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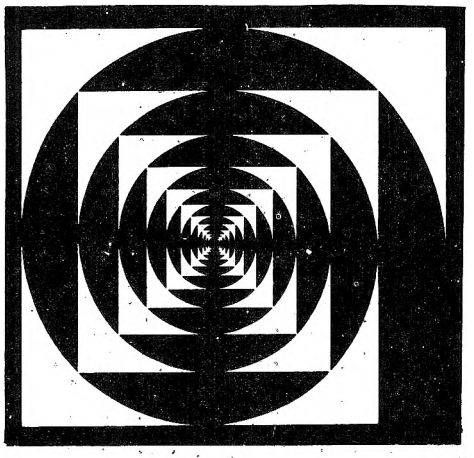

organic chemistry

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COMMUNICATIONS

AUTHOR INDEX

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FEBRUARY 23, 1973

Stereoselectivity in the Reduction of Aliphatic α-Ketols with Aluminum Hydride Reagents

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Received June 30, 1972

The reduction of six α-ketols with different patterns of substitution and size of substituents has been investigated using seven aluminum hydride reagents. The ratio of diastereomeric diols produced was determined by 220-MHz nmr analysis. In each case the predominant diol was the one predicted by Cram's cyclic model. The degree of stereoselectivity correlates well with α-ketol structure with only one reagent (triisobutylaluminum). With the other (agglomerated) reagents, selectivity is related only in an irregular manner to α-ketol structure.

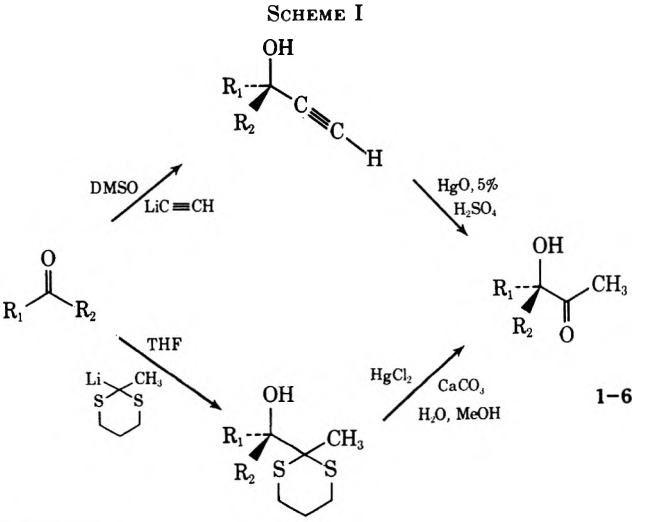
The stereoselective formation of olefins is a synthetic endeavor that has received considerable attention in recent years.[1] One of the approaches that has been successful in achieving complete stereospecificity is the conversion of 1,2-diols to the corresponding olefins, and a variety of methods for effecting this transformation has been reported.[2] Although the conversion of diol to olefin proceeds without loss of stereochemical integrity, the production of a single olefin isomer requires the availability of a single diastereomer of the precursor diol; hence, the problem of stereoselective olefin synthesis by this method is reduced to the problem of stereoselective diol synthesis.

Convenient precursors of diols are the related α-ketols. A number of recent synthetic methods have supplanted the classical acyloin condensation,[3] and permit the convenient synthesis of a wide variety of unsymmetrically substituted aliphatic α-ketols.[4] This report details the results of a study of the reductions of a number of di- and trisubstituted α-ketols using several aluminum hydride reagents with differing reduction properties.[5,6] As the resulting diols can be converted into olefins or epoxides, this work constitutes in a formal sense a stereoselective route to both of these systems.

Results

Synthesis of α-Ketols.—The α-ketols utilized in this study were prepared either by the mercuric ion catalyzed hydration of propargylic alcohols[4c] or by addition of 2-lithio-2-methyl-1,3-dithiane to carbonyl compounds, followed by mercuric ion assisted hydrolysis of the dithioketal[4a] (Scheme I). Yields, physical con-

SCHEME I



(1) For reviews see D. J. Faulkner, *Synthesis*, 175 (1971), and J. Reucroft and P. G. Sammes, *Quart. Rev., Chem. Soc.*, **25**, 135 (1971).

(2) E. J. Corey and R. A. E. Winter, *J. Amer. Chem. Soc.*, **85**, 2677 (1963); E. J. Corey, F. A. Carey, and R. A. E. Winter, *ibid.*, **87**, 934 (1965); F. W. Eastwood, K. J. Harrington, J. S. Josan, and J. L. Pura, *Tetrahedron Lett.*, 5223 (1970); J. N. Hines, M. J. Peagram, G. H. Whitman, and M. Wright, *Chem. Commun.*, 1593 (1968); G. Crank and F. W. Eastwood, *Aust. J. Chem.*, **17**, 1392 (1964); J. S. Josan and F. W. Eastwood, *ibid.*, **21**, 2013 (1968); J. F. McGhie, W. A. Ross, D. H. Laney, and J. M. Barker, *J. Chem. Soc. C*, 1 (1968).

(3) S. M. McElvain, *Org. React.*, **4**, 256 (1948).

(4) (a) D. Seebach, *Synthesis*, 17 (1969); (b) H. M. Walborsky, W. H. Morrison, and G. E. Niznik, *J. Amer. Chem. Soc.*, **92**, 6675 (1970); (c) M. Miocque, N. M. Hung, and V. Q. Yen, *Ann. Chim. (Paris)*, [13] **8**, 157 (1963); (d) T. Cohen and T. Tsuji, *J. Org. Chem.*, **26**, 1681 (1961); (e) S. Hoff, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **87**, 1179 (1968); (f) S.-O. Lawesson and S. Gronwall, *Acta Chem. Scand.*, **14**, 1445 (1960).

(5) Asymmetric induction in additions to aliphatic α-ketols has been studied extensively, but reactions involving attack by an organometallic (as opposed to a hydride) have received the closest scrutiny. For reviews see (a) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Engelwood Cliffs, N. J., 1971, Chapter 3; (b) S.-I. Yamada and K. Koga in "Selective Organic Transformations," Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1970, p 5 ff.

(6) Investigations which have examined the reduction of acyloins or their derivatives are (a) J. H. Stocker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *J. Amer. Chem. Soc.*, **82**, 3913 (1960); (b) S. Yamada and K. Koga, *Tetrahedron Lett.*, 1711 (1967); (c) D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952).

TABLE I

α-KETOLS. YIELDS AND PHYSICAL AND SPECTROSCOPIC PROPERTIES[a]

Compd	Substituent[b] R1	R2	Method[c]	Yield,[d] %	Bp, °C (mm)	Nmr[e] chemical shift, δ (multiplicity,[f] J, Hz) CH3	OH	R1	R2
1	n-C_5H_{11}	H	A	84	42 (0.17)	2.01 (s)	3.9 (u)	0.62 (t) 1.2 (u)	3.9 (u)
2	i-Pr	H	A	17		2.20 (s)	3.30 (s)	0.77 (d, 6.5)	4.06 (d, 2.5)
			B	24	68–72 (17)[g]			1.11 (d, 6.5) 2.20 (m)	
3	t-Bu	H	A	54	31–33 (0.25)[h]	2.20 (s)	3.35 (s)	1.0 (s)	3.76 (s)
4	Ph	CH_3	A	54	133 (10)[i]	2.07 (s)	4.1 (s)	7.2–7.5 (m)	1.74 (s)
5	i-Pr	CH_3	A	34		2.20 (s)	3.5 (s)	0.75 (d, 8.0)	1.30 (s)
			B	49	66–68 (10)			1.02 (d, 8.0) 1.97 (m)	
6	t-Bu	CH_3	B	31	178–180 (760)	2.18 (s)	3.5 (s)	0.92 (s)	1.20 (s)

[a] Satisfactory analytical data (± 0.4%) were obtained for all compounds and were made available to the Editor and referees. Compounds 2, 3, and 4 were analyzed as their semicarbazone derivatives. [b] Substitution per Scheme I. [c] A, *via* dithiane; B, *via* propargylic alcohol. [d] Isolated yield of pure α-ketol, based on starting carbonyl component. [e] 60 MHz, CCl_4 solution. [f] u = unresolved. [g] Semicarbazone mp 221–223° (methanol). [h] Semicarbazone mp 194–197° (aqueous ethanol). [i] Semicarbazone mp 182.5–184° (methanol).

TABLE II

PHYSICAL AND SPECTROSCOPIC PROPERTIES OF DIASTEREOMERIC DIOLS[a]

Compd	Substituent R1	R2	Configuration	Mp, °C	Nmr[b] chemical shift, δ (coupling, J, Hz) CH3	H	R1	R2
7	n-C_5H_{11}	H	erythro	42.5–44	1.13 (6.2)	*3.76* (6.2, 1.5)	*c*	3.58 (u)[d]
			threo	Liquid	1.18 (5.8)	3.58 (u)	*c*	*3.30* (u)
8	i-Pr	H	erythro	43.5–45.5	1.17 (6.3)	*3.88* (u)	0.85, 0.98 (6.0)[e]	*3.24* (3.5)
			threo	54–56	1.20 (6.0)	*3.76* (6.0)	0.88, 1.00 (4.0)[e]	*3.10* (u)
9	t-Bu	H	erythro	70–72	1.20 (6.4)	3.88 (6.2, 2.8)	0.96	*3.36* (u)
			threo	80.5–81.5	1.24 (6.4)	3.92 (6.4, 1.7)	0.94	*2.95* (1.7)
10	Ph	CH_3	erythro	Liquid	*0.90* (6.3)[f]	4.78 (6.3)	7.22	*1.50*
			threo	Liquid	*1.08* (6.3)[f]	4.78 (6.3)	7.22	*1.43*
11	i-Pr	CH_3	erythro	Liquid	1.19 (6.3)	3.59 (6.3)	*0.83, 0.98* (6.6)[e]	*1.11*
			threo	44–46	1.15 (6.0)	3.77 (6.0)	*0.93* (6.0)[e]	*1.02*
12	t-Bu	CH_3	erythro	96–97	1.26 (6.5)	3.95 (6.5)	*1.02*	*1.14*
			threo	22–24	1.21 (6.4)	3.80 (6.4)	*0.98*	*1.08*

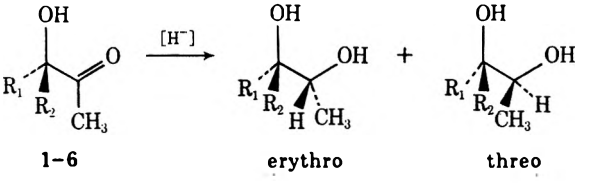
[a] Satisfactory analytical data (±0.4%) were obtained for all compounds and were made available to the Editor and referees. [b] 220 MHz, $CDCl_3$ or CCl_4 solution. Signals used for quantitative analysis are italicized. [c] Multiple resonances 0.8–1.7 ppm. [d] u = unresolved. [e] Isopropyl methyl resonances. [f] 60 MHz.

stants, and spectroscopic data for these compounds are shown in Table I.

While the propargylic alcohol route is better suited to large-scale preparations, the dithiane route was preferred as it gives a cleaner reaction. However, with the more severely hindered ketones, only the propargylic route gave satisfactory yields.

Identification of the Predominant Diastereomeric Diols.—Diastereomeric α-diols are generally distinguishable by nmr. Anet[7] has correlated the coupling constants of butane-2,3-diol acetonides; more recently Nakanishi, *et al.*,[8] have developed a method which utilizes the differences in NOE and W-type coupling to distinguish between diastereomers of α-diols and certain of their derivatives. While these methods are laudable in their general applicability for the identification of pure α-diols, they are ill-suited to the analysis of mixtures of diastereomers. Therefore, we have applied the observations of Anet[7] and Cavill[9] of the differing chemical shifts of substituents on the diastereomeric carbons in analyzing the mixtures formed in the reduction reactions (Scheme II). These regions of nonequivalence and potential analytical utility are summarized in Table II.

SCHEME II



1-6 erythro threo

7-12

In making these assignments, we were guided by the assumption that Cram's "cyclic" model[10] would be applicable to the reductions giving the diols; *i.e.*, in all cases the erythro isomer would predominate (Scheme II). However, to establish the assignments unequivocally, we prepared authentic samples of the diols by stereospecific epoxidation of isomerically pure olefins with *m*-chloroperbenzoic acid, followed by hydration with 30% aqueous perchloric acid in tetrahydrofuran. This procedure gave the isomerically pure diols, except in the case of 2-phenylbutane-2,3-diol (**10**), which gave the same mixture of diols from either isomer of 2-phenyl-2-butene. Samples of the pure diastereomers of **10** were prepared by cis hydroxylation of the pure olefin isomers, using magnesium sulfate buffered potassium permanganate in aqueous ethanol. In all

(7) F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 747 (1962).

(8) K. Nakanishi, D. A. Schooley, M. Koreeda, and I. Miura, *ibid.*, **94**, 2865 (1972).

(9) G. W. K. Cavill, D. G. Laing, and P. J. Williams, *Aust. J. Chem.*, **22**, 2145 (1969).

(10) D. J. Cram and D. R. Wilson, *J. Amer. Chem. Soc.*, **85**, 1245 (1963), and references cited therein.

TABLE III

YIELD OF DIOL PRODUCTS AND PER CENT ERYTHRO DIASTEREOMER PRODUCED IN THE HYDRIDE REDUCTION OF α-KETOLS

	Reactant[a]		% Erythro[b] (diol yield %)[c]						
Compd	R_1	R_2	TIBA ($PhCH_3$)	DIBAH ($PhCH_3$)	$LiAlH_4$ (THF)	$LiAl(OMe)_3H$ (THF)	REDAL ($PhH:PhCH_3$)	AlH_3 (THF)	$LiAl(O\text{-}t\text{-}Bu)_3H$ (THF)
1	$n\text{-}C_5H_{11}$	H	54 (97)	68 (98)	70 (95)	78 (73)	62 (91)	71 (93)	63 (85)
2	*i*-Pr	H	83 (90)	62 (74)	73 (62)	66 (53)			
3	*t*-Bu	H	>95 (73)	73 (79)	75 (97)	77 (88)			
4	Ph	CH_3	82 (62)	78 (79)	67 (86)	57 (85)			
5	*i*-Pr	CH_3	85 (72)	71 (89)	49 (87)	60 (86)			
6	*t*-Bu	CH_3	91 (73)	60 (85)	64 (87)	70 (90)			

[a] All reductions were conducted in the solvent indicated using a threefold molar excess of hydride reagent, for 4 hr at −78° with gradual warming to 25°. [b] Determined by 220-MHz nmr analysis, Table II. [c] Isolated yield.

cases, the nmr spectra of the authentic samples were in agreement with initial assignments based on Cram's cyclic model.

Quantitative Analysis of Mixtures of Diastereomeric Diols.—In our initial efforts to quantitate the ratio of diol products we utilized gas chromatographic analysis; however, the only phases capable of separating the diastereomeric diols gave poorly reproducible chromatograms. Furthermore, the diols were subject to extensive decomposition on the column.

It was found that 220-MHz nmr provided sufficient resolution to obtain meaningful integration data of selected signals in each mixture (Table II). Repetitive integration of these signals and, where possible, comparison of integrals of alternative signals as internal checks, gave average deviations of ±2%. Duplicate experiments performed in all cases gave results which were within these limits, except $LiAl(OMe)_3H$. In the case of $LiAl(OMe)_3H$, a larger variation (±6%) was found and was ascribed primarily to differences in the constitution of the reagent, which was prepared *in situ* immediately prior to addition of the substrate.

Reduction of α-Ketols.—The reducing agents utilized in this study were all of the aluminum hydride type. Lithium aluminum hydride ($LiAlH_4$), aluminum hydride (AlH_3), lithium trimethoxyaluminum hydride [$LiAl(OMe)_3H$], and lithium tri-*tert*-butoxyaluminum hydride [$LiAl(O\text{-}t\text{-}Bu)_3H$] reductions were conducted in tetrahydrofuran (THF) as solvent; triisobutylaluminum (TIBA) and diisobutylaluminum hydride (DIBAH) reactions were run in toluene, and sodium bis(2-methoxyethoxy)aluminum hydride (RED-AL)[11] in benzene–toluene (1:1). Reduction of all six α-ketols by TIBA, DIBAH, $LiAlH_4$, and $LiAl(OMe)_3H$ was examined. Only the reaction of the least selective primary substituted system (1) was investigated with all seven reagents.

The reduction reaction proceeded cleanly in all cases to give the product diols in moderate (*ca.* 55%) to excellent (>95%) yields. The yield and ratios of diastereomeric diols formed are summarized in Table III, and the degree of stereoselectivity in Table IV.

TABLE IV

STEREOSELECTIVITY OBSERVED IN α-KETOL REDUCTIONS

	Reactant		Stereoselectivity (diastereomer ratio)[a]			
Compd	R_1	R_2	TIBA	DIBAH	$LiAlH_4$	$LiAl(OMe)_3H$
1	$n\text{-}C_5H_{11}$	H	8 (1.17)	36 (2.13)	40 (2.33)	56 (3.55)
2	*i*-Pr	H	66 (4.88)	24 (1.63)	46 (2.70)	32 (1.94)
3	*t*-Bu	H	>90 (19)	46 (2.70)	50 (3.00)	54 (3.35)
4	Ph	CH_3	64 (4.56)	56 (3.55)	34 (2.03)	14 (1.33)
5	*i*-Pr	CH_3	70 (5.67)	42 (2.45)	−2 (0.96)	20 (1.50)
6	*t*-Bu	CH_3	82 (10.11)	20 (1.50)	28 (1.78)	40 (2.33)

[a] Data is taken from Table III and recast in form more suitable for comparison of stereoselectivities. Selectivity = % erythro − % threo (if >0, implies that cyclic model holds); diastereomer ratio is % erythro/% threo (if >1, implies that cyclic model holds).

Discussion

Cram's cyclic model for steric control in asymmetric induction was devised to predict the diastereomer that would predominate in the reaction of a nucleophile with a chiral ketone containing a group on the α carbon that is capable of complexing with the counterion of the reagent. The α-ketols we have studied, therefore, fall in the predictive domain of this model, and our results do indeed conform to the model's predictions to the extent that, in each example studied, the diastereomer that predominates (within experimental error) is the anticipated erythro isomer.

