

2,6-Naphthalenediacetonitrile (5). To a mixture of sodium cyanide (94.5 g, 1.93 mol) in water (114 ml), ethanol (227 ml), and dioxane (280 ml) stirred mechanically at room temperature was added 2,6-bis(bromomethyl)naphthalene (140 g, 0.446 mol). This mixture was stirred for 16 hr at room temperature and then was filtered. The filter cake was washed with *ca.* 2 l. of water and air-dried to give **5** as an off-white solid, 82 g (89%), mp 153–159°. This solid was recrystallized in four batches from 50:50 v/v acetone–absolute ethanol to give **5**, 65.4 g (71%), mp 163–166, 164–167, 163–165, 162–165° (lit.[4] mp 163.5–165.5°). The infrared spectrum of the product exhibited absorption due to a nonconjugated cyano group at 2275 cm^{-1} (lit.[4] 2280 cm^{-1}).

Diethyl 2,6-Naphthalene-α,α,α',α'-tetracyanodiacetate (7). To sodium ethoxide [freshly prepared from sodium metal (22.6 g, 0.548 g-atom) and absolute ethanol (240 ml), followed by removal of excess alcohol at reduced pressure] was added diethyl carbonate (292 g, 2.48 mol), toluene (100 ml), and **5** (52.5 g, 0.25 mol). This mixture was stirred mechanically and distilled until the boiling point reached 111°. Toluene (100 ml) was added, and the mixture was cooled to 0°. Cyanogen chloride (36.9 g, 0.60 mol) was distilled into the reaction mixture kept at 0–5°. After the completion of the cyanogen chloride addition (*ca.* 6 hr), the mixture was heated at 55–60° for 2 hr and then cooled to room temperature and filtered. The filter cake was washed with ice–water and recrystallized from benzene to give **7** as an off-white solid, 60 g (60%), mp 141.5–143.5°. Recrystallization from benzene gave mp 142–143.5°. This compound showed infrared absorption at 2270 (nonconjugated CN), 1750 (ester carbonyl), and 1240 cm^{-1} (ester C–O). The nmr spectrum of **7** exhibited absorption at δ 1.20–1.45 (triplet, J = 7.5 Hz, 6 H, -CH_2CH_3), 4.25–4.65 (quartet, J = 7.5 Hz, 4 H, -CH_2CH_3) and 7.75–8.35 (multiplet, 6 aromatic protons).

Anal. Calcd for $C_{22}H_{16}N_4O_4$: C, 66.00; H, 4.03; N, 13.99. Found: C, 65.68; H, 3.83; N, 14.12.

2,6-Naphthalenedimalononitrile (6).[14] To a magnetically stirred 10% potassium hydroxide solution was added **7** (4.00 g, 10 mmol), and this mixture was stirred at room temperature until homogeneous. Hydrochloric acid (6 *N*, 11.2 ml) was added carefully, and a quantitative yield of **6**, mp 233–240° dec, precipitated.[15] The precipitate was recrystallized from acetonitrile[4] to give **6**, 1.86 g (72%), mp 251–253° dec (lit.[4] mp 241–243° dec). The infrared spectrum of this material (Nujol and Fluorolube) is in accord with that previously reported.[4]

Anal. Calcd for $C_{16}H_8N_4$: C, 74.99; H, 3.15; N, 21.86. Found: C, 74.98; H, 3.18; N, 21.80.

11,11,12,12-Tetracyano-2,6-naphthoquinodimethan (TNAP, 1). General Method of Preparation from 7.[14] As described above, **7** (10.0 g, 25 mmol) and 10% potassium hydroxide (75 ml) were stirred until homogeneous. Hydrochloric acid (6 *N*, 28 ml) was added; a precipitate of **6** formed. To this suspension of **6** was added bromine (5.0 g, 31.2 mmol) in ice–water (250 ml), and a purple precipitate formed immediately. This precipitate was filtered and washed with ice–water, acetonitrile, and ether to give 6 g (100%) of crude **1**. This material was purified in batches as follows. Crude **1** (*ca.* 500 mg) was suspended in boiling acetonitrile (2000 ml), the suspension was filtered, and a precipitate (300–400 mg) of **1** and its oligomer[4] formed. This precipitate was dissolved in acetonitrile and chromatographed on Florisil (60–100 mesh) and eluted with acetonitrile until no more **1** was eluted, as judged by the color of the column effluent. As much as 1 g of **1** and its oligomer could be chromatographed on 350–400 g of Florisil. The column effluent was concentrated by evaporation under reduced pressure, and the precipitated **1** was recrystallized from acetonitrile to give **1** as metallic purple plates, mp >365° (lit.[4] mp >420°). The recovery of **1** from the chromatographic experiment is *ca.* 50%. The infrared and uv-visible spectra of **1** are in accord with those previously reported.[4]

Anal. Calcd for $C_{16}H_6N_4$: C, 75.58; H, 2.38; N, 22.04. Found: C, 75.57; H, 2.57; N, 21.98.

Tetrathiafulvalinium 11,11,12,12-Tetracyanonaphtho-2,6-quinodimethanide (TTF-TNAP). To a hot solution of **1** (16 mg, 0.063 mmol) in acetonitrile (65 ml) was added a hot solution of **3** (14.2 mg, 0.069 mmol) in acetonitrile (5 ml). The mixture slowly cooled to room temperature, was filtered, and vacuum dried, 240–245° dec.

Anal. Calcd for $C_{22}H_{10}N_4S_4$: C, 57.62; H, 2.20; N, 12.22; S, 27.96. Found: C, 57.75; H, 2.35; N, 12.51; S, 27.97.

Diethyl 1,12-Biphenylene-α,α,α',α'-tetracyanodiacetate. A mechanically stirred mixture of diethyl carbonate (146.1 g, 1.24 mol), sodium ethoxide (18.0 g, 0.265 mol), *p,p'*-bis(cyanomethyl)-biphenyl (29.0 g, 0.125 mol), and toluene (100 ml) was distilled until a boiling point of 111° was reached. The mixture was cooled to 0°, and cyanogen chloride (18.45 g, 0.30 mol) was distilled into the mixture, which was kept at 0–5°. After cyanogen chloride addition was completed, the mixture was heated at 50°55° for 2 hr. Addition of hexane to the mixture formed a precipitate which was washed with ice–water to give a gummy solid. The gummy solid was heated in benzene and filtered. Evaporation of the benzene solution gave an oil which slowly crystallized. Absolute ethanol was found to be a satisfactory recrystallization solvent, and three crystallizations from it gave 7.0 g (13%) of the desired compound, mp 125–127.5°. This compound showed infrared absorption at 2270 (nonconjugated CN), 1760 (ester carbonyl), and 1230 cm^{-1} (ester C–O). The nmr spectrum exhibited resonances at δ 1.20–1.50 (triplet, J = 7.5 Hz, 6 H, -CH_2CH_3), 4.20–4.65 (quartet, J = 7.5 Hz, 4 H, -CH_2CH_3), and 7.65–8.00 (complex, 8 H, aromatic protons).

Anal. Calcd for $C_{24}H_{18}N_4O_4$: C, 67.60; H, 4.25; N, 13.14. Found: C, 67.59; H, 4.22; N, 13.15.