The three models for asymmetric induction (open chain,[6c] dipolar,[12] and cyclic[6c]) were originally presented as means for predicting only which diastereomeric product would predominate in an addition to a chiral ketone, and not the degree to which it would predominate (stereoselectivity). Recently, Karabatsos[13] and Felkin[14] have attempted to extend the open-chain and dipolar models so that some correlation could be made between changes in ketone structure and the resulting changes in stereoselectivity of the addition. Substantially modified transition-state models have emerged from these two studies.

If one attempts to extend the cyclic model in a similar fashion, it is clear that the simple picture of the cyclic model with its attendant controlling interactions between the attacking reagent with R_S and R_L (Scheme III) cannot provide an adequate correlation for our data (*vide infra*). Indeed, Morrison and Mosher[15] have cautioned that, of the three models for asymmetric induction, the systems covered by the cyclic model are those most subject to alterations in stereoselectivity with change of solvent, reagent, and bulk associated with the metal–carbonyl complex. In some cases, the selectivity observed has even been the reverse of that predicted by the cyclic model;[5a,6a,10,16] discrepancies of this magnitude are only infrequently encountered with the open-chain and dipolar models.[15]

(11) Trademark of The Aldrich Chemical Co., Milwaukee, Wis.

(12) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959).

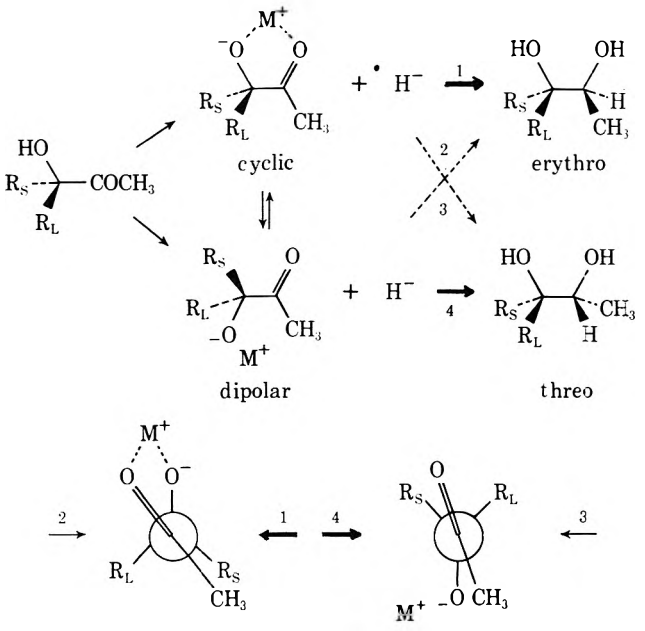
(13) G. J. Karabatsos, *J. Amer. Chem. Soc.*, **89**, 1367 (1967).

(14) M. Chérest, H. Felkin, and N. Pruduct, *Tetrahedron Lett.*, 2201 (1968).

(15) Reference 5a, pp 97 and 113.

(16) J. H. Stocker, *J. Amer. Chem. Soc.*, **88**, 2878 (1964).

SCHEME III



In order to rationalize the unreliability of the cyclic model, it has been proposed[10] that, in certain "cyclic model" systems, addition may actually be taking place *via* two competing transition states, the cyclic and the dipolar (Scheme III). As in each case the dipolar model predicts predominance of the diastereomer opposite to that of cyclic model, reversal of the stereochemical course of the reaction may be ascribed to a change in the partitioning of the reaction between the two transition states. If it is indeed true that so many courses of reaction are in competition, then prediction of the effect of alterations in reactant structure, solvent, and nature of reagent on reaction stereoselectivity becomes laden with ambiguity. However, there are a number of results from our study in which the relationship between stereoselectivity and reagent and reactant structure is worthy of discussion.

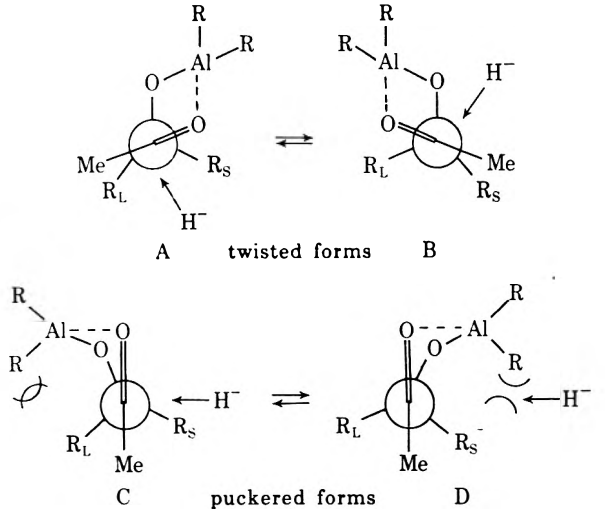
Aggregation of Reducing Reagent.—In his early work on the addition of organolithium reagents to α-ketols, Cram[10] noted that the stereoselectivity decreased with change of solvent from ether to pentane. He suggested that the increased agglomeration of the lithium reagent in the hydrocarbon solvent, with the attendant increase in steric bulk associated with the metal alkoxide–carbonyl complex, might allow a portion of the reaction to proceed *via* the less encumbered dipolar transition state. More recently, Ashby[17] has noted the concentration dependence of stereoselectivity in the hydride reduction of 2-methylcyclohexanone, and has ascribed these variations to changes in reagent aggregation; the stereoselectivity of reduction by $LiAl(OMe)_3H$ is most sensitive to change in the concentration range in which association of the reagent is changing most rapidly. Conversely, the stereoselectivity of reduction by $LiAl(O\text{-}t\text{-}Bu)_3H$, which is monomeric over the range investigated, is essentially concentration independent.

A comparison of our results with TIBA and DIBAH provides a striking example of this effect, especially in the case of disubstituted α-ketols. Thus, the reduction with TIBA, reported to be monomeric in solution,[18] is highly sensitive to changes in the steric requirements of the substituents on the α-ketol, and stereoselectivity changes in a regular manner consistent with the cyclic model. On the other hand, reaction with DIBAH, a considerably bulkier trimer[18,19] [as well as the agglomerated $LiAlH_4$ and $LiAl(OMe)_3H$],[17] displays neither regular nor marked increase in selectivity with increase in the bulk of R_L.

Nature of the Alkoxide–Carbonyl Complex.—In view of our results as discussed above, as well as those previously obtained by other workers, it is tempting to conclude that competition between the sterically more compressed cyclic model and the freer dipolar model is primarily dependent upon the state of aggregation of the reducing agent, and that it is this competition which determines the observed stereoselectivities of the reaction. It is disturbing, however, that in at least two cases we have studied (DIBAH and $LiAlH_4$) the change in selectivity is related in an irregular manner to the change in bulk of R_L *vs.* R_S. Alternative explanations for these observations may be that, in addition to reagent aggregation, (a) the steric bulk of R_L may also be of importance in creating an effective partitioning among cyclic, dipolar, and certain open-chain transition states (Scheme III) or that (b) the cyclic transition state predominates in all cases but is subject to conformational changes. More detailed analysis of hypothesis a is difficult, but hypothesis b deserves further comment.

If it is assumed that the chelated ring is planar and rigid, then the only effects that direct the stereochemical course of the reduction are the interactions between the attacking hydride reagent with R_L and R_S. Stocker[6a] has speculated that, in certain cases where neither the acyclic model nor a competing cyclic dipolar model provides an adequate explanation, a twisting of the five-membered ring (Scheme IV, A and

SCHEME IV



B) may be taking place. It should be noted that, in addition to possible relief of steric compression, such torsion would also allow a small decrease in dipolar in-

(17) E. C. Ashby, J. P. Sevenair, and F. R. Dobbs, *J. Org. Chem.*, **36**, 197 (1971).

(18) E. G. Hoffman, *Justus Liebigs Ann. Chem.*, **629**, 104 (1960); K. Ziegler, W. R. Kroll, W. Larbigand, and O. W. Steudle, *ibid.*, **629**, 53 (1960).

(19) H. W. Schroetter and E. G. Hoffman, *Ber. Bunsenges. Phys. Chem.*, **68**, 627 (1964).

teractions. Alternatively, conformational deformation may take the form of ring puckering (Scheme IV, C and D).

Either of these conformational models might suffice to explain an irregular dependence of stereoselectivity upon alteration in the relative sizes of R_L and R_S. For instance, in the twisted species A and B, increase in the size of R_L relative to R_S should favor attack by hydride from the side of R_S (bottom right), but at the same time this change would shift the conformational equilibrium in favor of species B to minimize the eclipsing interaction between Me and R_L; attack on the same carbonyl face in B, however, is now hindered by interactions between entering hydride ion and the bulky aluminum alkoxide–carbonyl chelate. Similarly, in the puckered species C and D, increase in the size of R_L relative to R_S makes interactions between hydride and R_S more favorable to attack from the side of R_S (right), but at the same time the increased interaction between the chelating metal and its ligands with R_L tend to favor the species D, in which attack from the right is subject to unfavorable interactions between entering hydride and the aluminum species.

Anomalous Behavior of a Phenyl Substituent.—With two reagents [TIBA and $LiAl(OMe)_3H$] the stereoselectivity observed in the reduction of the phenyl-substituted α-ketol **4** is less than that obtained in the analogous isopropyl-substituted case (**5**), and, with two reagents (DIBAH and $LiAlH_4$), the reduction is more selective than in the corresponding *tert*-butyl case (**6**). In numerous examples that follow Cram's open-chain model, a phenyl substituent is always rated as being greater in steric bulk than an isopropyl group, and is generally considered comparable to or even larger than a *tert*-butyl group.[20] In this connection, the alteration in selectivity in the reduction of the α-phenyl α-ketol is curious; it is possible that this case reflects mediation of effects other than the simple steric arguments discussed above.

Conclusions.—The stereoselectivities obtained in the hydride reduction of α-ketols do not appear to follow a generally regular pattern, other than that the predominant diastereomer formed is that predicted by Cram's cyclic model for asymmetric induction. In the case of a monomeric reagent (TIBA), the degree of stereoselectivity does correlate well with changes in the relative steric bulk of the substituents on the α carbon, but, with agglomerated reagents, selectivity changes in an irregular manner. It is perhaps safe only to say that the highest selectivities are not necessarily associated with the most hindered α-ketols or aggregated hydride donors, nor the lowest selectivities with the least hindered, but that each reagent retains a selectivity peculiar to the specific system with which one is working.

Experimental Section

General.—Melting points were determined on a Fisher-Johns apparatus, and are uncorrected. Nuclear magnetic resonance spectra were determined in CCl_4 or $CDCl_3$ solution on Varian A-60 or HR-220 spectrometers; chemical shifts are reported in parts per million downfield from internal tetramethylsilane (δ scale). Elemental analyses were performed by the microanalytical service of the University of Illinois.

(20) Reference 5a, p 89.

Glassware for reactions involving organometallic reagents was dried for a minimum of 3 hr at 120°. Solvents for these reactions were dried by distillation from appropriate reagents. All other reagents were used as supplied, unless otherwise noted. Solutions were dried over $MgSO_4$ unless otherwise noted.

Isomerically pure olefins used in the preparation of standard diols were obtained from Aldrich Chemical Co. or Chemical Samples Co. Lithium aluminum hydride was obtained from Ventron Corp. THF solutions of this reagent, aluminum hydride, and lithium trimethoxyaluminum hydride were prepared by the method of Brown.[21] THF solutions of lithium tri-*tert*-butoxyaluminum hydride were prepared from the pure material obtained from Aldrich Chemical Co. Sodium bis(methoxyethoxy)aluminum dihydride (RED-AL, 70% in benzene, Aldrich) was diluted with benzene–toluene (1:1) prior to use. Toluene solutions of triisobutylaluminum (TIBA) and diisobutylaluminum hydride (DIBAH) were prepared from the neat liquids as supplied by Ventron Corp.

All of the above solutions were assayed for available hydride by gas titration immediately prior to use.

3-Hydroxy-2-alkanones.—A series of 3- and 4-substituted 3-hydroxy-2-alkanones was prepared; yields, physical properties, and nmr data for these compounds are summarized in Table I. The procedure given below for the preparation of 3,4-dimethyl-2-pentanon-3-ol (**5**) was generally used in the preparation of other members of the series, as indicated in the Method column of Table I.

Method A. *Via* 1,3-Dithiane Mercaptal.—To 2-methyl-1,3-dithiane (1.34 g, 10 mmol), dissolved in *ca.* 60 ml of THF and stirred at −20° under a nitrogen atmosphere, was added an equivalent amount of *n*-butyllithium (1.23 *M*, in pentane). The mixture was stirred at −20° for 5 hr, the temperature was then reduced to −78°, and 3-methyl-2-butanone (0.86 g, 10 mmol) in 10 ml of THF was added over a period of 30 min. After an additional 30 min, the cold bath was removed and the solution was stirred at room temperature for several hours. The solution was poured onto 300 ml of ice and water, and extracted three times with chloroform. The organic extracts were washed twice with 10% KOH (0°), once with water, and dried (K_2CO_3), and the solvent was removed by flash evaporation.

A vigorously stirred solution of the crude dithiane in 100 ml of 80% aqueous methanol was treated with $CaCO_3$ (1.0 g, 10 mmol) and $HgCl_2$ (5.44 g, 20 mmol). After refluxing for 5 hr the mixture was cooled and filtered, and the methanol was removed by flash evaporation. The residue was diluted with brine and extracted with three portions of ether. The combined ether extracts were washed with water, saturated aqueous ammonium chloride, and again with water, and then dried. Evaporation of the solvent and distillation gave 0.44 g (34%) of the product, bp 65–69° (10 mm).

Method B. *Via* Propargylic Alcohol.—3-Methyl-2-butanone (8.6 g, 0.10 mol) dissolved in 20 ml of DMSO was added over a period of 45 min to a slurry of lithium acetylide–ethylenediamine complex (6.4 g, 0.2 mol) in 30 ml of DMSO, stirred at 0° under a nitrogen atmosphere. After 1 hr the ice bath was removed and the mixture was stirred for 12 hr. The mixture was slowly poured into *ca.* 900 ml of ice water, which was then continuously extracted with ether. The extract was dried and the solvent was removed by distillation.

The crude propynol was added over a period of 1.5 hr to a stirred solution, heated to 60°, of 100 ml of 5% H_2SO_4 in which 2.5 g of HgO (red) had been dissolved. After the addition was complete the mixture was heated for an additional 1 hr, cooled, and filtered. The filtrate was extracted three times with ether, the combined extracts were dried, and the solvent was removed by flash evaporation. Two distillations of the oily residue afforded 6.4 g (49%) of the product, bp 66–68° (10 mm).

Preparation of Authentic Samples of Diols. Trans Hydroxylation.—To a solution of *m*-chloroperbenzoic acid (5.1 g of 85% technical material, 25 mmol) in *ca.* 150 ml of methylene chloride was added over a period of 30 min 20 mmol of the olefin. The solution was stirred for 20–24 hr and then quenched by the addition of 10 ml of saturated Na_2SO_3. The mixture was diluted with saturated bicarbonate, and the layers were separated. The organic layer and two ether extracts of the aqueous layer were dried and the solvent was evaporated.

(21) H. C. Brown and P. M. Weissman, *J. Amer. Chem. Soc.*, **87**, 5614 (1965); H. C. Brown and N. M. Yoon, **88**, 1464 (1966).

The crude product was dissolved in 150 ml of THF and treated with 50 ml of 30% $HClO_4$. After stirring for 8 hr, the solution was neutralized with 10% NaOH, diluted with brine, and extracted twice with ether. The combined ether extracts were dried and the solvent was evaporated. Liquid products were purified by bulb-to-bulb distillation; solids were recrystallized from hexane or benzene–hexane solution.

Cis Hydroxylation.[22]—To 20 mmol of the olefin, dissolved in *ca.* 100 ml of ethanol and stirred at −20°, was added over a period of 20 min a solution of potassium permanganate (2.12 g, 13.4 mmol) and magnesium sulfate (1.5 g, 12.5 mmol) in *ca.* 200 ml of water. The mixture was immediately filtered through Celite, and the cake was washed with methanol and ether. The filtrate was concentrated, diluted with brine, and extracted several times with ether. The combined extracts were dried and the solvent was evaporated. Chromatography on silica gel (5% ether in hexane) gave the substantially pure diol, which was distilled (bulb to bulb) or recrystallized as necessary.

Physical constants and selected nmr data for compounds prepared by these methods are summarized in Table II. Nmr signals not given in Table II were fully consistent with the assigned structures.

Hydride Reduction of α-Ketols. General Procedure.—Into a dry nitrogen-flushed test tube, containing a magnetic spin ball and fitted with a septum cap, was injected 1.5 mmol of hydride solution. After cooling to −78°, the ketol (0.5 mmol in 0.5 ml of toluene) was added slowly with stirring. After 4 hr, the cold bath was removed and stirring was continued at room temperature for 18 to 20 hr. The reaction was quenched by the cautious addition of 3 ml of water, sufficient 6 *N* HCl to dissolve the gelatinous precipitate was added, and the mixture was extracted three times with 15-ml portions of ether. The combined extracts were dried and the solvent was evaporated. The residue was heated briefly under vacuum to drive off any unreacted ketol; the product diol thus obtained was *ca.* 95% pure.

(22) M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, 315 (1949).

Registry No.—**1**, 37160-77-3; **2**, 6986-70-5; **3**, 7737-47-5; **4**, 3155-01-9; **5**, 37160-81-9; **6**, 6196-59-4; *erythro*-**7**, 37163-97-6; *threo*-**7**, 37163-98-7; *erythro*-**8**, 6702-10-9; *threo*-**8**, 6464-40-0; *erythro*-**9**, 23646-57-3; *threo*-**9**, 23646-58-4; *erythro*-**10**, 37164-02-6; *threo*-**10**, 37164-03-7; *erythro*-**11**, 37164-04-8; *threo*-**11**, 37164-05-9; *erythro*-**12**, 37164-06-0; *threo*-**12**, 37164-07-1; TIBA, 100-99-2; DIBAH, 1191-15-7; $LiAlH_4$, 16853-85-3; $LiAl(OMe)_3H$, 12076-93-6; REDAL, 21608-56-0; AlH_3, 7784-21-6; $LiAl(t\text{-}AuO)_3H$, 17476-04-9.

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Stereochemistry of the Diels–Alder Reaction. V. Fluorinated Trans-Olefinic Acids and Derivatives with Cyclopentadiene

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The Diels–Alder reactions of a series of fluorinated *trans*-crotonic acids, esters, amides, an acid chloride, and an aldehyde with cyclopentadiene at 25° are discussed. The endo–exo ratios were determined by gas chromatographic and/or infrared analyses. The fluoroalkyl groups in all cases dominated the stereochemical course of the reactions, and in one series of crotonic acids the endo–exo ratios correlated very well with the inductive effects (σ_I) of these groups.

Two of the previous papers[1,2] in this series dealt with the Diels–Alder reactions of *trans*-4,4,4-trifluorocrotonic acid with various dienes. A third paper[3] examined the stereochemistry of the reaction of cyclopentadiene with several other *trans*-β-perfluoroalkylcrotonic acids. Olefins with fluorines in varying numbers and positions have also been studied with cyclopentadiene, butadiene, and anthracene.[4,5] In this paper we describe the stereochemistry of the products from the reactions of cyclopentadiene with a series of *trans*-β-fluoroalkyl-α,β-unsaturated acids, amides, esters, etc.

A list of dienophiles that were prepared for this study is given in Table I. The acids were prepared *via* hydrolysis of the corresponding esters, which in turn were prepared by means of the Knoevenagel reaction as generally described in previous papers.[6] Only one ester, ethyl 4-fluorocrotonate (**3**), was prepared differently owing to the fact that 2-fluoroethanal is relatively inaccessible. Numerous attempts to fluorinate methyl and ethyl 4-bromocrotonate using sodium, potassium, lithium, and silver fluorides under various conditions afforded only 7.5% of **3** as the best yield.[7]

All the dienophiles were assigned the trans configuration mainly on the basis of infrared absorption at *ca.* 5.95 and 10.30 μ, which is diagnostic for a trans system.[8] Proton magnetic resonance spectra for these compounds were very complex due to ^1H–^{19}F coupling.

Diels–Alder Reactions.—The dienophiles listed in Table I were stirred for 16–18 hr with a slight excess of cyclopentadiene at 25° in a constant-temperature

* Requests for information and reprints should be sent to this author at The Children's Hospital Research Foundation, Elland Ave. and Bethesda, Cincinnati, Ohio 45229.

(1) E. T. McBee, C. G. Hsu, and C. W. Roberts, *J. Amer. Chem. Soc.*, **78**, 3389 (1956).

(2) E. T. McBee, C. W. Roberts, and C. G. Hsu, *ibid.*, **78**, 3393 (1956).

(3) H. P. Braendlin, A. Z. Zielinski, and E. T. McBee, *ibid.*, **84**, 2109 (1962).

(4) H. P. Braendlin, G. A. Grindahl, Y. S. Kim, and E. T. McBee, *ibid.*, **84**, 2112 (1962).

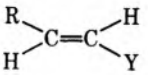
(5) E. T. McBee, C. G. Hsu, O. R. Pierce, and C. W. Roberts, *ibid.*, **77**, 915 (1955).

(6) (a) E. T. McBee, Y. S. Kim, and H. B. Braendlin, *ibid.*, **84**, 3154 (1962); (b) A. Z. Zielinski, E. T. McBee, and H. P. Braendlin, *Rocz. Chem.*, **37**, 905 (1963).

(7) (a) D. R. Bennett, K. S. Andersen, M. V. Anderson, Jr., D. N. Robertson, and M. B. Chenoweth, *J. Pharmacol. Exp. Ther.*, **122**, 489 (1958). (b) A 16% yield of ethyl 4-fluorocrotonate was obtained from 1-chloro-3-fluoropropan-2-ol by E. D. Bergmann, S. Cohen, and I. Shahak, *J. Chem. Soc.*, 3448 (1961). See also F. L. Pattison and B. C. Saunders, *J. Chem. Soc.*, 2745 (1949).

(8) (a) L. F. Hatch and S. S. Nesbitt, *J. Amer. Chem. Soc.*, **72**, 727 (1950); (b) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1956.

TABLE I
PREPARATION AND PROPERTIES OF DIENOPHILES



Compd	R	Y	Yield, %	Bp, °C (mm)[a]	n^{30}D or mp, °C	Ref
1	CH_3	CO_2H	*b*	81 (13)	71.4–71.7	*i*
2	CH_2F	CO_2H	7.5		88–90	*j*
3	CHF_2	CO_2H	36[c]	73–74 (3)	59–60.5	
4	CF_3	CO_2H	22[d]	68–69	55–56	*l*
5	C_2F_5	CO_2H	49[c]	73–76 (11)	43–44	*k*
6	*n*-C_3F_7	CO_2H	84[e]	83–85 (12)	46.5–48	*l*
7	CF_3	CO_2Et	25[d]	115	1.3597	*l*
8	C_2F_5	CO_2Et	44[c]	125	1.3480	*k*
9	*n*-C_3F_7	CO_2Et	54[c]	140–141	1.3442	*l*
10	*n*-C_7F_{15}	CO_2Et	39[c]	104 (20)	1.3369	*m*
11	*n*-C_3F_7	CO_2Me	46[c]	126–127	1.3386[f]	*n*
12	*n*-C_3H_7	COCl	68	107–108	1.3482	*o*
13	*n*-C_3F_7	CHO	60[g]	80–81	1.3324	
14	*n*-C_3F_7	$CONH_2$	88		95–96	
15	*n*-C_3F_7	$CONHCH_3$	40		42–43	*p*
16	*n*-C_3H_7	$CONHC_6H_5$	75		130.5–131.5	*l*
17	*n*-C_3F_7	CH_2OH	70[h]	80–81 (37)	1.3363	*q*

[a] At atmospheric pressure unless stated otherwise. [b] Can be purchased from a number of sources. [c] Overall yield from aldehyde (Knoevenagel reaction). [d] Yield from trifluoroacetic acid (ref *l*). [e] Yield from 9. [f] At 19°. [g] Yield from 17. [h] Yield from 4,4,5,5,-6,6,6-heptafluoro-2-iodo-2-hexen-1-ol. A mixture of cis and trans isomers was obtained. [i] W. M. Gearhart, "Kirk-Othmer Encyclopedia of Chemistry and Technology," 2nd ed, Vol. 6, 1965, p 464. [j] Reference 7. [k] Reference 6b. [l] E. T. McBee, O. R. Pierce, and D. D. Smith, *J. Amer. Chem. Soc.*, **76**, 3722 (1954). [m] E. T. McBee, C. W. Roberts, and C. Wilson, Jr., *ibid.*, **79**, 2323 (1957). [n] H. Albrecht and S. Smith, British Patent 904,263. [o] R. Filler, *J. Amer. Chem. Soc.*, **76**, 1376 (1954). [p] E. T. McBee, C. W. Roberts, and C. W. Wilson, Jr., *ibid.*, **81**, 1719 (1961). [q] J. D. Park, F. E. Rodgers, and J. R. Lacher, *J. Org. Chem.*, **26**, 2089 (1961).

bath.[9] The amides **14–16** reacted very slowly, but only the alcohol **17** failed to react at all. The yields and physical properties of the adducts are summarized in Table II.

Many methods exist for the determination of the configuration of a Diels–Alder adduct from cyclopentadiene and an unsaturated acid. The older techniques are based on the assumption that only the endo carboxyl group can interact with the double bond to form a lactone. These methods have the inherent drawback that they involve isolation procedures which can often lead to inaccurate product ratios. In addition, skeletal rearrangments are known, and certain exo acids have been observed to yield lactones.[10] Thus, while bromo- and iodolactonizations were used in this work to separate the endo from the exo adducts, gas–liquid chromatography (glpc) and infrared spectroscopy were used to determine the isomer ratios.[11] Since the methyl esters of **18**, **19**, and **20** were separable by glpc, the endo–exo ratios of the acids were determined from the glpc analyses of these esters. For the remaining adducts the general procedure followed was to first prepare authentic samples of endo and exo alcohols (**34–37**). This was accomplished through the lithium aluminum hydride reduction of the corresponding acids, which had been previously separated *via* iodolactonization. Glpc analyses demonstrated clearly that the endo acids quantitatively gave only endo alcohols, and likewise with the cis isomer. The compounds **21–30** were then reduced with lithium aluminum hydride, and the ratios of the resulting endo and exo alcohols were determined.

Since the amides **31–33** could not be reduced directly to the corresponding alcohols, quantitative infrared analysis was the only method used to determine the isomer ratios of these adducts. In the case of compound **23**, this analytical technique gave an endo–exo ratio of 3.6:1.0, which agreed well with the value of 3.76:1.00 obtained by glpc analysis.

Discussion

From the data given in Table II, it is readily apparent that fluorine substituents dominate the stereochemical course of the Diels–Alder reactions.[12a] For instance, the introduction of a single fluorine caused a complete reversal in the endo–exo ratio of **19** compared to that of **18**. Further insertion of fluorines caused additional changes in this ratio which correlate surprisingly well with the inductive effects (σ_I's of the R groups) of the substituents, as shown in Figure 1.[12b]

Many theories, hypotheses, and rationalizations have been proposed during the past 30 years to explain

(9) The effect of temperature on the ratio of stereoisomeric adducts can be fairly large.[10] In this study the reaction of cyclopentadiene with **9** at 25° gave a C_3F_7 endo–exo ratio of 5.06:1.00, whereas at 0° the ratio was 6.40:1.00.

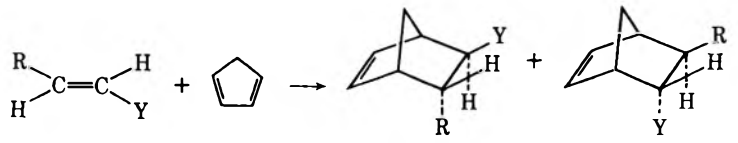
(10) (a) K. Adler, G. Stein, F. Buddenbrock, W. Eckardt, W. Frercks, and S. Schneider, *Justus Liebigs Ann. Chem.*, **514**, 1 (1934); (b) R. B. Woodward and H. J. Baer, *J. Amer. Chem. Soc.*, **70**, 1161 (1948); (c) S. Beckman, R. Schaber, and R. Bamberger, *Ber.*, **87**, 997 (1954); (d) C. D. Ver Nooy and C. S. Rondestvedt, Jr., *J. Amer. Chem. Soc.*, **77**, 3583 (1955); (e) J. A. Berson and A. Remanick, *ibid.*, **83**, 4947 (1961).

(11) Some of the values given in this paper differ from previously reported endo–exo ratios that were determined by bromolactonization and hydration.[3]

(12) (a) Chlorine and bromine substituents are apparently also very effective. Ethyl 4-chlorocrotonate and ethyl 4-bromocrotonate gave 78 and 73.5% endo (CH_2X) respectively when treated with cyclopentadiene; however, the conditions used were more drastic (170° for 7 hr). H. Christol, A. Donche, and F. Plénat, *Bull. Soc. Chem. Fr.*, 1315 (1966). (b) The Hammett σ_I values for CH_3 (−0.07), CH_2F (0.12), CHF_2 (0.29), and CF_3 (0.39) were taken from W. Sheppard, *Tetrahedron*, **27**, 945 (1971), and that of C_2F_5 (0.41) was obtained from W. Sheppard, *Trans. N. Y. Acad. Sci.*, **29**, 700 (1967). No value for the *n*-perfluoropropyl group is available.

Table II

Preparation and Properties of Diels–Alder Adducts



Compd[n]	R	Y	Yield, %	% endo R	endo R/exo R	Bp, °C (mm)	n_D or mp, °C
18	CH_3	CO_2H		37.4[a]	0.59	106–110 (3)	93–95[b]
19	CH_2F	CO_2H		63.0	1.70		Oil[c]
20	CHF_2	CO_2H	98.6	70.3	2.36	105–106 (1.5)	65–83[d]
21	CF_3	CO_2H	99	73.7	2.80	104–105 (2.5)	67–73[e]
22	C_2F_5	CO_2H	93	74.5	2.92	110–111 (1.8)	37–38[f]
23	n-C_3F_7	CO_2H	97	79.0	3.76	115–122 (2.5)[g]	54–71[h]
24	CF_3	CO_2Et	93	77.9	3.52	58–60 (1.3)	1.4250 (21)
25	C_2F_5	CO_2Et	96	81.7	4.46	78–79 (6.9)	1.4063 (20)
26	n-C_3F_7	CO_2Et	94	83.3	5.06	69–70 (2)	1.3960 (20)
27	n-C_7F_{15}	CO_2Et	88	84.3	5.37	85–87 (0.7)	1.3730 (20)
28	n-C_3F_7	CO_2Me	93	82.8	4.81	98–99 (21)	1.3950 (21)
29	n-C_3F_7	COCl	92	67.5	2.08	82–83 (11)	1.4087 (18)
30	n-C_3F_7	CHO	89	76.6	3.28	83–84 (19)	1.3963 (20)
31	n-C_3F_7	$CONH_2$	40.5[i]	>95	>19		104–107
32	n-C_3F_7	$CONHCH_3$	61[i]	>95	>19		82–83
33	n-C_3F_7	$CONHC_6H_5$	82.5[i,j]	>95	>19		94–98
34	n-C_3F_7	CH_2OH				104–108 (19)[k]	1.4043 (21)[k]
35	CF_3	CH_2OH					1.4402 (17.5)
36	C_2F_5	CH_2OH					1.4201 (17.5)[l]
37	n-C_7F_{15}	CH_2OH					34–49[m]

[a] Lit. 38.6%; ref 17b. [b] Lit. mp 95°: G. Komppa and S. Beckmann, *Justus Liebigs Ann. Chem.*, **523**, 68 (1936). [c] Benzylthiouronium salt, mp 144–145°. [d] **20n** (endo), mp 97–99°. [e] **21n**, mp 93.5–94° (ref 1); **21x** (exo), mp 118.5–119.5°. [f] **22n**, mp 53–54°. [g] Reference 3. [h] **23n**, mp 77–78°; **23x**, mp 82–83°. [i] Per cent conversion. [j] Reaction time was 70 hr. [k] Lit. bp 118° (21 nm), $n^{20}D$ 1.4030: ref 4. [l] α-Naphthylurethane derivative mp 106–108°. [m] Isomers were separated by preparative glpc on a 20% Carbowax 20 M column; **37n**, mp 58–60°; **37x**, mp 40.5–42°. [n] Satisfactory analytical data were reported for all new compounds listed in the table.

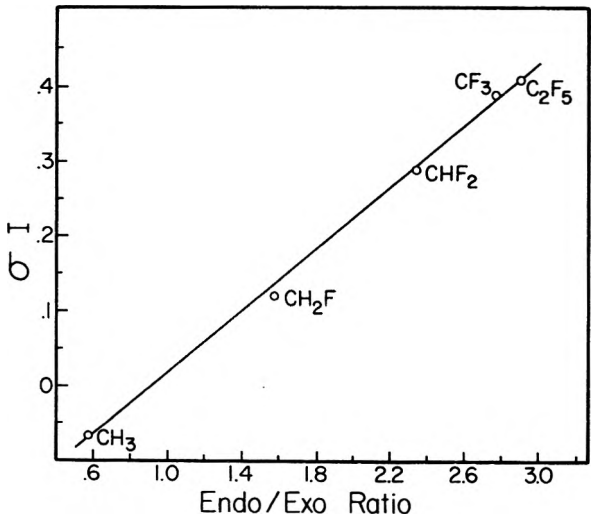


Figure 1.—Plot of the endo/exo ratios of compounds **18–22** *vs.* the Hammett σ_I values of the R groups.

the preference for endo addition.[13,14] We will simply explain the stereochemical results given in Table II as due to secondary attractive forces between nonbonding centers, and suggest that these forces, and consequently the endo-directive ability of small alkyl groups, parallel the electron inductive effects of these groups.[15] Lack of sufficient σ values prevented any attempt to similarly correlate quantitatively the esters **24–27**, but the same trend is also apparent in this series. This latter series also demonstrates the relatively small role which steric hindrance apparently plays in determining the endo–exo ratio. The per cent *endo*-C_7F_{15} (**27**) was determined to be only slightly larger than that found for the C_3F_7 group (**26**), but then the inductive effects of these two groups are probably only slightly different also. Steric requirements, on the other hand, continually increase in going down the series, but there seems to be little evidence here that these demands are forcing the larger perfluoroalkyl groups into the less hindered exo position.

No simple correlation could be obtained between the endo–exo ratios of compounds **23**, **26**, and **28–30** and the σ_I's and σ_R's of the various carboxyl functions. The endo-directive abilities parallel the electronegativity of these substituents, namely COCl > CHO = CO_2H > CO_2R > $CONR_2$. This same order has been reported for para-substituted *trans*-cinnamic acids, esters, etc.[16] The CH_2OH group would probably fit at the end of this list, but **17** does not react with the

(13) (a) K. Alder, W. Günyl, and K. Wolff, *Ber.*, **93**, 809 (1960); (b) Y. Kobuke, T. Fueno, and J. Furukawa, *J. Amer. Chem. Soc.*, **92**, 6548 (1970).

(14) K. N. Houk, *Tetrahedron Lett.*, 2621 (1970), and references cited therein.

(15) A multiple linear regression analysis using both σ_I and σ_R values was also run on compounds **18–22**. [See M. Charton, *J. Org. Chem.*, **31**, 3745 (1966)]. A correlation coefficient of 0.9994 was obtained with the values of α = 1.423, β = 6.210, and h = 1.625, but the very small σ_R values for these substituents make such a correlation almost meaningless. A correlation coefficient of 0.9964 was obtained with the σ_I values alone.

(16) C. S. Rondestvedt, Jr., and C. D. Ver Nooy, *J. Amer. Chem. Soc.*, **77**, 4878 (1955).

electron-rich cyclopentadiene under the same conditions used for the other dienophiles.

Experimental Section

Ethyl 4-Fluorocrotonate. A.—Ethyl 4-bromocrotonate (9.7 g, 0.05 mol) was treated under nitrogen with freshly prepared silver monofluoride (12.8 g, 0.1 mol) in 50 ml of ether and refluxed for 8 hr. Distillation gave 0.46 g (7%) of ethyl 4-fluorocrotonate, bp 53–56° (15 mm). Glpc indicated that this material was about 85% pure.

B.—When the same reaction was carried out with THF as the solvent, the yield was 5%.

C.—The ester was also added slowly to an equal amount of powdered silver monofluoride cooled in a water bath. When the vigorous reaction subsided another portion of AgF was added. The reaction mixture was poured into a slurry of NaF in pentane. Distillation gave a 7.5% yield of ethyl 4-fluorocrotonate which was *ca.* 90% pure.