Acknowledgments. The technical assistance of P. J. Nigrey, S. Goldberg, and Mrs. C. Folk is gratefully acknowledged.

Registry No.—**1**, 6251-01-0; **3**, 31366-25-3; **5**, 4949-02-4; **6**, 4948-93-0; **7**, 50764-74-4; TTF-TNAP, 50764-75-5; 2,6-bis(bromomethyl)naphthalene, 4542-77-2; *p,p'*-bis(cyanomethyl)biphenyl, 7255-83-6; diethyl 1,12-biphenylene-α,α,α',α'-tetracyanodiacetate, 50764-76-6.

References and Notes

(1) (a) This work was supported by the National Science Foundation through the Laboratory for Research on the Structure of Matter and Grant No. GP-29583 and by the Advanced Research Projects Agency through DAHC-15-72C-0174. (b) Portions of this paper were presented at the 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug. 26–31, 1973, Abstracts of Papers, ORGN 145. (c) Correspondence should be directed to this author at Xerox Corporation, Webster Research Center, W-114, Webster, New York 14580.

(2) L. B. Coleman, M. J. Cohen, D. J. Sandman, F. G. Yamagishi, A. F. Garito, and A. J. Heeger, *Solid State Commun.*, **12**, 1125 (1973).
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(4) J. Diekmann, W. R. Hertler, and R. E. Benson, *J. Org. Chem.*, **28**, 2719 (1963).

(5) This earlier publication[4] also reports the preparation of several anion-radical salts of **1** and a study of their resistivities as room temperature compactions. In all cases reported, the salts of **1** have resistivities comparable to, and in some cases lower than, those reported[6] for salts of **2**. Neither single crystal conductivity nor crystal structure data are available as yet for **1** and its anion-radical salts. Accordingly, it is not feasible at present to attempt a detailed discussion of the properties of **1** and its salts. However, the close resemblance of the resistivities observed for the salts of **1** to those of analogous salts of **2** makes it reasonable to assume that the topographical features to be found in crystal structures of the salts of **1** may be generally analogous to those found in salts of **2**.

(6) L. R. Melby, R. J. Harder, W. R. Hertler, W. Mahler, R. E. Benson, and W. E. Mochel, *J. Amer. Chem. Soc.*, **84**, 3374 (1962).
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(8) E. L. Martin, U. S. Patent 3,504,001.
(9) W. R. Hertler, U. S. Patent 3,153,658.
(10) H. D. Hartzler, *J. Amer. Chem. Soc.*, **86**, 2174 (1964).

(11) See preparation of 6 in Experimental Section, for example.

(12) D. D. Reynolds and K. R. Dunham, U. S. Patent 2,789,971.

(13) Melting points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., or Midwest Microlab, Ltd., Indianapolis, Ind. Infrared spectra were recorded as Nujol mulls on a Perkin-Elmer 700 spectrophotometer. Proton magnetic resonance spectra were recorded on a Varian A-60 spectrometer in *ca.* 10% $CDCl_3$ solution. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane.

(14) This experiment is best carried out in a glove box under an inert atmosphere.

(15) Material of this quality may be used for the preparation of **1**; indeed, **7** may be converted to **1** in one flask.[8]

Antimetabolites Produced by Microorganisms. IX. Chemical Synthesis of N^5-Hydroxyornithine and N^5-Hydroxyarginine[1]

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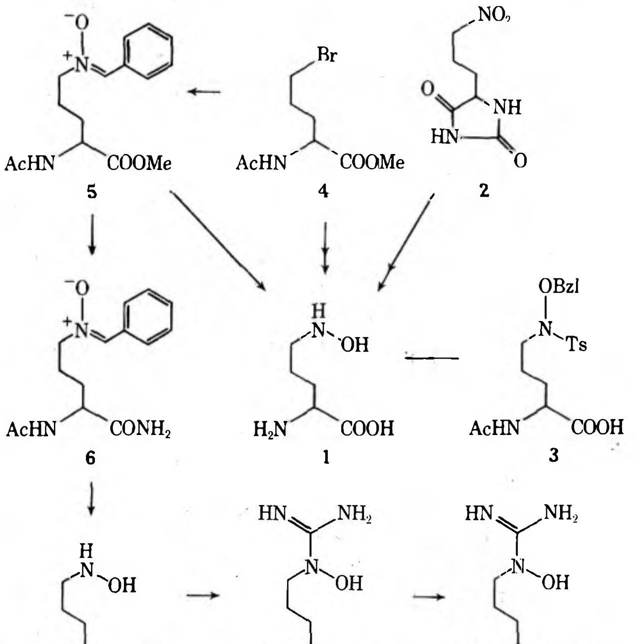
N^5-Hydroxyornithine (**1**), isolated as a degradation product of a host of naturally occurring hydroxamic acids,[2,3] has not as yet been observed free in nature. In view of its antimicrobial activity,[4] an efficient chemical synthesis of 1 has again become of interest. The first previous approach,[5] based on partial reduction of 2 followed by hydrolysis, gave racemic 1 in very low overall yield. Alternatively, alkylation of *O*-benzyl-*N*-tosylhydroxylamine with 1,3-dibromopropane, subsequent condensation with diethyl acetamidomalonate, hydrolysis, decarboxylation, and acetylation furnished racemic 3 which served as substrate for enzymatic resolution, eventually affording both enantiomers of 1 in unspecified yield.[6] N^5-Hydroxyornithine was also prepared,[7] analogous to the methods employed in the synthesis of ferrichrome,[8] by partial reduction of methyl 2-acetamido-5-nitrovalerate[9] followed by hydrolysis.

We synthesized racemic 1 by hydrolysis of nitrone 5, prepared by N-alkylation[10,11] of *anti*-benzaldoxime[12] with methyl 2-acetamido-5-iodovalerate[9] derived from 4.[13] In a modification of Buehler's procedure[10] crystalline thallium(I) *anti*-benzaldoximate was reacted with methyl 2-acetamido-5-iodovalerate in dimethylformamide, but the yield of nitrone 5 was essentially the same as that attained with lithium and sodium salts of *anti*-benzaldoxime in methanol. Hydrolysis of the purified nitrone 5 afforded 1 in crystalline form for the first time.



N^5-Hydroxy-L-arginine (9), recently isolated as a metabolite of *Nannizzia gypsea*, a mold belonging to the class of *Ascomycetes*,[14] and as a metabolite of a *Bacillus* species,[1] exhibits antibiotic properties reversible by L-arginine and L-citrulline.[15] To further evaluate the biological properties of this new amino acid, a chemical synthesis of 9 was desirable.

Racemic 9 was prepared starting with nitrone 5, which, after conversion to amide 6 and short treatment with hydrochloric acid, afforded 7 containing the proper protective groups. The carboxamide function in 7 was desirable in view of the facile ring closure of 1 to give 3-amino-1-hydroxy-2-piperidone.[16] Amide 7 was treated with *S*-methylisothiourea and the reaction mixture was hydrolyzed to afford 9, which was isolated as the crystalline hydrochloride. As expected, synthetic 9 exhibited 50% of the antibiotic activity of the naturally occurring L form.[1]

Experimental Section

Melting points were observed on a Reichert Thermopan hot stage and are uncorrected; pmr spectra were recorded on a Varian H-100 spectrometer with TMS as either internal ($CDCl_3$) or external (D_2O) standard depending upon the solvent. Precoated silica gel F-254 layers (E. Merck, Darmstadt) were employed for tlc in connection with systems 1 (chloroform-ether, 1:5, v/v), 2 (chloroform-methanol-concentrated ammonium hydroxide-water, 1:4:2:1, v/v), and 3 (chloroform-ethyl acetate-methanol, 5:5:1, v/v). Adsorption chromatography was performed with silicic acid, 100 mesh (Mallinckrodt), or with silica gel, 0.05-0.20 mm (M. Woelm).

***anti*-Benzaldoxime Thallium(I) Salt.** To a solution of 2.65 g (21.9 mmol) of *anti*-benzaldoxime[12] in 25 ml of anhydrous ethanol was added 100 ml of 0.219 *N* thallous ethoxide solution, whereupon the product immediately deposited as light-yellow prisms. The suspension was concentrated to near dryness after addition of 100 ml of anhydrous benzene, resuspended in hexane, and filtered to yield 6.85 g of the thallium(I) salt (96.5% yield), mp >175° dec.

Anal. Calcd for C_7H_6NOTl: C, 25.91; H, 1.86; N, 4.32. Found: C, 25.57; H, 1.77; N, 4.32.

Methyl 2-Acetamidovalerate 5-(α-Phenylnitrone) (5). Procedure A. To a solution of 2.416 g (8.08 mmol) of methyl 2-acetamido-5-iodovalerate[9] in 20 ml of methanol and 10 ml of dimethylformamide was added 2.621 g (8.08 mmol) of *anti*-benzaldoxime thallium(I) salt. After stirring for 22 hr the pH value had dropped to *ca.* 8.5 (wet indicator paper) and solid ammonium chloride was added to reach neutrality. The mixture was filtered, the thallium salts were washed with methanol, and filtrate and washings were concentrated to a syrup. This syrup was extracted repeatedly with boiling chloroform; the extracts were filtered, concentrated, and charged to a column containing 100 ml of a chloroform slurry of silicic acid. The column was developed with 250 ml of chloroform eluting benzaldoxime, O-alkylated benzaldoxime emerged from the column after continued development with 250 ml of chloroform containing 2.5% 2-propanol; 5 was eluted as a sharp band with chloroform-2-propanol, 3:1, v/v, and obtained as crystalline residue after evaporation of the solvent. Recrystallization from ethyl acetate gave 0.970 g of colorless needles (41% yield): mp 127°; R_f 0.35 (system 3); δ_{TMS} ($CDCl_3$) 1.98 [m, $(CH_2)_2$], 2.00 (s, CH_3CO), 3.72 (s, CH_3O), 3.98 (t, H-5, $J_{4,5}$ = 6 Hz), 4.62 (dt, H-2, $J_{2,3a}$ = 5 and $J_{2,3b}$ = $J_{2,NH}$ = 7.5 Hz), 6.59 (d, NH, $J_{2,NH}$ = 7.5 Hz), 7.41 (s, -CH=, superimposed H-3′, H-4′, and H-5′), and 8.22 (m, H-2′ and H-6′).

Anal. Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.89; H, 6.92; N, 9.56.

Procedure B. To a solution of 8.08 g (66.7 mmol) of *anti*-benzaldoxime and 19.95 g (66.7 mmol) of methyl 2-acetamido-5-iodovalerate in 48 ml of dimethylformamide was added 47.6 ml of 1.4 *M* lithium methoxide solution in methanol. The reaction mixture was concentrated to a syrup under reduced pressure after 20 hr, redissolved in chloroform, chromatographed, and purified as described in procedure A to yield 9.33 g of recrystallized 5 (48% yield).[17]

The yield of the N-alkylation step depends to a certain extent upon the purity of the *anti*-benzaldoxime employed, whose analysis is particularly desirable if older preparations are to be used. The ratio of syn/anti in a given preparation of benzaldoxime can be ascertained by nmr spectroscopy[18] but is more conveniently estimated by tlc (system 1), which permits differentiation between syn (R_f 0.82) and anti (R_f 0.72) isomers of benzaldoxime and its salts.

N^5-Hydroxy-DL-ornithine (1). A solution of 1.5 g (5.13 mmol) of nitrone 5 in 30 ml of 6 *N* hydrochloric acid was heated on the steam bath for 4 hr, and the solution was concentrated to dryness under reduced pressure and redissolved in 6 ml of solvent system 2. After 2 hr 374 mg (2.52 mmol) of crystalline 1 base (49%) was deposited: mp 197° dec; R_f 0.72 (system 2); δ_{TMS} (D_2O) 2.30 [m, broad, $(CH_2)_2$], 3.50 (t, H-5, $J_{4,5}$ = 7 Hz), 4.30 (t, H-2, $J_{2,3}$ = 6 Hz).

N^5-Hydroxyornithine (1) gave positive tests with ninhydrin and triphenyltetrazolium[19] and a negative test with $FeCl_3$, and could be degraded to ornithine (R_f = 0.55, system 2) upon treatment with 47% hydriodic acid at 100° for 10 hr.

Anal. Calcd for $C_5H_{12}N_2O_3$: C, 40.53; H, 8.16; N, 18.91. Found: C, 40.30; H, 8.19; N, 18.94.

The mother liquor was purified by chromatography on a column of Dowex 50[5] and the resulting 1 dihydrochloride was converted to the crystalline 2-nitro-1,3-indandione salt of 1[5] (415 mg, 1.22 mmol), exhibiting ir and nmr spectra identical with those of authentic N^5-hydroxy-L-ornithine 2-nitro-1,3-indandione salt obtained from a hydrochloric acid hydrolysate of iron-free albomycin,[20,21] δ_{TMS} (DMSO-d_6) 1.77 [m, broad, $(CH_2)_2$], 3.04 (m, broad H-5), 3.62 (m, broad, H-2), and 7.20 (broad envelope representing 6 protons) overlapping with 7.51 (m, H-5′–H-8′).

Anal. Calcd for $C_5H_{12}N_2O_3 \cdot C_9H_5NO_4$: C, 49.56; H, 5.05; N, 12.38. Found: C, 49.41; H, 5.00; N, 12.42.

2-Acetamidovaleramide 5-(α-Phenylnitrone) (6). A suspension of 4.00 g (13.68 mmol) of **5** in *ca.* 40 ml of liquid ammonia was kept in a sealed tube at 50° for 4.5 days. The residue obtained after evaporation of ammonia was recrystallized from methanol–ether to afford colorless needles (3.19 g, 84% yield) of **6**, mp 170°, R_f 0.06 (system 3).

Anal. Calcd for $C_{14}H_{19}N_3O_3$: C, 60.64; H, 6.91; N, 15.15. Found: C, 60.43; H, 6.92; N, 15.21.