D.—Potassium fluoride in ethylene glycol gave trace amounts of product. Sodium fluoride in THF and in acetone did not react. Solvents such as *N*-methylpyrrolidinone caused decomposition of the esters.

***trans*-4-Fluorocrotonic Acid (2).**—Ethyl-4-fluorocrotonate (2.3 g, 7 mmol) was saponified by adding 10 ml of 20% NaOH dropwise and heating at 70°. After 1 hr the solution was homogeneous and after acidification and extraction with ether an oil was isolated. Sublimation (60°, 1 mm) gave 1.37 g (75%) of **2**, mp 88–90°.

Anal. Calcd for $C_4H_5FO_2$: C, 46.15; H, 4.84. Found: C, 46.52; H, 4.82.

3-Hydroxy-4,4-difluorobutyric Acid (Knoevenagel Procedure).—Difluoroacetaldehyde (13.0 g, 0.16 mol) was distilled into a 100-ml flask with 17.7 g (0.17 mol) of malonic acid, 40 ml of pyridine, and 0.3 ml of piperidine. After the carbon dioxide evolution ceased, the solvent was stripped off. Distillation of the residue afforded 15.5 g (69%) of 3-hydroxy-4,4-difluorobutyric acid, bp 93–96° (12 mm). The distillate turned to a glass on standing.

Ethyl 3-Hydroxy-4,4-difluorobutanoate (Reformatsky Procedure).—Difluoroacetaldehyde (22 g, 0.275 mol) and ethyl bromoacetate (47.0 g, 0.28 mol) were placed in a dropping funnel. Approximately one-half of this solution was added to 18 g (0.28 g-atom) of zinc dust in freshly distilled benzene. The mixture was refluxed until reaction began (a light green color appeared). The remainder of the solution was then added slowly, and enough heat was supplied to maintain reflux for an additional 1 hr. Distillation afforded 19.8 g (48%) of ethyl 3-hydroxy-4,4-difluorobutanoate, bp 95–97° (35 mm), $n^{20}D$ 1.4016.

Anal. Calcd for $C_6H_{10}F_2O_3$: C, 42.63; H, 6.56; F, 22.48. Found: C, 43.10; H, 6.18; F, 22.95.

Ethyl *trans*-4,4-Difluorocrotonate.—Ethyl 3-hydroxy-4,4-difluorobutanoate (17 g, 0.1 mol) was poured over excess P_2O_5 and heated for 1 hr at 60°. After distillation 12 g (80%) of ethyl *trans*-4,4-difluorocrotonate was collected, bp 65° (35 mm), $n^{20}D$ 1.3945.

Anal. Calcd for $C_6H_8F_2O_2$: C, 48.01; H, 5.47; F, 25.17. Found: C, 48.14; H, 5.50; F, 25.18.

***trans*-4,4-Difluorocrotonic Acid (3).**—Ethyl 4,4-difluorocrotonate (7.5 g, 0.05 mol) and 20 ml of 10% sodium hydroxide were stirred and heated until a homogeneous solution was obtained. After the usual work-up 5.0 g (82%) of **3** was obtained, bp 73–74° (3 mm), mp 59–60.5°. The ir spectrum showed absorption at 10.25 μ characteristic of a trans olefin. In addition **3** was converted with diazomethane to the methyl ester and glpc showed at most only a trace of the cis isomer.

***trans*-4,4,5,5,6,6,6-Heptafluoro-2-hexenal (13).**—To 90 g (1 mol) of "active" manganese dioxide in 300 ml of pentane was added in one portion 9.00 g (39.8 mmol) of **17**. After stirring for 4 hr the reaction mixture was filtered, and the filtrate was fractionally distilled. Thus, 5.34 g (60%) of **13** was obtained: uv max (hexane) 213 mμ (log ϵ 3.35); nmr ($CDCl_3$) δ 6.63 (complex multiplet, 2) and 9.62 (complex multiplet, 1).

Anal. Calcd for $C_6H_3F_7O$: C, 32.16; H, 1.35. Found: C, 32.12; H, 1.35.

***trans*-4,4,5,5,6,6,6-Heptafluoro-2-hexenamide (14).**—To 11 ml of ice-cold concentrated ammonium hydroxide was slowly added 5.3 g (20.5 mmol) of **12**. The white precipitate was filtered, washed, and recrystallized from hexane–chloroform (4:1). Isolated in this manner was 4.32 g (88%) of **14**, uv max (EtOH) 209 mμ (log ϵ 3.53), 229 (3.43).

Anal. Calcd for $C_6H_4F_7NO$: C, 30.14; H, 1.69; F, 55.62; N, 5.86. Found: C, 30.17; H, 1.70; F, 55.25; N, 5.91.

General Procedure for the Preparation and Isolation of the Diels–Alder Adducts.—A slight molar excess of freshly distilled cyclopentadiene was added over a period of 5–10 min to the various dienophiles. The reaction was then stirred for 15–18 hr at 25°. Distillation *in vacuo* yielded the pure adducts except with the amide adducts where column chromatography was used.

Lithium Aluminum Hydride Reduction of the Diels–Alder Adducts. General Procedure.—To 3.2–9.3 mmol of the Diels–Alder adduct in 40 ml of absolute ether was added over a 30-min period under nitrogen a slurry of $LiAlH_4$ (3.4–9.5 mmol) in 30 ml of ether. The reaction was kept at 0° during the addition and for 30 min thereafter. The mixture was then gently refluxed for 2–3 hr, after which 95% ethanol was slowly added to decompose the excess $LiAlH_4$. The reaction mixture was then poured onto a slurry of concentrated H_2SO_4 (10 ml) and 200 g of crushed ice. The organic layer was separated, filtered, and dried and the ether was evaporated. The yield of the bicyclic alcohol was determined either by actual isolation or by the use of *N*-undecane as an internal standard and comparison of glpc peak heights with mixtures of known compositions. The endo–exo isomer ratios were determined by direct comparison of the relative peak areas with a K & E compensating planimeter, and reproducibility was found to be ±2%.

Analysis of Amide Adducts. General Procedure.—The uv extinction coefficients of a series of standard solutions of the amide dienophiles were found to obey Beer's law in the range 10^{-5}–10^{-4} *M*. Consequently, quantitiative uv analysis was used to determine the amount of unreacted dienophile in the crude Diels–Alder adducts of the amides.

The exo–endo-isomer distributions were determined by quantitative ir analysis. Pure exo amides were easily prepared from the exo acid **23n**. An endo-rich sample was obtained from **29** enabling artificial mixtures to be prepared.

Iodolactonization of 3-Heptafluoropropylbicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (23).—A sample of **23** (18.38 g, 0.060 mol) was dissolved in 60 ml of CH_3OH and almost neutralized with 6 *N* NaOH. The solution was then treated with 100 ml of 5% $NaHCO_3$ and the volume was adjusted to 520 ml with water. After treatment with 40 ml of iodine stock solution,[18d] the mixture was allowed to stand for 2 hr at 0° and then it was extracted with two 75-ml portions of ether. The combined ether fractions were washed successively with 1% sodium thiosulfate and water. After evaporation of the ether, the residue was dried over $CaSO_4$ *in vacuo* to give 4.70 g of crude iodolactone. This material was chromatographed (alumina, benzene) and recrystallized from hexane, mp 46–48°.

Anal. Calcd for $C_{11}H_8F_7IO_2$: C, 30.58; H, 1.87; F, 30.78; I, 29.37. Found: C, 30.60; H, 2.03; F, 31.00; I, 29.40.

Isolation of 3-*endo*-Heptafluoropropylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic Acid (23n).—The aqueous fraction from the above iodolactonization was treated with 1% sodium thiosulfate and dilute HCl, respectively. Crude **23n** precipitated and was filtered *in vacuo* from the ice-cold solution. Recrystallization from hexane at Dry Ice temperature gave 10.6 g (57%) of **23n**: mp 77–78°; ir (Nujol) 3.42 (s), 5.81 (s), 6.84 (s), 7.24 (m), 7.38 (m), 7.50 (m), 7.71 (m), 7.84 (m), 7.95 (m), 8.09 (s), 8.20 (s), 8.37 (m), 8.48 (s), 8.90 (m), 8.96 (m), 9.17 (m), 10.76 (m), 13.51 (m), 13.74 (s), 14.58 μ (m).

3-*exo*-Heptafluoropropylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic Acid (23x).—To 1.20 g (2.77 mmol) of the iodolactone prepared above was added 1.00 g (0.0155 g-atom) of powdered zinc in 10 ml of glacial acetic acid. The mixture was stirred for 69 hr at 23° and then filtered. Dilute sodium hydroxide was added and the mixture was ether extracted. The ether yielded 0.06 g of unreacted iodolactone. When the aqueous layer was acidified with 6 *N* HCl, **23x** precipitated. Sublimation at 50° (0.5 mm) gave 0.61 g (75%) of **23x**, mp 77–83°. After two recrystallizations from hexane the melting point was 82–83°; mixture melting point with **23n** (25%) was 52–73°; ir (Nujol) 3.40–3.50 (s), 5.84 (s), 7.03 (m), 7.30 (m), 7.45 (s), 7.53 (s), 7.78 (s), 7.89 (s), 8.04–8.65 (vs), 8.89 (s), 9.00 (s), 9.10 (s), 10.10 (m), 10.27 (m), 10.84 (m), 10.96 (m), 11.59 (m), 13.75 (s), 14.10 (s), 14.61 (s).

Registry No.—2, 37759-72-1; 3, 37759-73-2; 4, 406-94-0; 5, 37759-75-4; 6, 37759-76-5; 7, 25597-16-4; 8, 37759-78-7; 9, 37759-79-8; 10, 37759-80-1; 11, 37759-81-2; 12, 37759-82-3; 13, 37759-83-4; 17, 37759-84-5; 15, 37759-85-6; 16, 37759-86-7; *cis*-17, 37759-87-8; *trans*-17, 37759-88-9; *endo*-19 benzylthiouronium, 37746-47-7; *exo*-19 benzylthiouronium, 37746-48-8; *endo*-20, 37746-49-9; *exo*-20, 37705-54-7; *endo*-21, 37746-50-2; *exo*-21, 37746-51-3; *endo*-22, 37746-52-4; *exo*-22, 37746-53-5; *endo*-23, 37746-54-6; *exo*-23, 37746-55-7; *endo*-24, 37746-56-8; *exo*-24, 37746-57-9; *endo*-25, 37746-58-0; *exo*-25, 37746-59-1; *endo*-26, 37746-60-4; *exo*-26, 37746-61-5; *endo*-27, 37705-55-8; *exo*-27, 37705-56-9; *endo*-28, 37746-62-6; *exo*-28, 37746-63-7; *endo*-29, 37746-64-8; *exo*-29, 37746-65-9; *endo*-30, 37746-66-0; *exo*-30, 37746-67-1; *endo*-31, 37746-68-2; *exo*-31, 37746-69-3; *endo*-32, 37746-70-6; *exo*-32, 37746-71-7; *endo*-33, 37746-72-8; *exo*-33, 37746-73-9; *endo*-35, 37746-74-0; *exo*-35, 37746-75-1; *endo*-36 α-naphthylurethane, 37705-57-0; *exo*-36 α-naphthylurethane, 37746-76-2; *endo*-37, 37705-58-1; *exo*-37, 37705-59-2; cyclopentadiene, 542-92-7; ethyl 4-fluorocrotonate, 37746-77-3; ethyl 4-bromocrotonate, 37746-78-4; 3-hydroxy-4,4-difluorobutyric acid, 37746-79-5; difluoroacetaldehyde, 430-69-3; ethyl 3-hydroxy-4,4-difluorobutanoate, 37746-81-9; ethyl *trans*-4,4-difluorocrotonate, 37746-82-0.

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Stereochemistry of Asymmetric Silicon. XXII. Preparation and Properties of Optically Active Perfluorophenyl Compounds[1,2]

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The synthesis and resolution of two new optically active organosilicon systems has been achieved. These are α-naphthylperfluorophenylmethylsilanes, α-NpPh$_F$MeSi*X, and phenylmethylpentafluorophenylsilanes, PhMePh$_F$Si*X. Synthesis and resolution of these compounds is of special significance for organosilicon stereochemistry and reaction mechanisms because of the highly electron-withdrawing polar effect of the pentafluorophenyl group. The available data relating to the magnitude of the electron-withdrawing effect of the C_6F_5 group indicate that it approximates Br.

Since the electronegativity of the pentafluorophenyl group is approximately equal to that of Br[3] and is much greater than that of other "nonreactive" substituents previously bonded to asymmetric silicon,[4-7] it was of considerable interest to undertake the preparation and study of optically active compounds containing this group, in order to determine whether its presence would change the stereochemical course of substitution reactions at asymmetric silicon. The synthetic methods for preparation of C_6F_5MgBr[8,9] and C_6F_5Li[10,11] have been well established, and the coupling of either of these organometallic reagents with the appropriate chlorosilane has been shown to yield compounds containing the pentafluorophenyl group bonded to silicon.[12] The synthesis and properties of optically active perfluorophenylsilicon compounds is discussed in the next section.

(1) For the preceding paper in this series, see L. H. Sommer, K. T. Rosborough, and J. McLick, *J. Amer. Chem. Soc.*, **94**, 4217 (1972).

(2) We thank National Science Foundation for vital support of this work.

(3) See M. C. Hays, *J. Inorg. Nucl. Chem.*, **26**, 2306 (1964); J. Dalton, I. Paul, and F. G. A. Stone, *J. Chem. Soc. A*, 1212 (1968); R. R. Schrieke and B. O. West, *Aust. J. Chem.*, **22**, 49 (1969).

(4) L. H. Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill, New York, N. Y., 1965.

(5) L. H. Sommer, C. L. Frye, G. A. Parker, and K. W. Michael, *J. Amer. Chem. Soc.*, **86**, 3271 (1964).

(6) L. H. Sommer, K. W. Michael, and W. D. Korte, *ibid.*, **89**, 868 (1967).

(7) L. H. Sommer and K. T. Rosborough, *ibid.*, **91**, 7067 (1969).

(8) W. J. Plummer and L. A. Wall, *J. Res. Nat. Bur. Std.*, **63A**, 167 (1959).

(9) E. Nield, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 166 (1959).

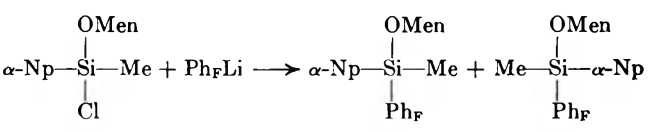
(10) R. J. Harper, Jr., E. J. Soloski, and C. Tamborski, *J. Org. Chem.*, **29**, 2385 (1964).

(11) P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 3227 (1962).

(12) For a recent paper containing pertinent earlier references, see A. J. Oliver and W. A. G. Grahm, *J. Organometal. Chem.*, **19**, 17 (1969).

Optically Active Perfluorophenylsilicon Compounds.—Two new monofunctional triorganosilicon systems incorporating the pentafluorophenyl group have been prepared by two methods and these are discussed below.

Reaction of α-naphthylmagnesium bromide with methyltrimethoxysilane gave a 68% yield of α-naphthylmethyldimethoxysilane, α-NpMeSi(OMe)$_2$, bp 118–119° (1.0 mm). Lithium aluminum hydride reduction of α-NpMeSi(OMe)$_2$ in refluxing ether gave an 88% yield of α-naphthylmethylsilane, α-NpMeSiH$_2$, bp 77–79° (0.35 mm). This substance was treated with chlorine in CCl_4 to give predominantly α-naphthylmethylchlorosilane, α-NpMeSiHCl. It is interesting that the electron-withdrawing effect of chlorine in α-NpMeClSiH is sufficient to prevent the substitution of chlorine for the remaining hydrogen atom. Without purification, α-NpMeSiHCl was then mixed with (−)-menthol in pentane to give a 78% yield of α-naphthylmethyl-(−)-menthoxysilane, bp 118° (0.13 mm). α-NpMeSi(H)-(−)-OMen was then treated with chlorine to give α-naphthylmethyl-(−)-menthoxychlorosilane. Without purification, α-NpMeClSi-(−)-OMen was



treated with a previously prepared solution of pentafluorophenyllithium at −78° in ether (or tetrahydrofuran) to give a 69% yield of the desired diastereomeric mixture of (±)-α-naphthylmethylpentafluorophenyl-(−)-menthoxysilane, bp 160–164° (0.1 mm).

When this very viscous oil was dissolved in hexane and chilled at −5°, a white, crystalline material, identified as (+)-α-NpPh$_F$MeSi-(−)-OMen (the higher melting diastereomer), was deposited on the sides of the flask, mp 93–95°, $[\alpha]_D$ −11° (*c* 1.6, pentane). If one assumes that the two diastereomers were formed in equal amounts, only 30–40% of the above diastereomer can be cleanly separated from the diastereomeric mixture. After removal of the above crystalline diastereomer and some hexane from the flask, further crystallization from the chilled hexane solution usually results in a mixture of diastereomers. Because crystals of the higher melting diastereomer are distinctly harder and different in appearance than the lower melting diastereomer, they can be physically separated and recrystallized. By such a process, (−)-α-NpPh$_F$-MeSi-(−)-OMen (the lower melting diastereomer) was purified, mp 80–81°, $[\alpha]_D$ −75° (*c* 2.0, pentane). With a great deal of patience, substantial quantities of both diastereomers can be isolated and recrystallized in this fashion.

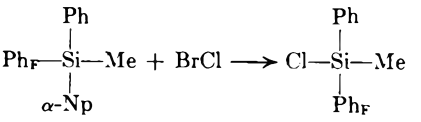
Recently it was shown that (−)-α-NpPhMeSi-(−)-OMen can be reduced with diisobutylalane in good yields in hexane and ether, at room temperature, in 2 and 14 hr, respectively.[13] Similarly, reduction of (+)-α-NpPh$_F$MeSi-(−)-OMen with diisobutylalane in hexane at 46° for 19 hr gave (+)-α-naphthylpentafluorophenylmethylsilane, (+)-α-NpPh$_F$MeSi*H, in 88% yield, mp 73.5–74°, $[\alpha]_D$ +40° (*c* 0.88, pentane).

It is probable that the enantiomers of α-NpPh$_F$-MeSi*H form a racemic mixture (not a racemic compound), since the melting point of racemic α-NpPh$_F$-MeSi*H (mp 54–55°) is raised by the addition of either enantiomer, and since both enantiomers of α-NpPh$_F$-MeSi*H of low optical purity can be recrystallized up to high optical purity. The enantiomers of α-NpPh-MeSi*H behave similarly.

We turn now to the synthesis and resolution of phenylmethylpentafluorophenylsilane, PhMePh$_F$Si*H. A previously prepared solution of pentafluorophenyllithium in ether was mixed with α-NpPhMeSi*Cl, $[\alpha]_D$ −6.3°, to give (after fractional distillation) a 74% yield of extremely viscous α-naphthylphenylmethylpentafluorophenylsilane, bp 175–178° (0.15 mm), $[\alpha]_D$ +8.2° (*c* 1.6, pentane).

The cleavage of the naphthyl group from α-NpPh-MeSi*Ph$_F$ proved to be the most difficult part of the synthesis of PhMePh$_F$Si*H, and was the prime factor in preventing more extensive stereochemical studies on this system. Although bromine in benzene has been successfully used in the cleavage of the naphthyl group from α-NpPhMeSi*-neo-C_5H_{11} and α-NpPhMeSi*Et,[6] no optically active PhMePh$_F$Si*H (after reduction of the halosilane formed) could be obtained by this procedure. Cleavage attempts with Br_2 in carbon tetrachloride and chloroform, and BrCl in benzene and carbon tetrachloride at room temperature and at 0°, give, after reduction, some optically active PhMePh$_F$Si*H, but the yields were disappointingly low (20–30%).

Cleavage of the naphthyl group *was accomplished* by the formation of a BrCl–chloroform solution at −78°, followed by addition of α-NpPhMeSiPh$_F$. A vigorous, exothermic reaction indicated that cleavage occurring. However, the presence of Br_2 in equilibrium with the reagent BrCl possibly results in some formation of bromosilane.



The halosilane was not isolated but was promptly reduced with $LiAlH_4$ at room temperature.

Purification of the silane gave a 53% yield of phenylmethylpentafluorophenylsilane, (+)-PhMePh$_F$Si*H, $[\alpha]_D$ + 3.2 (*c* 5.31, pentane), bp 75–79° (0.3 mm). PhMePh$_F$Si*H can be obtained with a specific rotation as high as +4.3° at the sacrifice of reasonable yields.

Experimental Section

α-Naphthylmethyldimethoxysilane.—A Grignard reagent was prepared from 3.3 mol of α-bromonaphthalene and 4.5 g-atoms of magnesium chips in a solvent mixture containing ether (300 ml), tetrahydrofuran (100 ml), and benzene (200 ml).

The Grignard reagent was then added to 3 mol of methyltrimethoxysilane (supplied by Dow Corning Corp.) which was dissolved in ether (250 ml) and tetrahydrofuran (250 ml). Stirring overnight at room temperature was followed by extraction of the organic layer with pentane (3 l.), filtration to remove suspended salts, and subsequent removal of solvents. Distillation gave 461 g (68% yield) of α-naphthylmethyldimethoxysilane, bp 118–119° (1.0 mm).

Anal. Calcd for $SiC_{13}H_{16}O_2$: C, 67.20; H, 6.94. Found: C, 67.45; H, 6.80.

The infrared spectrum has all the characteristic absorbances of the CH_3OSi, α-$C_{10}H_7Si$, and CH_3Si moieties.

α-Naphthylmethylsilane.—To a solution of lithium aluminum hydride (2.2 mol) and ether (500 ml) was added α-naphthylmethyldimethoxysilane (2 mol) in an ether solvent (500 ml). Refluxing for 20 hr was followed by treatment with concentrated hydrochloric acid and pentane at 0°, washing with water, drying the organic phase (sodium sulfate), and subsequent removal of the solvent. Distillation gave 303 g (88% yield) of α-naphthylmethylsilane, bp 77–79° (0.35 mm).

Anal. Calcd for $SiC_{11}H_{12}$: C, 76.68; H, 7.02. Found: C, 76.38; H, 6.92.

The infrared spectrum provided positive proof of structure, since it showed absorption bands characteristic of the α-NpMeSi- group as well as the strong band at 2130 cm^{-1} characteristic of the Si–H stretch.

α-Naphthylmethyl-(−)-menthoxysilane.—A solution of carbon tetrachloride (600 ml) and 1.76 mol of α-naphthylmethylsilane maintained at 0° was treated with chlorine gas until the solution was distinctly yellow. Nitrogen was then used to purge the reaction mixture of excess hydrogen chloride and chlorine gas until the solution became colorless. Removal of the solvent under reduced pressure yielded α-naphthylmethylchlorosilane. The chlorosilane is characterized by its infrared spectrum, exhibiting all the characteristics of the α-NpMe(H)Si- group and in addition containing an absorbance at 505 cm^{-1} (s) characteristic of Cl–Si. Without further purification, a solution of 1.7 mol of α-naphthylmethylchlorosilane and pentane (700 ml) was added to a filter flask fitted with an addition funnel and gas inlet tube. A solution of pentane (500 ml) and 1.9 mol of (−)-menthol was then slowly added to the stirred chlorosilane–pentane solution while a continuous stream of nitrogen was bubbled through the reaction mixture to remove the hydrogen chloride which had formed. After the addition, the reaction mixture was warmed to room temperature, stirred for 0.5 hr with continuous nitrogen purging, concentrated, and distilled to give 432 g (78% yield) of α-naphthylmethyl-(−)-menthoxysilane, bp 118° (0.13 mm).

Anal. Calcd for $SiC_{21}H_{30}O$: C, 77.24; H, 9.26. Found: C, 77.36; H, 9.37.

The infrared spectrum is consistent with the presence of the α-NpMe(H)Si- group, and in addition contains the following absorption bands attributed to the $C_{10}H_{19}OSi$ moiety: 2930 (s), 2870 (s), 1460 (m), 1370 (m), 1180 (w), 1085 (s), 1070 (s), 1055 (s), 1000 (m), 930 (m), 855 cm^{-1} (m).[4]

(13) Unpublished results of L. H. Sommer and J. McLick.

Preparation of Diastereomeric α-Naphthylmethylpentafluorophenyl-(−)-menthoxysilane.—A solution of carbon tetrachloride (400 ml) and 0.46 mol of α-naphthylmethyl-(−)-menthoxysilane was treated with chlorine gas by the same procedure used to chlorinate α-naphthylmethylsilane. Disappearance of the strong infrared absorbance at 2120 cm^{-1} (SiH) and appearance of the peak at 505 cm^{-1} verified formation of α-naphthylmethyl-(−)-menthoxychlorosilane.

Pentafluorophenyllithium (0.5 mol in tetrahydroduran) was then prepared by the procedure of Harper, Soloski, and Tamborski. While the pentafluorophenyllithium solution was maintained at −75°, a solution of α-naphthylmethyl-(−)-menthoxychlorosilane (0.45 mol) and tetrahydrofuran (200 ml) was added over a 1-hr period and then warmed to room temperature over a 16-hr period.

The majority of the solvent was then removed under reduced pressure and the reaction mixture was treated with concentrated hydrochloric acid and pentane at 0°, washed with water, dried (sodium sulfate), and concentrated. Distillation of the diastereomeric mixture gave 90 g (39% yield) of an extremely viscous, clear pale yellow fraction, bp 155–160° (0.1 mm), and 70 g (30% yield) of a second fraction, bp 160–164° (0.1 mm), which was clear and colorless.

The infrared spectrum of each fraction is the same and contains the absorption bands attributed to the α-naphthylmethyl-(−)-menthoxysilyl group, and in addition contains the following bands attributed to the C_6F_5Si moiety: 1645 (s), 1520 (s), 1470 (vs), 1380 (s), 1292 (s), 1140 (w), 1098 (s), 1030 (m), 977 cm^{-1} (s).

Crystallization of (+)-α-Naphthylmethylpentafluorophenyl-(−)-menthoxysilane, the Higher Melting Diastereomer.—Separation of the mixed diastereomers was achieved with fractions 1 and 2 described in the distillation above. For simplification, however, the separation procedure will be described only for fraction 2. The clear, colorless, viscous liquid of fraction 2 was diluted to approximately twice its volume with purified *n*-hexane, and chilled in a cold room (−5°). After 24 hr, 14.5 g (mp 88–90°) of a hard, flat, rectangular crystalline material was obtained from the flask. Recrystallization of this material at at −5° to a constant melting point, in twice its volume of pentane, gave 9.8 g of (+)-α-naphthylmethylpentafluorophenyl-(−)-menthoxysilane, mp 93–95°, $[\alpha]_D$ −11° (*c* 1.6, pentane).

Anal. Calcd for $SiC_{27}H_{29}F_5O$: C, 65.83; H, 5.93. Found: C, 65.82; H, 5.98.

Crystallization of (−)-α-Naphthylmethylpentafluorophenyl-(−)-menthoxysilane, the Lower Melting Diastereomer.—The volume of fraction 2, now enriched in the (−)-α-naphthylmethylpentafluorophenyl-(−)-menthoxysilane (*vide supra*), was reduced in volume by 30 ml of the steam bath and again placed in the cold room (−5°). After several days, 11 g (mp 65–85°) of white solid was removed from the flask. After it was dried under reduced pressure, close examination of the solid revealed two different crystalline layers. The upper layer, deposited in the flask, consisted of soft, small, needlelike crystals, which were very dissimilar to the crystals previously isolated. The lower layer (permeated in spots by the layer above) was hard and resembled (+)-α-naphthylmethylpentafluorophenyl-(−)-menthoxysilane. With a spatula, the soft crystals were scraped from the hard crystals, giving 5.4 g (mp 71–75°) and leaving 5.6 g (mp 91–93°) of the hard crystalline diastereomer. Subsequent recrystallization of the soft, lower-melting diastereomer at 4°, in twice its volume of hexane, gave 1 g of the needle crystals of (−)-α-naphthylmethylpentafluorophenyl-(−)-menthoxysilane (mp 80–81°), $[\alpha]_D$ −75° (*c* 2.0, pentane).

Anal. Calcd for $SiC_{27}H_{29}F_5O$: C, 65.83; H, 5.93. Found: C, 65.70; H, 6.01.

The subsequent crystallization from the flask containing the remaining 46 g of mixed diastereomer gave 14 g of a soft, white, flocculent solid, which was literally poured onto a large filter paper fitted over a watch glass, and air dried (mp 71–74°). Several recrystallizations with at least 80% loss of solid diastereomer to the various mother liquors gave crystalline (−)-α-naphthylpentafluorophenyl-(−)-menthoxysilane (mp 80–81°).

Diisobutylalane Reduction of the Diastereomeric (+)-α-Naphthylmethylpentafluorophenyl-(−)-menthoxysilane.—A solution of purified hexane (180 ml) and 29 g (59 mmol) of (+)-α-naphthylmethylpentafluorophenyl-(−)-menthoxysilane, $[\alpha]_D$ −11° (*c* 2.3, pentane), was placed in a 500-ml, three-necked flask equipped with a dropping funnel and condenser. Diisobutylalane, 33.3 ml (180 mmol), was syringed into 80 ml of purified hexane and then poured into the addition funnel. The diisobutylalane–hexane solution was added slowly over a 15-min period, under an inert atmosphere, to the stirred (+)-α-naphthylmethylpentafluorophenyl-(−)-menthoxysilane. During the addition, the flask temperature increased from 28 to 32°. After the addition was completed, the flask was heated to 47° and maintained at that temperature for 19 hr. When the reaction mixture had cooled down, it was cautiously added to a 2-l. separatory funnel and washed in ice water, concentrated hydrochloric acid (30 ml), and pentane (500 ml). After the aqueous layer was discarded, a second washing with concentrated hydrochloric acid was necessary to remove the remaining suspended aluminum salts from the organic layer. Following the second washing with acid, the organic phase was washed four times with distilled water, dried over sodium sulfate, and partially concentrated on the steam bath. The remaining organic layer was transferred to a sublimator, where heating for 5 hr at 80° (0.3 mm) removed the remaining volatile solvent by distillation and 7.4 g (80%) of the (−)-menthol by sublimation.

After cooling to room temperature the remaining solid (+)-α-naphthylmethylpentafluorophenylsilane–menthol mix was removed from the sublimator, dissolved in pentane (60 ml), and poured onto a wet (pentane) 1.8 × 46 cm column of silica gel. Elution with 650 ml of 30% benzene (by volume) in pentane gave 17.6 g (88%) of (+)-α-naphthylmethylpentafluorophenylsilane (mp 54–64°). Repeated crystallizations to a constant melting point gave 13.2 g of α-naphthylmethylpentafluorophenylsilane (mp 73.5–74°), $[\alpha]_D$ +40° (*c* 0.88, pentane).

Anal. Calcd for $SiC_{17}H_{11}F_5$: C, 60.34; H, 3.28. Found: C, 60.04; H, 3.49.

The infrared spectrum contains the absorbance bands attributed to α-$C_{10}H_7Si$, C_6F_5Si, and CH_3Si, and in addition contains a band at 2190 cm^{-1} attributed to the Si–H moiety.

Preparation of α-Naphthylphenylmethylpentafluorophenylsilane.—A solution of ether (100 ml) and 0.2 mol of α-NpPhMeSi*Cl, $[\alpha]_D$ −6.3° (*c* 4.5, pentane),[4] was added to a chilled (−78°) solution of pentafluorophenyllithium (0.2 mol in ether) over a 2-hr period. While being continuously stirred, the reaction mixture was allowed to warm to room temperature overnight, and was then treated with concentrated hydrochloric acid and pentane at 0°, washed with water, dried (sodium sulfate), and concentrated. Distillation gave 50 g (74% yield) of an extremely viscous, colorless liquid, characterized as (+)-α-naphthylphenylmethylpentafluorophenylsilane (α-NpPhMeSi*-Ph_F), bp 175–178° (0.15 mm), $[\alpha]_D$ +8.2° (*c* 1.6, pentane).

The infrared spectrum is completely consistent with the structural assignment.

Preparation of Phenylmethylpentafluorophenylsilane.—A solution of 0.075 mol of (+)-α-NpPhMeSi*Ph_F, $[\alpha]_D$ +8.2° (*c* 1.40, pentane), and chloroform (25 ml) was added rapidly to a solution of chloroform (15 ml) and 0.08 mol of BrCl (prepared from 0.04 mol of Br_2 and 0.04 mol of Cl_2) maintained at −60°. The immediate ensuing exothermic reaction caused the reaction mixture to warm up to room temperature. The mixture was stirred for 30 min and then syringed from the reaction flask into a flask containing ether (150 ml) and lithium aluminum hydride (0.600 equiv) chilled to 0°.

Stirring the hydride solution at room temperature for 15 min, was followed by treatment with aqueous 10% HCl and pentane at 0°, washing with water, drying (sodium sulfate), and subsequent removal of the solvents. Distillation gave 11.4 g (53% yield) of (+)-phenylmethylpentafluorophenylsilane (PhMe-Ph_FSi*H), bp 75–79° (0.3 mm), $[\alpha]_D$ +3.2° (*c* 5.31, pentane). (A specific rotation of 4.3° for PhMePh_FSi*H was obtained by a procedure which gave significantly lower yields.)

Anal. Calcd for $SiC_{13}H_9F_5$: C, 54.16; H, 3.15. Found: C, 54.02; H, 3.31.

The infrared spectrum is completely consistent with the above structure and contains ir maxima (C_6H_5Si) at 1430, 1120, 700 cm^{-1}; CH_3Si at 1265 cm^{-1}; C_6F_5Si, same as for α-NpMePh_FSi-(−)-OMen; SiH at 2180 cm^{-1}.

Registry No.—α-Naphthylmethyldimethoxysilane, 37787-14-7; α-bromonaphthalene, 90-11-9; methyltrimethoxysilane, 1185-55-3; α-naphthylmethylsilane, 37787-15-8; α-naphthylmethylchlorosilane, 17998-65-1; (−)-menthol, 2216-51-5; α-naphthylmethyl-(−)-menthoxysilane, 37787-17-0; α-naphthylmethylpentafluorophenyl-(−)-menthoxysilane, 37787-18-1; pentafluoro-

phenyllithium, 1076-44-4; α-naphthylmethyl-(−)-menthoxychlorosilane, 37787-19-2; (+)-α-naphthylmethylpentafluorophenyl-(−)-menthoxysilane, 37787-20-5; (−)-α-naphthylmethylpentafluorophenyl-(−)-menthoxysilane, 37787-21-6; (+)-α-naphthylmethylpentafluorophenylsilane, 36411-23-1; (+)-α-naphthylphenylmethylpentafluorophenylsilane, 37781-10-5; (+)-phenylmethylpentafluorophenylsilane, 36358-49-3.

Photochemistry of 2-Acetylbenzonorbornenes

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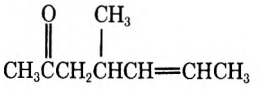
The synthesis and photochemistry of *exo*- and *endo*-2-acetylbenzonorbornenes (**8** and **9**) is described. The exo isomer yields benzonorbornene upon irradiation at 310 nm, conditions under which the endo isomer is inert.

The presence of proximate n electrons is known to significantly modify the reactivity of photoexcited carbonyl groups. Examples include reactions of amino ketones,[1,2] alkoxy ketones,[3] and thiaketones.[4] In one of these studies,[2] the magnitude of the effect was shown to be a function of the distance between the interacting centers.

Similarly, the presence of π electrons can modify the excited-state behavior of ketones. Thus, neither ketone **4** or **5** undergoes appreciable type II photo-



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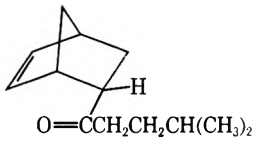

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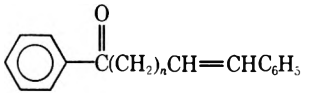
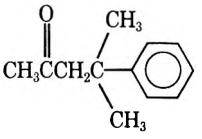
elimination.[4,5] Rapid exciplex formation between the carbonyl singlet state and the double bond has been postulated to rationalize the diminished reactivities. In a related study, Cowan and Baum[6] have shown that intramolecular energy transfer was the principal mode of deactivation of the carbonyl triplets in systems **6a–c**.