N^5-Hydroxy-DL-arginine (9). A solution of 3.19 g (11.5 mmol) of **6** in 70 ml of concentrated hydrochloric acid (*d* 1.188) was heated on the steam bath for 15 min. The solution was concentrated to dryness under reduced pressure and the resulting crude **7** was dried over sodium hydroxide *in vacuo* overnight. The entire residue was dissolved in 8 ml of water, 3.19 g (22.9 mmol) of *S*-methylisothiourea sulfate was added, and the pH of the solution was adjusted to 7 with dilute sodium hydroxide solution. The mixture was kept at room temperature for 5 days. During this period the pH of the solution was occasionally readjusted to 7. The solution of crude **8** was evaporated to dryness under reduced pressure, and the residue was redissolved in 100 ml of 6 *N* hydrochloric acid and heated on the steam bath for 10 hr, evaporated, and dried over sodium hydroxide. The resulting residue was dissolved in 50 ml of water and the solution, after pH adjustment to 3, was charged to a column (25 × 680 mm) of Dowex 50W X-8, 200–400 mesh (Na^+), previously rinsed with 3.4 l of a pH 6.1 buffer, prepared by adding 0.1 *M* citric acid to 0.2 *M* dibasic sodium phosphate solution until pH 6.1 was reached (approximate ratio of solutions was 15:8).

The column was subsequently developed with the pH 6.1 buffer to which 0.1 mol of sodium chloride per liter had been added. After 800 ml of effluent had been collected the column was eluted with the pH 6.1 buffer containing 0.3 mol of sodium chloride per liter. The effluent was now collected in 20-ml fractions, the antibiotic activity of the fractions was monitored bioautographically,[1] and fractions 50–120 were pooled and desalted by charging to a column (50 × 400 mm) of Dowex 50W X-4, 50–100 mesh (H^+). This column was rinsed with water until the effluent was neutral and then developed with 1 *N* ammonium hydroxide solution. Fractions of 500 ml each were collected as soon as ammoniacal development had started; fractions 7–11, containing the bioactive material, were pooled and concentrated to yield 1.1 g of viscous **9**. This material was redissolved in water, and the solution was adjusted to pH 5 with hydrochloric acid, concentrated, and diluted with ethanol to afford 1.04 g of **9** hydrochloride as needles (40% yield based on the conversion of **6** to **9** hydrochloride) with identical R_f values and pmr spectrum as reported for the L form.[1]

Anal. Calcd for $C_6H_{14}N_4O_3 \cdot HCl$: C, 31.79; H, 6.67; N, 24.72. Found: C, 31.75; H, 6.91; N, 24.86.

Registry No.—**1**, 40162-08-1; **1** dihydrochloride, 50678-85-8; **1** 2-nitro-1,3-indandione salt, 50678-86-9; **5**, 50585-17-6; **6**, 50585-18-7; **9** hydrochloride, 50585-19-8; *anti*-benzaldoxime thallium(I) salt, 50585-20-1; *anti*-benzaldoxime, 622-32-2; methyl 2-acetamido-5-iodovalerate, 21753-88-8.

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Coupling Reactions between Resonance Stabilized Organolithium Reagents and Cycloalkyl Halides[1]

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Both lithium dialkylcuprates and organolithium reagents have recently been shown to be extremely useful reagents for the synthesis of unsymmetrical hydrocarbons *via* a Wurtz-type coupling process between the organometallic reagents and alkyl halides.[2] Lithium dialkylcuprates couple readily with a wide variety of alkyl, aryl, and vinyl halides[2a,b] and organolithium reagents condense with primary and secondary halides.[2c-g] The products from the coupling reaction can frequently serve as key intermediates for the synthesis of carbonyl compounds.[2c,g] One of the limitations of these versatile reagents appeared to be the low yields associated with the reaction when performed with cycloalkyl halides. Although lithium dimethylcuprate and cyclohexyl iodide did condense to give a 75% yield of methylcyclohexane,[2a] the reaction between cyclohexyl bromide and lithium di-*n*-butyl-(tri-*n*-butylphosphine)cuprate only gave a 25% yield of the coupled product, *n*-butylcyclohexane.[2b]

Resonance stabilized organolithium reagents, such as benzyllithium and allyllithium, are both strong nucleophiles and relatively weak bases compared to alkyllithium reagents such as *n*-butyllithium.[3] This combination of properties has proved to be compatible with the displacement of both bromide and iodide ions from cyclohexyl and cyclopentyl systems so that high yields of substituted cycloalkanes can be obtained by a direct Wurtz-type coupling procedure

$$RLi + R'X \longrightarrow RR' + LiX$$

Tables I and II summarize the results of this study with five different organolithium reagents and two cycloalkyl systems.

Four trends in reactivity are indicated from the data in Table I. (1) The use of cyclohexyl bromide and cyclohexyl iodide led to much higher yields of coupled products than the corresponding reactions with cyclohexyl chloride or cyclohexyl tosylate. (2) The yields from reactions with cyclohexyl bromide were greater than yields from reactions with cyclopentyl bromide. (3) Benzylic reagents, benzyl- and benzhydryllithium, were slightly superior to the allylic reagent in the displacement reaction. (4) Diethyl ether appeared to be slightly superior to tetrahydrofuran as a solvent for these reactions.[4] It should also be noted that displacement of the tosylate group was accomplished

Table I
Coupling Reactions with Cycloalkyl Halides[a,b]

RLi	% yield of coupled products, RR'[c]						
	R'Cl[d]		R'Br			R'I	R'OTs[e]
$CH_2{=}CHCH_2Li$ (3052-45-7)	10[f] (2114-42-3)		78	(68)[g]	(70)[h] (3524-75-2)	86	21
$PhCH_2Li$ (766-04-1)	35 (4410-75-7)	(20)[g]	90	(75)[g]	(56)[h] (4410-78-0)	89	55
$PhCH_2MgCl$						24	80
$(Ph)_2CHLi$ (881-42-5)			93 (50585-08-5)		(85)[h] (50585-09-6)		67

[a] All reactions were run in diethyl ether solvent at room temperature under an atmosphere of dry N_2 unless otherwise noted. [b] Registry no. for cycloalkyl halides: cyclohexyl chloride, 542-18-7; cyclohexyl bromide, 108-85-0; cyclopentyl bromide, 137-43-9; cyclohexyl iodide, 626-62-0. Registry no. for compounds are in parentheses under compound or yield. [c] Yields are based on R'X added (not consumed) and represent distilled samples at least 98% pure by glc. [d] R' = cyclohexyl unless otherwise noted. [e] Ts = tosyl. Registry no. for cyclohexyl tosylate, 953-91-3. [f] The reaction mixture was refluxed for 24 hr before work-up. About 80% of the cyclohexyl chloride was recovered. [g] The reaction was run in tetrahydrofuran solvent. [h] R' = cyclopentyl.

Table II
Reactions with Methyl-Substituted Allyllithium Reagents[a,b]

Reaction	RLi	R'Br	% coupling at		Total yield, %
			C-1	C-3	
1	$CH_3C_{(3)}H{=}CHC_{(1)}H_2Li$ (1637-44-9)	$c\text{-}C_6H_{11}Br$	68 (5860-28-6)	32 (50585-11-0)	75
2	$CH_3C_{(3)}H{=}CHC_{(1)}H_2Li$	$PhCH_2CH_2Br$	63	37	74
3	$(CH_3)_2C_{(3)}{=}CHC_{(1)}H_2Li$ (50585-10-9)	$c\text{-}C_6H_{11}Br$	85 (50585-12-1)	15 (50830-96-1)	70
4	$(CH_3)_2C_{(3)}{=}CHC_{(1)}H_2Li$	$PhCH_2CH_2Br$	100		75

[a] All reactions were run in diethyl ether solvent. [b] Registry no. are found in parentheses.

more effectively with the benzyl Grignard reagent than with the benzyllithium reagent.[5]

The greatest synthetic potential of these reactions may reside in the selectivity of reaction when there are two different and competitive anionic sites, on C-1 and C-3 of the allylic reagent, where coupling can occur. Resonance forms indicate the two possible positions for substitution

$$R_1R_2C_{(3)}{=}CH\bar{C}_{(1)}H_2 \longleftrightarrow R_1R_2\bar{C}_{(3)}CH{=}C_{(1)}H_2$$

$$R_1 \text{ and } R_2 = CH_3 \text{ or } H$$

When R_1 and R_2 are both methyl groups, substitution occurs almost exclusively at the terminal position C-1 and not at the internal position C-3. The reaction of (2-bromoethyl)benzene with 3-methylbutenyllithium (reaction 4, Table II) led to only one product, (5-methyl-4-hexenyl)-benzene, and when the same organolithium reagent was coupled with cyclohexyl bromide (reaction 3, Table II), 85% of the coupling product was (3-methyl-2-butenyl)cyclohexane. This would indicate that hydrocarbons of the structure type $RCH_2CH{=}CR'R''$, of considerable interest in terpene synthesis, can be readily prepared by this procedure, and that the procedure of generating allyllithium from allyl phenyl ether surmounts the synthetic difficulties observed when allylic reagents are prepared from allyl mesitoates and coupled with saturated alkyl halides.[2d] When crotyllithium was used, $R_1 = CH_3$, $R_2 = H$ (reactions 1 and 2, Table II), there was an increase in substitution at C-3, but the predominant product (about 70%) was still derived from substitution at C-1 in contrast to reactions with crotyl Grignard reagent which produces *sec*-butenyl derivatives.[6] The exact ratio of substitution at C-1 and C-3 appears to be a complex relationship between the solvent type, and the structure of the organolithium reagent and alkyl halide.[7]

At room temperature and with diethyl ether solvent, the coupling reactions with cyclohexyl iodide and cyclohexyl tosylate were complete in less than 2 hr, but the reactions with cyclohexyl bromide required up to 8 hr for completion when a 50% excess of the organolithium reagent was used. The ease of preparing the relatively stable resonance stabilized organolithium reagents in diethyl ether or tetrahydrofuran, the rapid rate of reaction, and the high yields of hydrocarbons obtained should make Wurtz-type coupling reactions with allylic and benzyllic reagents attractive for general organic synthesis.

Experimental Section

The general method of performing these reactions as well as the procedures for preparing allyllithium, benzyllithium, and benzhydryllithium have been described previously.[2e,8] Crotyllithium and 3-methylbutenyllithium were prepared in a manner analogous to that of the preparation of allyllithium. Comparison of physical constants with those reported in the literature as well as the agreement of infrared and nmr spectra with the assigned structures confirmed the identity of the products. An example of the experimental procedure is described below.

Reaction of 3-Methylbutenyllithium with Cyclohexyl Bromide. The organolithium reagent was prepared by slowly adding an ethereal solution (50 ml) containing 3-methyl-3-butenyl phenyl ether (12.1 g, 0.075 mol) to a rapidly stirred mixture of anhydrous diethyl ether (100 ml) and lithium metal wire (1.4 g, 0.2 mol). As the reaction proceeded, the solution turned a deep red color. Occasionally, a mixture containing about 20% of the total allyl phenyl ether must be stirred up to 2 hr and gently heated before the reaction starts. The organolithium reagent was separated from excess lithium metal by carefully pumping the ethereal solution by N_2 pressure into a clean reaction vessel. Cyclohexyl bromide (7.9 g, 0.05 mol), dissolved in ether (50 ml), was slowly added to the organolithium reagent and the mixture stirred for 8 hr. Work-up consisted of washing the organic layer with 10% NaOH, three times with water, and drying over sodium sulfate. Gc analysis of the crude mixture showed two principal peaks corresponding to the two isomers. (3-methyl-2-butenyl)cyclohexane, and (1,1-dimethyl-2-propenyl)cyclohexane, in a ratio of 85:15. Four fractions (5.3 g) of the desirable hydrocarbons were collected on distillation through a spinning band column. The first three fractions contained mixtures of the two isomers. However, fraction 1 (0.2 g), bp 100–102° (16 Torr), contained about 80% (gc purity) (1,1-dimethyl-2-propenyl)cyclohexane: nmr ($CDCl_3$) δ 0.9 (s, 6 H, methyl protons), 5.2 (m, 3 H, vinyl protons), and 1.5 (broad m, 11 H, cyclohexyl protons). Fraction 4 contained 2.6 g (98% gc purity) of (3-methyl-2-butenyl)cyclohexane: bp 106–108° (16 Torr), $n^{25}D$ 1.4613, nmr ($CDCl_3$) δ 1.8 (s, 6 H, methyl protons), 1.5 (broad m, 13 H, cyclohexyl and methylene protons), and 5.5 (m, 1 H, vinyl proton) [lit.[9] bp 101-102.5° (10 Torr), n^{26}_D 1.4640].

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Cooxidation of α Olefins and Arenethiols with Oxygen. Synthesis of β-Hydroxy Sulfoxides

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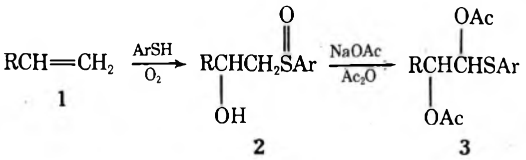
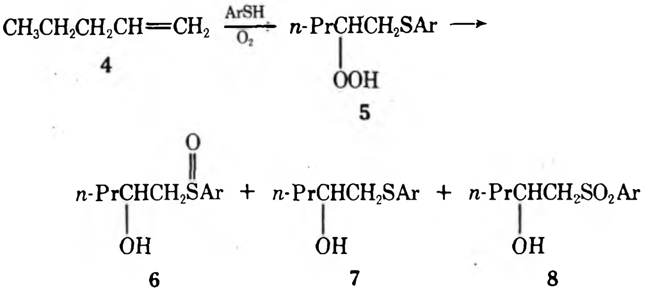
We have found a new method to transform β-hydroxy sulfoxides (2) into a protected form of α-hydroxy aldehydes (3) by the Pummerer reaction with acetic anhydride in the presence of sodium acetate.[1] Since β-hydroxy sulfoxides are obtained by the cooxidation of olefins and thiols with oxygen,[2] a combination of the cooxidation and the subsequent Pummerer reaction will provide an attractive route to α-hydroxy aldehydes from α olefins (1). However, the cooxidation is actually limited to olefins conjugated with electron-attacting groups such as aromatic rings, ester, and nitrile.[3] After some experimentation to establish a general method to get 2 from 1, we have found that the irradiation of a black-light fluorescent lamp is most suitable for the cooxidation of 1 and arenethiol with oxygen because the light is effective enough to give the porduct and does not decompose it. The use of approximately 2 equiv of 1 to thiol affords the product in good yield. The various types of 2 were prepared as summarized in Table I.