6a, $n = 2$
b, $n = 3$
c, $n = 4$

Lastly, several groups[7,8] have recently reported on the diminished reactivity of certain α- and β-phenyl ketones toward photoreduction and/or type II eliminations. Thus, ketone **7** undergoes photoelimination with unusually low efficiency, $\Phi = 0.02$.[8]



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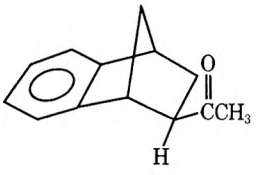
The foregoing results may be summarized with the statement that the presence of electrons in n or π orbitals significantly shortens the excited state lifetimes of nearby carbonyl groups. Although varied mechanisms may prevail, a common feature would appear to require significant overlap of the orbitals on the two interacting groups. In view of the fact that this orientational factor has not been tested, we wished to investigate the behavior of rigid analogs of **7** in which the relative positions of the two functions were more restricted. To this end, we synthesized *exo*- and *endo*-2-acetylbenzonorbornenes (**8** and **9**, respectively), and initiated photochemical studies which were designed to evaluate their relative excited state lifetimes.



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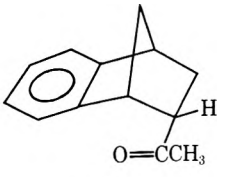

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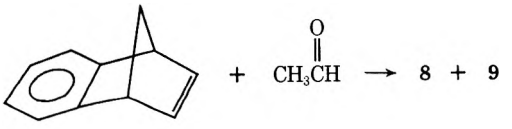
Syntheses.—A mixture of **8** and **9** was produced by the addition of acetaldehyde to benzonorbornadiene (**10**) as catalyzed by azobisisobutyronitrile.[9] By



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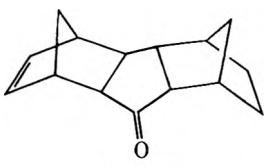
analogy with norbornene,[9] it was assumed that the major product (*ca.* 90%) was the exo isomer and this supposition was supported by spectral evidence presented below. For example, the chemical shifts of the methyl protons in the two isomers were found in the expected relative positions (δ 2.15 and 1.87 for **8** and **9**, respectively) if it is assumed that the

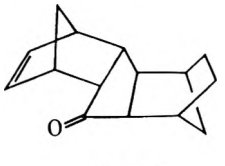
(1) A. Padwa, W. Eisenhardt, R. Gruber, and D. Pashayan, *J. Amer. Chem. Soc.*, **93**, 6998 (1971).
(2) P. J. Wagner and T. Jellinek, *ibid.*, **93**, 7328 (1971).
(3) F. D. Lewis and N. J. Turro, *ibid.*, **92**, 311 (1970).
(4) A. Padwa and A. Battisti, *ibid.*, **94**, 521 (1972).
(5) S. R. Kurowski and H. Morrison, *ibid.*, **94**, 507 (1972); R. R. Sauers, A. D. Rousseau, and B. Byrne, Abstracts, XXIIIrd IUPAC Meeting, Boston, Mass., July 1971, p 96.
(6) D. O. Cowan and A. A. Baum, *J. Amer. Chem. Soc.*, **93**, 1153 (1971); see also P. A. Leermakers, J.-P. Montillier, and D. R. Rauh, *Mol. Photochem.*, **1**, 57 (1969).
(7) P. J. Wagner and P. A. Kelso, *Tetrahedron Lett.*, 4151 (1969); R. A. Caldwell and P. M. Fink, *ibid.*, 2987 (1969).
(8) D. G. Whitten and W. E. Punch, *Mol. Photochem.*, **2**, 77 (1970); P. J. Wagner, P. A. Kelso, A. E. Kemppainen, A. Haug, and D. R. Graber, *ibid.*, **2**, 81 (1970); F. R. Stermitz, D. E. Nicodem, V. P. Muralidharan, and C. M. O'Donnell, *ibid.*, **2**, 87 (1970).
(9) H. Stockmann, *J. Org. Chem.*, **29**, 245 (1964).

methyl group of **9** resides at least part of the time in the shielding cone of the phenyl ring.[10]

The finding that the compound assigned the exo structure showed an enhanced ultraviolet absorption for the n,π^* transition (ϵ_{293}^{max} 77) relative to the endo system (ϵ_{293}^{max} 28) may be taken as further proof of the stereochemistry of **8** and **9**. As a literature analogy, the following example is illustrative.[11]



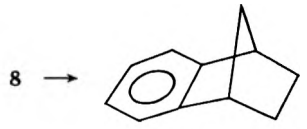
ε_{307}^{max} 79



ε_{303}^{max} 27.5

Results and Discussion

Irradiation of the exo isomer **8** in benzene with Pyrex-filtered light ($\lambda > 290$ nm) or in cyclohexane with short-wavelength light (254 nm) produced one major volatile product and several very minor ones. The major product was isolated by preparative gas chromatography and shown by spectral comparisons to be benzonorbornene (**11**). Quantum yields were



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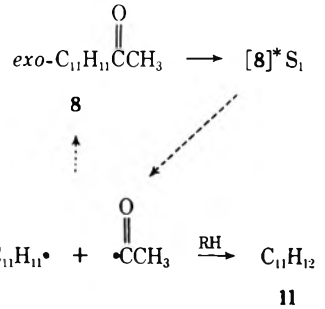
determined in degassed benzene at 313 nm: Φ_{11} = 0.015, Φ_{-K} = 0.018. Similar irradiations of **9** for extended periods yielded no significant amounts of volatile products and led to a very slow loss of starting material. Intersystem crossing yields[12] for **8** and **9** were 0.83 and 0.20, respectively.

Quenching studies were carried out using *cis*-cyclooctene[13] (0.1 *M*) and either 0.1 *M* or 0.01 *M* ketone. In both cases, the rate of production of **11** from **8** decreased by *ca.* 43%. We interpret these results to mean that most of the reaction proceeds *via* triplet states.[14] The following scheme is proposed to rationalize our results.



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The low quantum yield for the formation of **11** and the near equivalency of the efficiency of formation of **11** *vs.* the loss of **8** requires an efficient deactivation step. The most likely possibility is recombination of the radical pair.[15] The nature of the hydrogen donor (RH) in this reaction is unknown. It seems unlikely that the solvents or impurities in them play this role, since few by-products, *e.g.*, bicyclohexyl, could be found in the cyclohexane photolyses. One intriguing possibility is that the radical pair disproportionates to give **11** and ketene. The latter would have been too volatile to detect by our analytical procedures. Although this mode of disproportionation is not normally observed in type I cleavage products,[16] it may be that the normal reaction is inhibited as a consequence of the unusually high degree of strain associated with norbornene double bond formation.[17]

In contrast to the behavior of **8**, the endo ketone **9** proved to be quite stable toward irradiation at 310 nm. This observation and the lower intersystem crossing yield obtained for **9** are indications that the carbonyl triplet state is less efficiently formed and/or has a shorter lifetime than that in **8**. We cannot say whether or not the exo system itself behaves entirely normally, but there was no obvious manifestation of any behavior which could be related to the anomalous absorption of **8**, with the possible exception of the somewhat high intersystem crossing yield compared to **7** (0.15).

In any event, we wish to emphasize that the *differences* in behavior between **8** and **9** clearly require an explanation which takes into account their relative geometries. Thus, the anomalous absorption of **8** is associated with the exo configuration,[11] while the diminished reactivity of **9** is associated with the endo structure. We assume that direct interaction of the n orbital of oxygen with the π system is a requisite feature of whatever mechanism is responsible for the rapid deactivation of the excited carbonyl groups of these[8] β-phenyl ketones.

Experimental Section

Nuclear magnetic resonance (nmr) data was obtained from a Varian Model T-60 spectrometer in carbon tetrachloride solution using tetramethylsilane as an internal standard. Infrared (ir) spectra were determined on thin films using a Perkin-Elmer Model 137 spectrometer. Ultraviolet (uv) spectra was recorded on a Cary 14 spectrometer. Gas chromatograms (gc) were obtained on either a Varian Aerograph Model A-90-P or a Barber-Colman Model 5000 chromatograph. The following three columns were used: A, 15% FFAP (5 ft × 0.25 in.); B, 20% FFAP (8 ft × 0.25 in.); C, 15% β,β'-oxydipropionitrile (20 ft × 0.25 in.). Chromosorb G was the solid phase in all cases.

Benzene was purified by washing with portions of sulfuric acid until no coloration developed. The benzene was then washed with water, 10% sodium carbonate solution, and water. After drying over anhydrous calcium chloride the benzene was distilled and stored over calcium chloride.

(10) A similar, but smaller, difference has been found for the analogous protons in the 5-norbornenyl methyl ketones: $\delta_{CH_3}^{exo}$ 2.12; $\delta_{CH_3}^{endo}$ 2.00. See Y. Kobuke, T. Fueno, and J. Furukawa, *J. Amer. Chem. Soc.*, **92**, 6548 (1970), for other examples.

(11) R. C. Cookson, J. Henstock, and J. Hudec, *ibid.*, **88**, 1059 (1966); 5-norbornenyl methyl ketones also show this trend.

(12) A. A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965).

(13) It has been shown that acetone triplets react with *cis*-cyclooctene with a rate constant of $1.3 \times 10^8\ M^{-1}\ sec^{-1}$; see K. Shima, Y. Sakai, and H. Sakuri, *Bull. Chem. Soc. Jap.*, **44**, 215 (1971).

(14) This analysis is based on the assumption of a normal rate of intersystem crossing, *ca.* $2–5 \times 10^8\ sec^{-1}$, and similar rates of reaction of singlets and triplets with the olefin.[13] For references see N. J. Turro and P. A. Wriede, *J. Amer. Chem. Soc.*, **92**, 320 (1970).

(15) For a recent demonstration of this process in aliphatic systems, see J. A. Den Hollander, R. Kaptein, and P. A. T. M. Brand, *Chem. Phys. Lett.*, **10**, 430 (1971).

(16) For recent references see ref 15 and N. C. Yang and E. D. Feit, *J. Amer. Chem. Soc.*, **90**, 504 (1968); M. Tomkiewicz, A. Groen, and M. Cocivera, *Chem. Phys. Lett.*, **10**, 39 (1971).

(17) R. D. Miller and V. Y. Abraitys, *J. Amer. Chem. Soc.*, **94**, 663 (1972). It is significant that we could not detect any buildup of **10** during the photolysis. This finding rules out formation–destruction of **10** as an explanation for its absence.

Benzonorbornadiene (10) was prepared by the method of Wittig and Knauss.[18]

exo,endo-**2-Acetylbenzonorbornene (8, 9).**—A mixture of 3.0 g (0.021 mol) of benzonorbornadiene, 6.0 g (0.136 mol) of freshly distilled acetaldehyde, and 150 mg (0.0011 mol) of azobisisobutyronitrile was heated at 80° in a pressure tube for 43 hr. The resulting mixture was distilled at 96–98° (0.6 mm) to yield 1.51 g (39%) of a mixture of **8** and **9**. Gc analysis (A, 200°) revealed two components in a 10:1 ratio. The separate isomers were collected by preparative gc (B, 200°).

The structure assigned to the major component was that of *exo*-2-acetylbenzonorbornene (**8**): nmr δ 7.02 (m, 4 H), 3.42 (m, 2 H), 2.15 (s, CH_3), 1.82 (m, 5 H); ir 5.84 (C=O) and 13.36 μ (*o*-ArH); uv max (cyclohexane) 293 nm (ϵ 77), 272 (1104), 266 (1037), and 259 (684); mass spectrum (70 eV) molecular ion at *m/e* 186.

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 84.05; H, 7.88.

The structure assigned to the minor component was that of *endo*-2-acetylbenzonorbornene (**9**): nmr δ 7.03 (m, 4 H), 3.58 (m, 1 H), 3.32 (m, 1 H), 3.07 (m, 1 H), 1.87 (s, CH_3), 1.82 (m, 4 H); ir 5.84 (C=O) and 13.27 μ (*o*-ArH); uv max (cyclohexane) 293 nm (ϵ 28), 272 (958), 264 (844), 258 (538); mass spectrum molecular ion at *m/e* 186.

Anal. Found: C, 84.25; H, 7.50.

Photolysis Apparatus.—Preparative-scale irradiations were carried out in a Rayonet photoreactor[19] using either the 3000-Å or the 2537-Å sources. From the literature supplied by the manufacturer it may be calculated that, of the irradiation emitted between 2537 and 3129 Å, *ca.* 72% appears between 2537 and 2652 Å and 28% appears between 2804 and 3129 Å. Quantum yields were determined on an optical bench using an Osram 200W super-pressure mercury arc and a 5-cm quartz cell containing 0.00139 *M* aqueous potassium chromate solution buffered with 1% potassium carbonate. This filter solution used in conjunction with 13 × 100 mm Pyrex test tubes served to isolate the 310-nm line.

Irradiations of 8. A.—A benzene solution of **8** (0.181 g in 10 ml) was flushed with nitrogen and irradiated for 19 hr with the 3000-Å source. Preparative gc (B, 217°) yielded 0.119 g of recovered starting material whose ir spectrum was unchanged. Also isolated was 5.3 mg of benzonorbornene (**11**), which was identified by its ir spectrum by direct comparison.[20]

B.—In a second experiment, 0.0984 g of **8** in 5 ml of cyclohexane was purged with nitrogen and irradiated in a quartz nmr tube with the 2537-Å source. The reaction was monitored periodically by gc (A, 200°). A gradual accumulation of **11** and two other very minor photoproducts with similar retention times was observed. Since the gc conditions used were capable of effecting separation of **11** and **10**, it can also be noted that essentially no **10** was formed at any time. In addition, no bicyclohexyl could be detected. Although small amounts of **9** did appear, it was not established that its formation was the direct result of the irradiation as opposed to a chemically catalyzed route.

C.—The quantum yield for the formation of **11** was determined by use of octadecane (0.0053 *M*) as an internal standard. A benzene solution of **8** (0.101 *M*) and the standard in duplicate 13 × 100 mm Pyrex test tubes was degassed by four freeze–thaw cycles and sealed under vacuum (*ca.* 5×10^{-4} Torr). The light intensity was monitored by benzophenone-sensitized isomerization of *cis*-piperylene.[21] The quantum yield for appearance of **11** was 0.018 after 180 min of irradiation and 0.015 after 335 min. The quantum yield of disappearance of **8** was 0.018 after 335 min, at which time 5% of the starting material had disappeared.

D.—The following cyclohexane solutions were prepared and irradiated at 2537 Å in standard 10-mm quartz cells by means of a rotating cell holder which was suspended in the Rayonet reactor: A, 0.10 *M* **8**, 0.043 *M* octadecane; B, 0.010 *M* **8**, 0.0043 *M* octadecane; C, 0.10 *M* **8**, 0.10 *M* *cis*-cyclooctene, 0.016 *M* octadecane; D, 0.010 *M* **8**, 0.016 *M* octadecane, and 0.10 *M* *cis*-cyclooctene. Solutions A and B were irradiated together for 200 min. Solutions C and D were subsequently irradiated for 210 min. After irradiation, the solutions were analyzed by gc (A, 180°) with the following results expressed in terms of molarity of **11**: A, 0.0047; B, 0.0030; C, 0.0027; D, 0.0017.

Irradiation of 9. A.—A solution of **9** (0.0768 *M*) in benzene was degassed and irradiated as in C above. After 210 min the concentration of **9** was measured against octadecane (0.0405 *M*) and found to be 0.0798 ± 0.004 *M*. Essentially no **11** was detected.

B.—The same solution was irradiated for 67 hr at 3000 Å in the Rayonet reactor with similar results. Likewise, irradiation of this solution with the 2537-Å source produced no significant changes.

Intersystem Crossing Yields.—A benzene solution of **9** was prepared which contained 0.5 *M* freshly distilled *cis*-piperylene and 0.0898 *M* ketone. After 60-min irradiation on the optical bench the per cent conversion to *trans*-piperylene was 8.7 from which ϕ_T was calculated to be 0.83.

Similarly, a solution of **8** (0.0885 *M*) was irradiated for 305 min with a 10.6% conversion to *trans*-piperylene. The calculated ϕ_T was 0.20.

Registry No.—**8**, 23537-82-8; **9**, 37614-83-8; **10**, 236-73-7; acetaldehyde, 75-07-0.

Acknowledgments.—We wish to acknowledge the financial support of the National Science Foundation (GP 26371) and the NDEA Title IV Fellowship Program.

(18) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 895 (1958).

(19) Available from the Southern New England Ultraviolet Co., Middletown, Conn.

(20) The authentic sample was prepared by catalytic reduction of benzonorbornadiene; see P. Bruck, *Tetrahedron Lett.*, **No. 10**, 449 (1962).

(21) A. A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965).

Reductive Cleavage of Polycyclic Oxetanes

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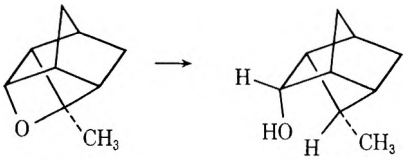
The action of hydrogen and catalysts, lithium–ethylenediamine, lithium–ammonia, and alane on several polycyclic oxetanes is reported. In general, ring cleavages were effected which produced several novel alcohols.

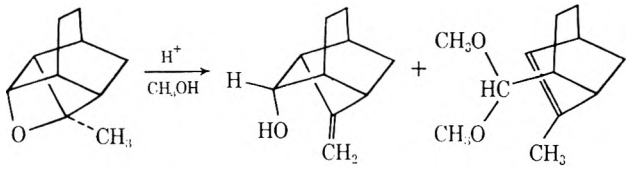
In previous publications[1] we have emphasized the synthetic utility of polycyclic oxetanes.[2] For example, oxetane **1** can be cleaved by lithium aluminum hydride in refluxing *N*-ethylmorpholine to form alcohol **2**.



1 **2**

This mode of cleavage was unexpected,[3] since it has the characteristics of an electrophilic rather than a nucleophilic ring opening. Significantly, certain oxiranes undergo cationic-type rearrangements on treatment with lithium aluminum hydride.[4]

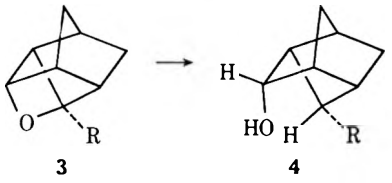
By contrast, acid-catalyzed ring openings may result in two-bond cleavages, as shown by the example below.[1b] In fact, many of these oxetanes are so sensitive to acid that they cannot be readily handled as such; in these cases they may be routinely converted to unsaturated dinitrophenylhydrazones on treatment with acidic 2,4-dinitrophenylhydrazine.[1b,c]



In this report we wish to detail and expand our results on the synthesis and cleavage reactions of polycyclic oxetanes. In particular, the cleavage of oxetanes with hydrogen and metal catalysts, lithium–amine combinations, and alane are discussed.