$$\underset{\mathbf{1}}{\mathrm{RCH{=}CH_2}} \xrightarrow[\mathrm{O_2}]{\mathrm{ArSH}} \underset{\mathbf{2}}{\mathrm{R}\underset{\mathrm{OH}}{\mathrm{CH}}\mathrm{CH_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{S}}}\mathrm{Ar}} \xrightarrow[\mathrm{Ac_2O}]{\mathrm{NaOAc}} \underset{\mathbf{3}}{\mathrm{R}\underset{\mathrm{OAc}}{\mathrm{CH}}\overset{\mathrm{OAc}}{\mathrm{CH}}\mathrm{SAr}}$$

The similar cooxidation of 1-pentene (4) and *p*-toluenethiol in hexane did not give the corresponding β-hydroxy sulfoxide (6) but many unidentified substances. The reaction in hexane-ethyl acetate (4:1) or hexane-acetone (4:1) as solvent, however, afforded the corresponding β-hydroperoxy sulfide (5) in good yield. It was found that 5 can be converted into 6 by simply stirring the reaction mixture in the presence of a catalytic amount of V_2O_5, oxobis(acetylacetonato)vanadium(IV), or dioxobis(acetylacetonato)-molybdenum(VI). The sulfoxide 6 was isolated in 63-67% yields (see Table I). The by-products were the corresponding sulfide 7 and sulfone 8.



$$\underset{\mathbf{4}}{\mathrm{CH_3CH_2CH_2CH{=}CH_2}} \xrightarrow[\mathrm{O_2}]{\mathrm{ArSH}} \underset{\mathbf{5}}{n\text{-}\mathrm{Pr}\underset{\mathrm{OOH}}{\mathrm{CH}}\mathrm{CH_2SAr}} \longrightarrow$$

$$\underset{\mathbf{6}}{n\text{-}\mathrm{Pr}\underset{\mathrm{OH}}{\mathrm{CH}}\mathrm{CH_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{S}}}\mathrm{Ar}} + \underset{\mathbf{7}}{n\text{-}\mathrm{Pr}\underset{\mathrm{OH}}{\mathrm{CH}}\mathrm{CH_2SAr}} + \underset{\mathbf{8}}{n\text{-}\mathrm{Pr}\underset{\mathrm{OH}}{\mathrm{CH}}\mathrm{CH_2SO_2Ar}}$$

Thus, in the cooxidation of olefins and thiols with oxygen, olefins can be classified into three groups: (1) the conjugated olefins such as styrene, acrylonitrile, and methacrylate, which are known to be easily cooxidized to the corresponding β-hydroxy sulfoxides,[3] (2) the α olefins as shown in Table I, which are cooxidized under the irradiation of a black-light fluorescent lamp, and (3) 1-alkenes, which need catalyst in the transformation of β-hydroperoxy sulfides to β-hydroxy sulfoxides.

The β-hydroxy sulfoxides (2) obtained here are all new compounds, and this work in conjunction with the Pummerer process[1] constitutes a new and simple two-step synthesis of α-hydroxy aldehyde derivatives (3) from α olefins (1). Recently β-hydroxy sulfoxides were found to be converted to α,β-unsaturated sulfoxides,[4] β-chloro sulfones,[5] and α,β-unsaturated sulfones.[6]

Experimental Section

The cooxidation reactions were carried out using freshly distilled olefins. The product is a diastereomeric mixture.

Procedure A-1. Preparation of 3-Acetoxy-2-hydroxypropyl *p*-Tolyl Sulfoxide (2, R = $AcOCH_2$). A solution of *p*-toluenethiol (0.89 g, 7.15 mmol) and allyl acetate (1.30 g, 13.0 mmol) in hexane (100 ml) contained in a 100-ml cylinder was efficiently bubbled with oxygen by means of a sintered-glass bubbler from the bottom of the container under the irradiation of a black-light fluorescent lamp (Toshiba FL-20BLB)[7] at room temperature overnight. The formed white crystals were freed from the solvent by decantation to give 1.515 g (82%) of 2 (R = $AcOCH_2$). The product was recrystallized from chloroform-hexane: ir (Nujol) 1008, 1025, 1243, 1728, and 3265 cm^{-1}; nmr ($CDCl_3$) δ 2.06 (3 H), 2.44 (3 H), 2.55-3.35 (2 H), 4.0-4.65 (4 H), and 7.45 (4 H).

Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.24; H, 6.29; S, 12.51. Found: C, 56.15; H, 6.10; S, 12.54.

Procedure A-2. Preparation of 2-Hydroxy-3-phenylpropyl *p*-Tolyl Sulfoxide (2, R = $PhCH_2$). A solution of *p*-toluenethiol (1.13 g, 9.09 mmol) and allylbenzene (2.15 g, 18.2 mmol) in hexane (200 ml) was subjected to the cooxidation under the same condition as above for 2 days. The formed crystals were collected to afford 1.83 g (73%) of 2 (R = $PhCH_2$). The mother liquor was stirred with *ca.* 30 mg of V_2O_5 for 5 hr to give 0.25 g (10%) of the additional product as insoluble crystals. The product was recrystallized from benzene-hexane: ir (Nujol) 700, 810, 1045, 1085, and 3325 cm^{-1}; nmr ($CDCl_3$) δ 2.39 (3 H), 2.85 (4 H), 4.00 (1 H), 4.95 (1 H), and 7.30 (9 H).

Anal. Calcd for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.61; S, 11.69. Found: C, 70.05; H, 6.60; S, 11.73.

Procedure A-3. Preparation of 3-Acetoxy-2-hydroxybutyl *p*-Tolyl Sulfoxide [2, R = $CH_3VH(OAc)$]. A solution of *p*-toluenethiol (1.00 g, 8.05 mmol) and 3-acetoxy-1-butene (2.21 g, 19.4 mmol) in hexane (300 ml) was stirred in a 500-ml flask under the atmosphere of oxygen and the irradiation of a black-light fluo-

Table I
β-Hydroxy Sulfoxides (2) from α Olefins (1) and Arenethiols

Ar[a]	R (equiv)[b]	Registry no.	Mp,[c] °C	Yield, %	Registry no.
C[j]	$AcOCH_2$ (1.0)	591-87-7	140–143	63[d]	50921-23-8
C	$AcOCH_2$ (2.0)			92[d]	
T[k]	$AcOCH_2$ (1.8)		136–145	82[d]	50921-24-9
Ph[l]	$AcOCH_2$ (1.2)		107–109	54[f]	50921-25-0
T	$HOCH_2$ (2.4)	107-18-6	117–126	90[d]	50921-26-1
T	$CH_3CH(OAc)$ (2.4)	6737-11-7	88–109	76[f]	50921-27-2
T	$PhCH_2OCH_2$ (2.1)	14593-43-2	135–136	87[d]	50921-28-3
T	$PhOCH_2$ (2.2)	1746-13-0	92–98	80[d]	50921-29-4
T	$ClCH_2$ (2.4)	107-05-1	134–136	79[d]	50921-30-7
T	$ClCH_2CHCl$ (2.0)	760-23-6	202–204	82[d]	50921-31-8
T	$PhCH_2$ (2.0)	300-57-2	136–141	83[e]	50921-32-9
T	4-Acetoxy-3-methoxybenzyl (1.05)	93-28-7	129–138	77[f]	50921-33-0
T	$CH_3(CH_2)_2$	109-67-1	43–75	67[g]	50921-34-1
T	$CH_3(CH_2)_2$			66[h]	
T	$CH_3(CH_2)_2$			63[i]	
T	$CH_3(CH_2)_5$	111-66-0	68–71	68[i]	50921-35-2

[a] C = *p*-chlorophenyl, T = *p*-tolyl. [b] Equivalent of olefins to thiol. [c] Melting point of diastereomeric mixtures after a few recrystallizations. [d] By procedure A-1. [e] By procedure A-2. [f] By procedure A-3. [g] With V_2O_5 by procedure B. [h] With $VO(acac)_2$ by procedure B. [i] With $MoO_2(acac)_2$ by procedure B. [j] Registry no., 106-54-7. [k] Registry no., 106-45-6. [l] Registry no., 108-98-5.

rescent lamp overnight. The solvent was evaporated under vacuum to give an oil, which was chromatographed on silica gel with benzene. The elution with benzene-ethanol (95:5) furnished 1.65 g (76%) of **2** [R = $CH_3CH(OAc)$]. The product crystallized on standing and was recrystallized from benzene-hexane: ir (Nujol) 810, 1040, 1245, 1375, 1735, and 3300 cm^{-1}; nmr ($CDCl_3$) δ 1.24 (3 H), 2.02 (3 H), 2.42 (3 H), ~3.1 (2 H), 4.2 (1 H), 4.53 (1 H), 5.0 (1 H), and 7.46 (4 H).

Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71; S, 11.86. Found: C, 58.04; H, 6.85; S, 11.90.

Procedure B. Preparation of 2-Hydroxypentyl *p*-Tolyl Sulfoxide (2, R = $CH_3CH_2CH_2$). A solution of *p*-toluenethiol (1.00 g, 8.05 mmol) and 1-pentene (1.29 g, 18.4 mmol) in 200 ml of hexane-ethyl acetate (4:1) was stirred in the same condition as procedure A-3 overnight. Then the solution was stirred with *ca.* 30 mg of V_2O_5 for 5 hr. The solvent was removed under vacuum to give an oil, which was chromatographed with benzene. The elution with benzene-ethyl acetate (8:2) furnished 1.23 g (67%) of 2 (R = $CH_3CH_2CH_2$). The product crystallized on standing and was recrystallized from benzene-hexane: ir (Nujol) 803, 1026, and 3320 cm^{-1}; nmr ($CDCl_3$) δ 0.87 (3 H), 1.41 (4 H), 2.36 (3 H), 2.5–3.25 (2 H), 4.06 (1 H), 4.14 (1 H), and 7.1–7.7 (4 H).

Anal. Calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02; S, 14.16. Found: C, 63.67; H, 8.15; S, 14.00.

Acknowledgment. We are grateful to the Kawakami Memorial Foundation for the financial support.

References and Notes

(1) The addition of sodium acetate is required for this transformation. S. Iriuchijima, K. Maniwa, and G. Tsuchihashi, submitted for publication in *J. Amer. Chem. Soc.*

(2) For a review see A. A. Oswald and T. J. Wallace in "The Chemistry of Organic Sulfur Compounds," Vol. 2, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, Oxford, 1966, pp 217-232.

(3) For example, (a) A. A. Oswald, *J. Org. Chem.*, **26**, 842 (1961); (b) H. Bredereck, A. Wagner, and A. Kottenhahn, *Chem. Ber.*, **93**, 2415 (1960).

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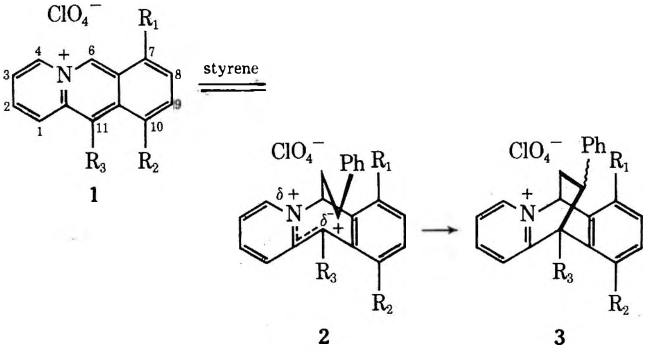
(7) Emission spectrum: 300-400 nm (maximum at 360 nm).

Communications

Evidence for Steric Enhancement of Rate in Cycloaddition

Summary: The acceleration in the rate of cycloaddition observed when methyl groups are introduced into the meso positions of anthracene or the acridizinium ion must be largely steric rather than electronic in origin.

Sir: Since the acridizinium ion (**1a**) is electrophilic[1] in nature, it was surprising to find that introduction of a methyl group at position 11 (see **1b**) produced over a 13-fold *increase* in the rate of cycloaddition with styrene.[2] An alternative to the earlier[2,3] electronic explanation for the rate enhancement, and one compatible with the increasing evidence[1,4] of the importance of position 6 of the acridizinium ion in the rate-controlling process, is that the methyl at position 11 is under strain as the result of peri interactions with adjacent hydrogens (at positions 1 and 10) and that this strain is relieved when the methyl group moves out of plane during cycloaddition (see **2**). If this assumption is correct, the introduction of a methyl group into a position peri to the 11-methyl should result in a further rate enhancement.



a, R$_1$ = R$_2$ = R$_3$ = H;
b, R$_1$ = R$_2$ = H, R$_3$ = Me;
c, R$_1$ = R$_2$ = R$_3$ = Me

For convenience in synthesis, the 7,10,11-trimethylacridizinium ion (**1c**) was studied. The observed rate of cycloaddition with styrene was more than 10 times that of the 11-methyl derivative, direct evidence of steric acceleration.[5]

Steric acceleration in the conventional Diels–Alder reaction has been overlooked because of a general inability to assess the relative importance of such acceleration when polar effects would also be expected to speed the reaction. An obvious, but hitherto unrecognized, example of such steric acceleration may be seen in published data[6] concerning anthracene derivatives. The introduction of methyl groups into both of the meso positions of anthracene results in a 218-fold acceleration of the rate of cycloaddition with maleic anhydride, while methoxyl groups at the same positions actually cause a *decrease* in rate. The suggestion,[6] "the increase in rate produced by methoxy groups is smaller than that of alkyl groups because of the impaired coplanarity (*peri*-hydrogens)," would imply that steric inhibition of resonance had rendered the methoxyl groups less electron-releasing than methyl groups. That this is not the case is evidenced by recent[7] ^{19}F substituent chemical shift data for 10-substituted 9-fluoroanthracenes. It is more likely that the greater effective size of the methyl group is largely responsible for the rapid rate of cycloaddition reported[6] for 9,10-dimethylanthracene.