Results and Discussion

Catalytic Hydrogenolyses.—Aromatic oxetanes which contain the Ar–CO linkage may be smoothly hydrogenolyzed with hydrogen and Raney nickel[1b] but not with palladium on charcoal. It is believed that the cleavages proceed with retention of configuration on the basis of chemical-shift data and by analogy with similar cleavages.[5] Thus, oxetanes **3a** and **3b** are converted to tricyclic alcohols **4a** and **4b** on treatment with hydrogen and nickel. The stereochemical assignments are based on the chemical shifts of the benzylic and naphthylic protons (δ 4.12 and 4.75 ppm, respectively). The deshielding[6] of these protons is attributed to steric interactions with syn hydroxyl groups, a well-documented effect.[7]

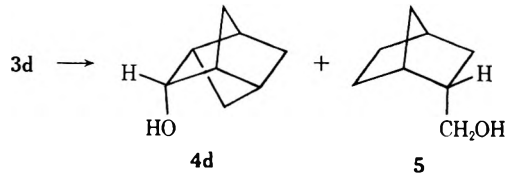


3 **4**

a, R = C_6H_5
b, R = α-$C_{10}H_7$
c, R = $C_6H_5CH_2$
d, R = H

The most interesting result in this series of experiments was observed on reduction of the benzyl oxetane **3c**. In view of the examples provided by Bonner[8] it was anticipated that hydrogenolysis would be accompanied by debenzylation. In fact, only hydrogenolysis was observed: **3c** → **4c**. Relief of ring strain provides added driving force for the hydrogenolysis pathway, but the presence of the aromatic ring was shown to be necessary since the methyl analog **1** proved to be stable to the same reaction conditions.

Lithium–Amine Reductions.—Reduction of an oxetane with a metal–amine combination had been reported only once previously.[9] This procedure appeared promising as a general method for reductive cleavage of oxetanes under relatively mild conditions. The first case studied was the symmetrical system **3d**. On treatment with lithium in ethylenediamine (EDA)[10] the oxetane was reduced to a mixture of two alcohols in the ratio 25:75. The major product was identified as tricyclo[3.3.0.$0^{3,7}$]octan-2-ol (**4d**). The minor prod-



4d **5**

(1) (a) R. R. Sauers, W. Schinski, and M. M. Mason, *Tetrahedron Lett.*, 79 (1969); (b) R. R. Sauers and J. A. Whittle, *J. Org. Chem.*, **34**, 3579 (1969); (c) R. R. Sauers and K. W. Kelly, *ibid.*, **35**, 498 (1970); (d) R. R. Sauers, K. W. Kelly, and B. R. Sickles, *ibid.*, **37**, 537 (1972).

(2) S. Searles, Jr., in "Heterocyclic Compounds with Three- and Four-membered Rings," Part II, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, Chapter IX.

(3) S. Searles, E. F. Lutz, and M. Tamres, *J. Amer. Chem. Soc.*, **82**, 2932 (1960); C. Schaal and J. Seyden-Penne, *C. R. Acad. Sci., Ser. C*, **266**, 217 (1968).

(4) P. D. Bartlett and W. P. Giddings, *J. Amer. Chem. Soc.*, **82**, 1240 (1960); J. P. Monthéard and Y. Chrétien-Bessière, *Bull. Soc. Chim. Fr.*, 336 (1968); H. Kwart and T. Takeshita, *J. Org. Chem.*, **28**, 670 (1963).

(5) For an example which involves a tetrahydrofuran, see S. Mitsui, Y. Senda, and K. Konno, *Chem. Ind. (London)*, 1354 (1963); for an example which involves an oxirane, see S. Mitsui and Y. Nagahisa, *ibid.*, 1975 (1965).

(6) The analogous protons in phenylcycloalkanes are found at δ 3.4–2.7; *cf.* A. M. Khan, F. J. McQuillin, and I. Jardine, *J. Chem. Soc. C*, 136 (1967).

(7) S. Winstein, P. Carter, F. A. R. Anet, and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **87**, 5247 (1965).

(8) W. A. Bonner, *ibid.*, **82**, 1382 (1960); nearly equivalent amounts of cleavage to toluene and ethylbenzene were observed on hydrogenolysis of β-phenylethanol.

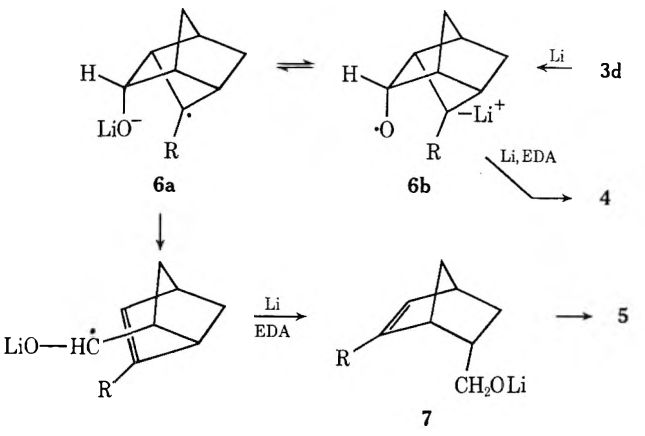
(9) A. S. Hallsworth and H. B. Henbest, *J. Chem. Soc.*, 3571 (1960).

(10) This procedure was patterned after that used for epoxide reductions: H. C. Brown, S. Ikegami, and J. H. Kawakami, *J. Org. Chem.*, **35**, 3243 (1970).

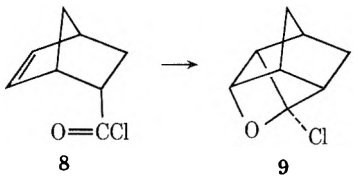
uct proved to be *endo*-2-norbornylmethanol (**5**) by direct comparison of infrared and nuclear magnetic resonance data.

A reasonable, if incomplete, mechanistic picture of the course of these reactions is presented in Scheme I. The exact timing of the electron and proton transfers cannot be specified, but it seems likely that the unsaturated carbinol salt **7** (R = H) is an intermediate. Krapcho and Nadel[11] had shown that norbornene can be reduced by lithium in amines, an important analogy in this context.

SCHEME I



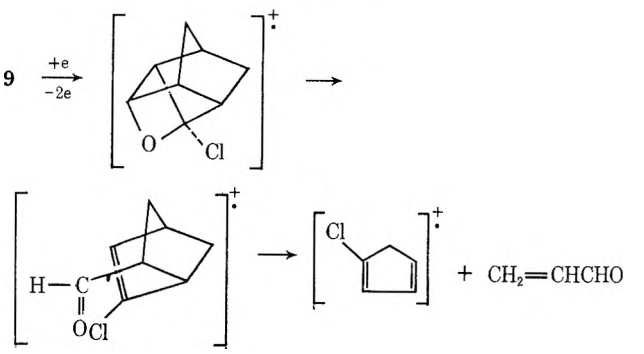
These results proved useful in providing chemical evidence for the structure of the photocyclization product of acid chloride **8**.[12] The photoproduct proved to be an isomer of **8** as shown by elemental analyses and mass spectral data. Interestingly, no significant peak could be detected in the molecular ion region, but a prominent pair of peaks in the ratio of *ca.* 3:1 did appear at *m/e* 100 and 102, respectively. We interpret this data in terms of structure **9** for the photoproduct in view of the fact that the methyloxetane (**1**) likewise undergoes cleavage of acrolein in the mass spectrometer. These cleavages seem best rationalized in terms of initial ring openings followed by reverse Diels–Alder reactions (Scheme II).



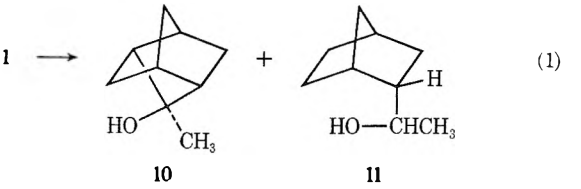
Although oxetane **9** was inert toward ethanolic silver nitrate solution, it was smoothly reduced by lithium in EDA to an identical mixture of **4d** and **5** as was obtained from **3d**. In all likelihood, **9** was initially reduced to **3d**, and thence to **4d** and **5**.

A mixture of five products was obtained on extension of the lithium–EDA reduction to the methyl-

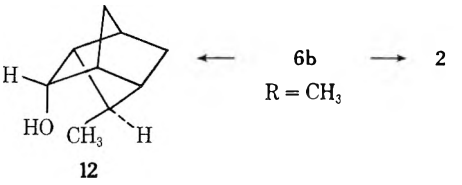
SCHEME II



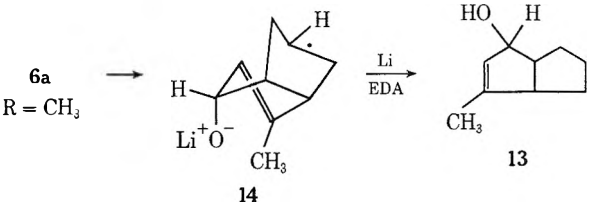
oxetane **1**. Three of the products were identified by spectral comparisons and are shown in eq 1. The



other two products were identified tentatively and were assigned structures **12** and **13**. Compound **12**



is a reasonable product to be expected from protonation of **6b** (R = CH_3). Product **13** is best explained *via* cleavage of **6a** (R = CH_3) to form radical **14**,



which is further reduced. This mode of cleavage has precedent in the behavior of the unsubstituted radical.[1c]

Under milder reaction conditions (lithium in liquid ammonia) unreacted oxetane **1** was recovered along with compound **2** (81%) and smaller amounts of **10** and **12**. On the other hand, the phenyloxetane **3a** was reduced completely and gave mainly alcohol **4a** under these conditions.

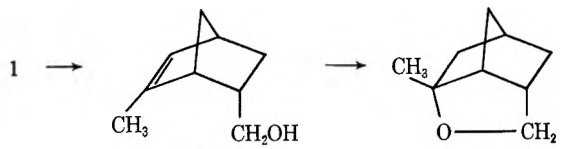
The usefulness of these reductions is restricted by the lack of high selectivity in the direction of cleavage of unsymmetrical oxetanes.[9] A similar lack of selectivity was observed in reductions of epoxides by amine–lithium systems,[10] and the direction of cleavage is apparently a function of structure of the oxide and of the rates of electron transfer.

Alane Reduction.—In an effort to circumvent the vigorous conditions required (*vide supra*) for lithium hydride reductions of these polycyclic oxetanes, the

(11) A. P. Krapcho and M. E. Nadel, *J. Amer. Chem. Soc.*, **86**, 1096 (1964).

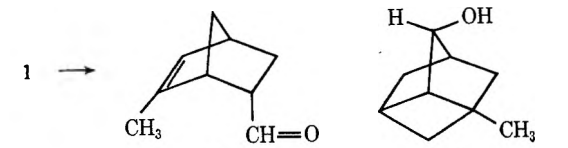
(12) This case represents the first example of an intramolecular photocyclization of an acid chloride. For intermolecular examples, see D. R. Arnold, *Advan. Photochem.*, **6**, 301 (1968).

use of alane was investigated.[13] Oxetane **1** was cleanly reduced under mild conditions (refluxing ether) with the formation of an 80:20 mixture of products. The major product was assigned structure **15**, since the nmr spectrum indicated a primary alcohol, one olefinic proton, and a methyl bonded to a double bond. This material rapidly and spontaneously cyclized on standing and the new material is believed to be the ether **16**.[14]



15 **16**

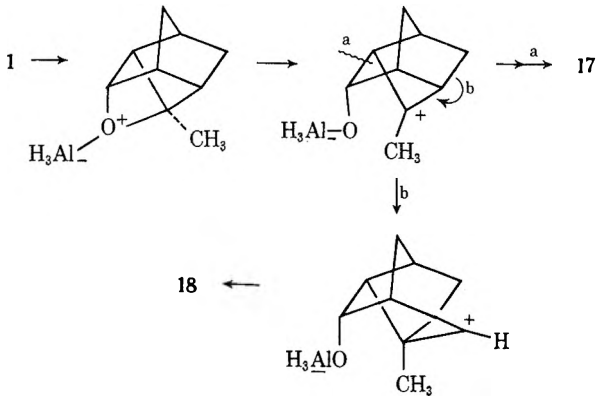
Presumably, the oxetane rearranges first to aldehyde **17**, which ultimately undergoes reduction to the carbinol. The minor product was a tricyclic secondary alcohol, and the methyl resonance was unsplit in the nmr spectrum. Although several possibilities exist, the most likely structure for this product is **18**. Thus,



17 **18**

the reduction proceeds *via* initial complexation followed by rearrangements, as shown in Scheme III.

SCHEME III



The aldehyde **17** is formed as a complex and most likely undergoes reduction directly. The tricyclic alcohol could arise by path b, a sequence which has precedent in the behavior of the deoxy derivative.[1d]

Summary and Conclusions.—Several new reactions of polycyclic oxetanes have been reported, including catalytic hydrogenolysis, metal amine reductions, and reduction with alane. In general, these reactions represent useful synthetic transformations and further extend the usefulness of oxetanes as synthetic intermediates.

(13) (a) P. T. Lansbury, D. J. Scharf, and V. A. Pattison, *J. Org. Chem.*, **32**, 1748 (1967); (b) E. L. Eliel, L. A. Pilato, and V. G. Badding, *J. Amer. Chem. Soc.*, **84**, 2377 (1962).

(14) The corresponding demethyl analog undergoes a similar cyclization in the presence of acid; see H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 227 (1959).

Experimental Section

Nuclear magnetic resonance (nmr) data was obtained from a Varian Model T-60 spectrometer in carbon tetrachloride solutions using tetramethylsilane as an internal standard. Infrared spectra (ir) were determined on a Perkin-Elmer Model 137 spectrometer. Gas chromatograms (gc) were obtained on a Varian Aerograph Model A-90-P chromatograph using the following columns: A, 18% Carbowax 20M (5 ft × 0.25 in.); B, 10% Carbowax 20M (5 ft × 0.25 in.). Mass spectra were determined at 70 eV on an Hitachi RMU 7 mass spectrometer.

5-Norbornen-2-yl Phenyl Ketone.—A solution of 24.7 g (0.20 mol) of norbornene-5-carboxaldehyde[15] (*ca.* 90% endo) in 15 ml of anhydrous ether was added over 1 hr to the Grignard reagent prepared from 34.1 g (0.20 mol) of bromobenzene and magnesium (6.0 g, 0.24 g-atom) in 50 ml of ether. The reaction mixture was heated at reflux for 0.5 hr, after which time it was quenched with 200 ml of water and 150 ml of 10% hydrochloric acid. The mixture of alcohols was extracted into ether, which was washed with sodium bicarbonate solution and saturated salt solution. The dried extracts were evaporated to give 21.5 g (54%) of a white solid, mp 66–68° (lit.[16] mp 66–67°) after crystallization from pentane.

The alcohols were oxidized to 5-norbornen-2-yl phenyl ketone using Jones[17] reagent. The yield of ketone was 67% (12 g) and the nmr spectrum was identical with that of a sample isolated (alumina chromatography) from a commercial mixture of the endo and exo isomers (Aldrich Chemical Co.).

5-Norbornen-2-yl Benzyl Ketone.—The above sequence was repeated using benzylmagnesium chloride and 98% *endo*-5-norbornene-2-carboxaldehyde. A 65% yield of carbinols was isolated, bp 160–162° (12 mm).

Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.16; H, 8.60.

Oxidation with Jones reagent[18] gave a 52% yield of ketone: bp 156–161° (12 mm); nmr δ 7.25 (s, 5 H, ArH), 5.85 (octet, 2 H, HC=); ir (film) 5.85 μ (s, C=O).

Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 85.17; H, 7.88.

5-Norbornen-2-yl 1-Naphthyl Ketone.—1-Naphthylmagnesium bromide was treated with 90% *endo*-5-norbornene-2-carboxaldehyde to yield a mixture of carbinols in 34% yield, mp 101–102° after crystallization from methanol and hexane.

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.24. Found: C, 86.22; H, 6.93.

Oxidation with Jones[17] reagent gave the ketone in 55% yield as a colorless solid: mp 78–79° after crystallization from methanol; nmr δ 7.68 (m, 7 H, ArH), 5.90 (octet, 2 H, HC=); ir (Nujol) 6.22 μ (s, C=O).

Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found:[19] C, 86.93; H, 6.52.

Preparation of Oxetanes. General.—The ketones were photocyclized in an immersion apparatus with the light from a 450-W Hanovia lamp. Filters and solvents are indicated for each compound. A slow nitrogen stream was passed through the solutions during irradiation. The reactions were monitored by ir or gc and were carried to >95% completion.

3-Phenyl-4-oxatetracyclo[4.2.1.0^{2,5}.0^{3,7}]nonane (3a).—Irradiation of 6 g of ketone in 220 ml of hexane with a Pyrex filter gave an oil which was washed with potassium permanganate solution and chromatographed on basic alumina to yield 4.2 g (70%) of oxetane **3a**, nmr δ 7.27 (s, 5 H, ArH), 4.62 (q, 1 H, HCO).

Anal. Calcd for $C_{14}H_{14}O$: C, 84.81; H, 7.12. Found: C, 85.38; H, 7.34.

3-Benzyl-4-oxatetracyclo[4.2.1.0^{2,5}0.^{3,7}]nonane (3c).—A solution of 8.05 g of ketone and 3.40 g of piperylene in 450 ml of spectral grade benzene was irradiated (Corex filter). After removal of solvents the residue was distilled to give 4.26 g (53%) of oxetane **3c**: bp 89–91° (0.75 mm); nmr δ 7.22 (s, 5 H, ArH), 4.44 (q, 1 H, HCO); ir 10.23 (s), 14.30 μ (s).

(15) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460**, 117 (1928).

(16) F. Kasper and H. G. Muller, *J. Prakt. Chem.*, **34**, 283 (1966).

(17) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(18) The procedure of C. Djerassi, R. R. Engle, and A. Bowers [*J. Org. Chem.*, **21**, 1547 (1956)] was followed.

(19) We are indebted to A. Rousseau for the preparation and purification of this sample.

Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 85.15; H, 7.74.