Acknowledgment. We are indebted to Dr. John P. Sherer for the synthesis of 7,10,11-trimethylacridizinium perchlorate.

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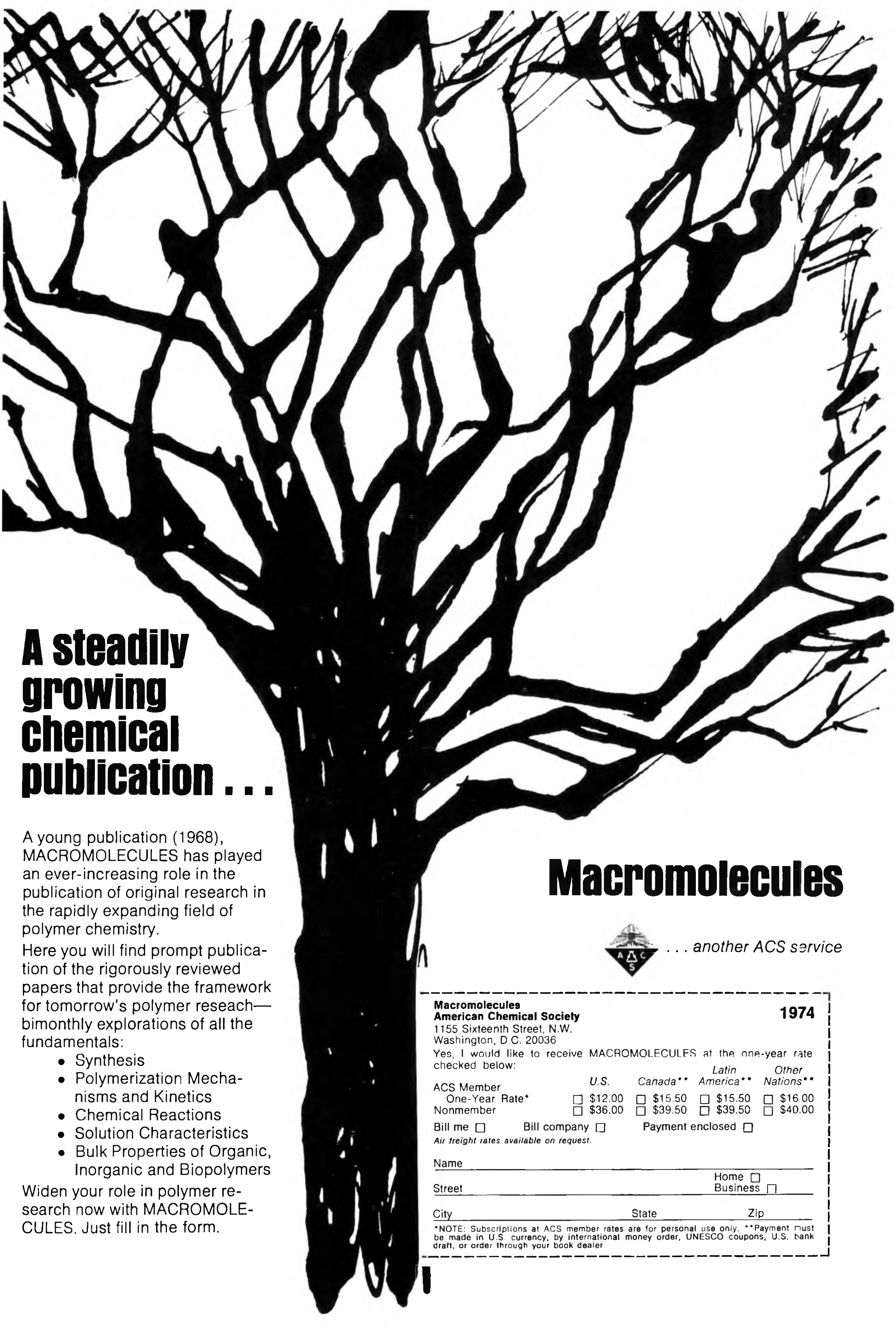

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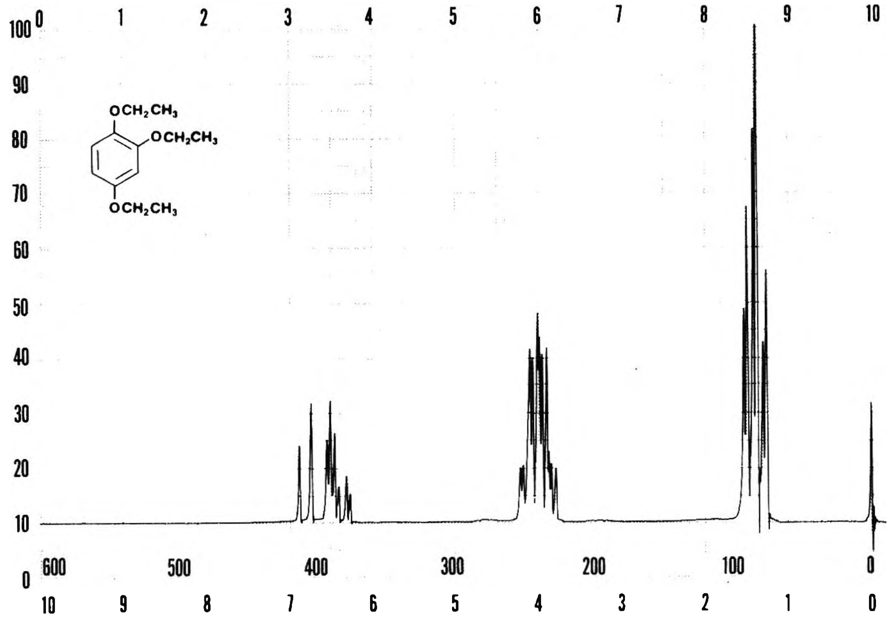

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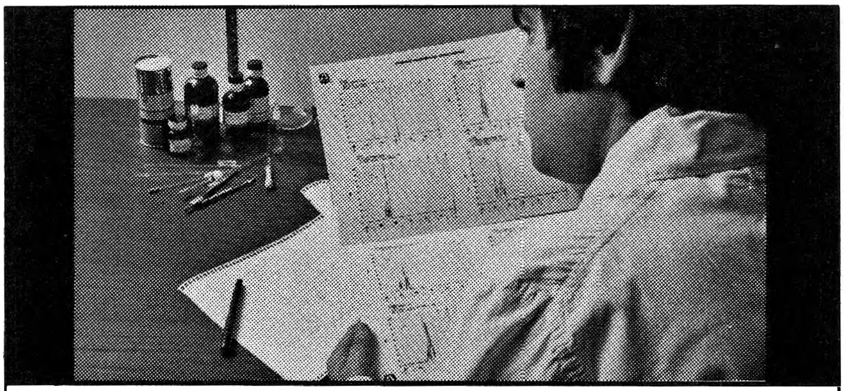

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