3-(1-Naphthyl)-4-oxatetracyclo[4.2.1.0^{2,5}.0^{3,7}]nonane (3b).—A solution of 6.0 g of ketone in 210 ml of hexane was irradiated using a Pyrex filter. A viscous oil was obtained which was washed with potassium permanganate solution and chromatographed on basic alumina to yield 3.27 g (55%) of a viscous oil, nmr δ 8.57–7.0 (m, 7 H, ArH), 4.72 (q, 1 H, HCO).

Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.50. Found: C, 87.62; H, 6.62.

3-Chloro-4-oxatetracyclo[4.2.1.0^{2,5}.0^{3,7}]nonane (9).—A sample of 5-norbornene-2-carbonyl chloride was prepared by addition of acryloyl chloride to cyclopentadiene. A solution of the chloride (149 g, 1.65 mol) in 150 ml of anhydrous ether was added to 104.5 g (1.58 mol) of cyclopentadiene in 325 ml of ether over 1 hr. The resulting solution was stirred at 25° for 19 hr, after which the volatile materials were evaporated. The residue was distilled at 63.5° (4.5 mm) to give 158 g (64%) of the adduct. The exo-endo ratio (5:95) was estimated from the relative amounts of methyl esters produced on methanolysis.

A solution of 15 g (0.096 mol) of the acid chloride in 1.2 l. of dry benzene was purged with dry nitrogen and irradiated with the unfiltered light from a 450-W Hanovia lamp. The total irradiation time was 14 days and the lamp well was cleaned every other day. The solution was washed vigorously with an aqueous solution of potassium hydroxide (40 g in 200 ml). The benzene layer was dried over potassium carbonate, after which the solvents were removed *in vacuo*. The residue was distilled to yield 1.5 g (10%) of an oil: bp 44° (0.025 mm); nmr δ 4.62 (q, J = 2, 4 Hz, 1 H, HCO), 2.72 (m, 1 H), 2.48 (m, 1 H), 2.14 (m, 2 H), 1.58 (m, 3 H); ir 9.10 (s), 9.30 (s), 9.92 (s), and 11.35 μ (s).

Anal. Calcd for C_8H_9ClO: C, 61.35; H, 5.79; Cl, 22.64. Found: C, 61.30; H, 5.96; Cl, 22.64.

2-*syn*-Hydroxy-4-*anti*-phenyltricyclo[3.3.0.0^{3,7}]octane (4a).—A slurry of **3a** (0.90 g, 0.0045 mol) and *ca.* 1 g of Raney nickel (W. R. Grace Co., #28 in water) in 25 ml of ethanol was pressured to 40 psi with hydrogen. After 2 hr the catalyst was removed by filtration and the solvents were evaporated, giving 0.88 g (98%) of a white solid, mp 77–81°. Crystallization from petroleum ether–methylene chloride gave colorless needles: mp 88–89°; nmr δ 7.05 (t, 5 H, ArH), 4.12 (s, 1 H, HCO), 3.81 (d, J = 3 Hz); ir (Nujol) 3.11 μ (br, OH).

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.06. Found: C, 83.72; H, 8.04.

The same product was obtained on refluxing a slurry of 1 g of catalyst and 1.0 g of **3a** in 25 ml of ethanol which contained 4.0 ml of 100% hydrazine hydrate.[20] The oxetane was inert to the action of 10% palladium on charcoal with hydrogen in ethanol.

2-*syn*-Hydroxy-4-*anti*-(1-naphthyl)tricyclo[3.3.0.0^{3,7}]octane (4b).—A slurry of oxetane **3b** (0.70 g, 0.0028 mol) and *ca.* 1 g of Raney nickel (W. R. Grace Co., #28 in water) in 25 ml of ethanol was pressured to 14 psi with hydrogen. After 17 hr the catalyst was removed and the solvents were evaporated. A white solid was obtained which was triturated with pentane. The insoluble material (0.49 g) was crystallized from benzene–hexane: mp 174–175°; nmr δ 8.60–6.90 (m, 7 H, ArH), 4.75 (s, 1 H, HCO), 3.97 (d, J = 3 Hz, 1 H); ir (Nujol) 3.11 μ (br, OH).

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.24. Found: C, 86.39; H, 6.98.

2-*syn*-Hydroxy-4-*anti*-benzyltricyclo[3.3.0.0^{3,7}]octane (4c).—A slurry of 10 g of damp Raney nickel[21] was stirred at reflux in a solution of 1.07 g of **3c** in 30 ml of ethanol. After 4 hr the reaction was stirred overnight at 25°. Water (150 ml) was added and the product was extracted into pentane. The extracts were washed with water and dried (Na_2SO_4) prior to evaporation. An oil was obtained which was distilled in a molecular still at 26 mm (block temperature 175–180°): yield 0.96 g (89%); nmr δ 7.11 (s, 5 H, ArH), 3.62 (d, J = 3 Hz, HCO), 3.12 (t, J = 7.5 Hz), 2.55 (d, J = 7.5 Hz, CH_2Ar); ir 2.95 μ (br, OH).

A 2,4-dinitrobenzoate derivative was prepared, mp 113.5–114.5°.

Anal. Calcd for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.46; H, 5.19; N, 6.66.

Reduction of 3d with Lithium in EDA.—A solution of 8.5 g (0.07 mol) of **3d** in 35 ml of pentane was added to 45 ml of ethylenediamine in a flask equipped with a magnetic stirrer and condenser. The flask was placed in an 80° bath and lithium wire (1.9 g, 0.28 g-atom) was added over 0.5 hr with vigorous stirring. The reaction mixture was stirred for an additional 6 hr and subsequently hydrolyzed. The products were extracted into pentane and ether, and the combined extracts were washed with water and dried (Na_2SO_4). Evaporation of the extracts and sublimation of the residue gave 4.8 g (55%) of a white solid. Gc analysis (B, 150°) revealed two components in a 25:75 ratio. The minor product was identified as *endo*-2-norbornylmethanol[22] (**5**) by ir and nmr comparisons. The major component was shown to be tricyclo[3.3.0.0^{3,7}]octan-2-ol (**4d**) by comparative ir and nmr spectra.[1]

Reduction of 9 with Lithium in EDA.—Similar treatment of chlorooxetane **9** gave a 70% yield of alcohols. Gc analysis showed two products in a ratio of 73:27. The two components were isolated and identified as **4d** and **5**, respectively, by comparative ir and nmr spectra.

Reduction of 1. A. Lithium in EDA.—Similarly, oxetane **1** gave an 81% yield of alcohols. Gc separation (A, 160°) revealed five components in the following relative amounts: **11** (10%), **10** (18%), **13** (10%), **12** (7%), and **2** (55%). The three known compounds were separated by preparative gc and identified by comparisons of their ir spectra with those of authentic samples.[23]

The nmr spectrum of **13** showed the following absorbances: δ 5.26 (m, 1 H, HC=), 4.18 (m, 1 H, HCO), 2.99 (br m, 1 H), 2.44 (s, 1 H, OH), 1.65 (d, J = 1 Hz, CH_3); ir 3.00 (s, OH), 9.92 (s, CO), 6.06 μ (w, C=C); mass spectrum (70 eV) molecular ion m/e 138, base peaks at m/e 91 and 92, $M^+ - H_2O$ at m/e 120.

Compound **12** showed the following nmr absorbances: δ 4.05 (m, HCO), 2.27 (m), 1.93 (m), 1.27 (d, J = 6 Hz); ir 9.14 (m), 9.37 μ (m); mass spectrum (70 eV) molecular ion m/e 138, base peak m/e 66, prominent ion at m/e 105 ($M^+ - H_2O - CH_3$).

B. Lithium in Ammonia.—Oxetane **1** (0.20 g, 1.47 mmol) in 75 ml of ether and 25 ml of liquid ammonia was allowed to react with 0.29 g (42 mg-atoms) of lithium for 4 hr at reflux. The solvents were allowed to evaporate at room temperature, and the residue was treated with water. Ether extraction followed by gc analysis revealed the following components: **1** (26%), **10** (4%), **12** (10%), **2** (60%).

Reduction of 3a with Lithium in Ammonia.—To a stirred solution of 0.46 g (2.3 mmol) of **3a** in 25 ml of liquid ammonia and 5 ml of pentane was added 0.126 g (18 mg-atoms) of lithium wire. The reaction mixture was stirred at reflux for 1.5 hr, after which the ammonia was evaporated. Water (10 ml) was added to the residue and the products were extracted into ether. Gc analysis (B, 180°) revealed three minor components (10% total) and one major component. The retention time and nmr spectrum of the major product were virtually identical with those of authentic **4a** as prepared above.

Reduction of 1 with Alane.—A solution of alane was prepared by slow addition of 1.20 g (0.032 mol) of powdered lithium aluminum hydride to an ice-cold solution of 1.42 g (0.011 mol) of freshly sublimed aluminum chloride in 100 ml of dry ether. After the resulting mixture was stirred for an additional 1 hr at 25°, a solution of 2.86 g (0.021 mol) of oxetane **1** in 100 ml of ether was added over 15 min. The reaction mixture was then refluxed for 9 hr, after which water was cautiously added until no further reaction was observed. The salts were removed by filtration and the ether was dried (Na_2SO_4) and evaporated. A simple distillation served to remove nonvolatile materials and yielded 2.65 g of an oil. Gas chromatographic analysis on a 15-ft 10% Carbowax 20M column (170°) revealed two components in an 80:20 ratio. On standing, the major component disappeared and a new product with shorter retention time appeared.

The unstable major component **15** was isolated and characterized by its nmr spectrum: δ 5.57 (s, 1 H, HC=), 1.77 (d, J = 1.8 Hz, CH_3), 0.5 (octet, 1 H, 5 endo).[24] The volatile transformation product **16** was isolated as an oil: nmr δ 3.56 (m, 2 H, (CH_2O)), 1.22 (s, 3 H, CH_3); ir (film) 9.65 (s), 10.00 μ (s).

(20) F. P. Robinson and R. K. Brown, *Can. J. Chem.*, **39**, 1171 (1961).

(21) R. Mozingo, *Org. Syn.*, **21**, 15 (1941).

(22) R. R. Sauers and R. J. Tucker, *J. Org. Chem.*, **28**, 876 (1963).

(23) A sample of **11** was prepared by reduction of *endo*-2-norbornyl methyl ketone with lithium aluminum hydride. We are indebted to Michael Hearn for the ketone.

(24) The 5-endo proton in norbornene derivatives frequently appears as an octet at high fields. For examples and references see R. V. Moen and H. S. Makowski, *Anal. Chem.*, **43**, 1629 (1971); E. Pretsch, H. Immer, C. Pascual, K. Schaffner, and W. Simon, *Helv. Chim. Acta*, **50**, 105 (1967).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.98; H, 10.43.

The minor component had mp 99.5–101.5° and was assigned structure **18** on the basis of spectral data: nmr δ 3.99 (br s, 1 H, HCO), 1.11 (s, 3 H, CH_3); ir (Nujol) 3.00 (br, OH), 9.30 (s), 9.45 μ (s).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.92; H, 10.43.

Registry No.—**1**, 22398-67-0; **3a**, 22398-69-2; **3b**, 22398-43-2; **3c**, 22398-41-0; **3d**, 22398-42-1; **4a**, 22398-47-6; **4b**, 22398-48-7; **4c**, 22398-46-5; **4c** 2,4-dinitrobenzoate, 37750-49-5; *endo*-**8**, 37750-50-8; *exo*-**8**, 34733-86-3; **9**, 37750-52-0; **12**, 37750-53-1; **13**, 37750-54-2; **15**, 37750-55-3; **16**, 37750-56-4; **18**, 37750-57-5; 5-norbornen-2-yl phenyl ketone, 37750-58-6; *endo*-norbornene-5-carboxaldehyde, 19926-90-0; bromobenzene, 108-86-1; 5-norbornen-2-ylphenylcarbinol, 13305-26-5; 5-norbornen-2-ylbenzyl ketone, 37750-61-1; benzylmagnesium chloride, 6921-34-2; 5-norbornen-2-ylbenzylcarbinol, 13305-27-6; 5-norbornen-2-yl-1-naphthyl ketone, 36171-23-0; 1-naphthylmagnesium bromide, 703-55-9; 5-norbornen-2-yl-1-naphthylcarbinol, 37750-66-6; cyclopentadiene, 542-92-7.

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Ring Contraction of Bicyclo[2.2.1]heptanes[1]

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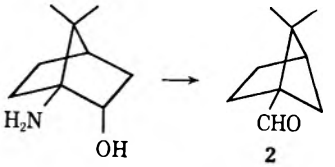
Received July 31, 1972

A convenient synthesis of 1-substituted bicyclo[2.1.1]hexanes by ring contraction of 1-substituted bicyclo[2.2.1]heptan-2-ols has been achieved. This method is highly efficient for the synthesis of 5,5-dimethylbicyclo[2.1.1]hexane-1-methanol and 5,5-dimethylbicyclo[2.1.1]hexane-1-carboxylic acid from camphor.

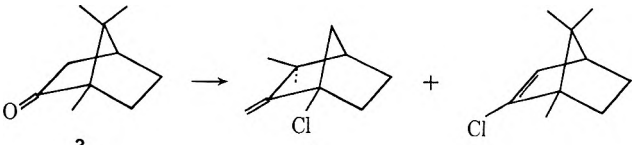
Ring contraction of bicyclo[2.2.1]heptanes has been achieved by deamination of 1-amino-3,3-dimethylbicyclo[2.2.1]heptan-2-ol (**1**)[3] to give 5,5-dimethylbicyclo[2.2.1]hexane-1-carboxaldehyde (2) and by



1 2

Favorskii rearrangement of 1-bromo-7,7-dimethylnorbornanone[4] to give 5,5-dimethylbicyclo[2.1.1]hexane-1-carboxylic acid. Other methods of synthesis of bicyclo[2.1.1]hexanes are known,[5] including the photochemical ring contraction of α-diazo ketones of bicyclo[2.2.1]heptanes and bicyclo[3.1.1]heptanes,[6-9] photolytic cycloaddition of olefins,[10-12] ketone decomposition,[13] solvolysis,[14] intramolecular alkylations,[15-17] and carbene ring contraction.[18] Bicyclo[3.1.1]heptane glycol monotosylates have been rearranged to 2-substituted bicyclo[2.1.1]hexanes and complements this work.[19,20] Many of the above procedures are not synthetically useful if large quantities of materials are desired. We have a procedure by which large quantities of 5,5-dimethylbicyclo[2.1.1]hexane-1-methanol or -1-carboxylic acid can be made in a few steps and in high yield.[21] The sequence utilizes *d*-camphor as the starting material so that all of the products in the sequence are optically active.

Treatment of *d*-camphor (**3**) with phosphorus trichloride and phosphorus pentachloride is known to give 1,7,7-trimethyl-2,2-dichlorobicyclo[2.2.1]heptane, which can be readily rearranged to 1-chlorocamphene (**4**).[22] 1-Chlorocamphene can be obtained in 70%



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yield in one step if the by-product, 1,7,7-trimethyl-2-chlorobicyclo[2.2.1]hept-2-ene, obtained in 25% yield, is removed by spinning band distillation. Ozonolysis in methanol[23] at −78° and decomposition of the ozonide with dimethyl sulfide[24] gave 1-chloro-3,3-dimethylbicyclo[2.2.1]heptan-2-one (**5**). Reduction of **5** or the

(1) Financial support from National Science Foundation Grant No. 15334 and an instrument grant to the Department of Chemistry for the purchase of a XL-100-15 and T-60 nmr spectrometers is gratefully acknowledged.

(2) Taken in part from the Ph.D. Thesis of B. W. M., Kansas State University, 1971.

(3) K. Ebisu, L. B. Batty, J. M. Higaki, and H. O. Larson, *J. Amer. Chem. Soc.*, **87**, 1399 (1965); **88**, 1995 (1966).

(4) W. C. Fong, R. Thomas, and K. V. Scherer, Jr., *Tetrahedron Lett.*, 3789 (1971).

(5) J. Meinwald and Y. C. Meinwald, *Advan. Alicycl. Chem.*, **1**, 1 (1966).

(6) L. Homer and E. Spietschka, *Ber.*, **88**, 934 (1955).

(7) J. Meinwald and P. G. Gassman, *J. Amer. Chem. Soc.*, **82**, 2857 (1960).

(8) J. Meinwald and P. G. Gassman, *ibid.*, **82**, 5445 (1960).

(9) K. B. Wilber, B. R. Lowry, and T. H. Colby, *ibid.*, **83**, 3988 (1961).

(10) R. C. Cookson, J. Hudec, S. A. Knight, and B. R. D. Whitear, *Tetrahedron*, **19**, 1995 (1963).

(11) R. S. H. Liu and G. S. Hammond, *J. Amer. Chem., Soc.*, **86**, 1892 (1964).

(12) R. Srinivasan, *J. Phys. Chem.*, **67**, 1367 (1963).

(13) R. Srinivasan, *J. Amer. Chem. Soc.*, **83**, 4923 (1961).

(14) R. N. McDonald and C. E. Reinecke, *ibid.*, **87**, 3020 (1965).

(15) W. H. Brown, Doctoral Dissertation, Columbia University, 1959.

(16) E. Wenkert and D. P. Strike, *J. Org. Chem.*, **27**, 1883 (1962).

(17) K. B. Wilberg and G. W. Klein, *Tetrahedron Lett.*, 1043 (1963).

(18) P. G. Gassman and T. J. Atkins, *J. Amer. Chem. Soc.*, **92**, 5810 (1970).

(19) T. Hirata and T. Suga, *J. Org. Chem.*, **36**, 412 (1971).

(20) R. G. Carlson and J. K. Pierce, *Tetrahedron Lett.*, 6213 (1968).

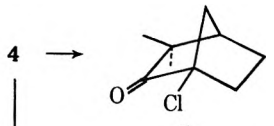
(21) J. V. Paukstelis and B. V. Macharia, Abstracts, Midwest Regional Meeting of the American Chemical Society, Lincoln, Nebr., 1970, No. 508.

(22) H. Meerwein and R. Wortman, *Justus Liebigs Ann. Chem.*, **435**, 190 (1924).

(23) P. S. Bailey, *Ber.*, **88**, 795 (1955).

(24) J. J. Pappas and W. P. Keaveney, *Tetrahedron Lett.*, 4273 (1966).

direct reduction of the ozonide[25] with sodium borohydride gave a mixture of two epimeric alcohols in a ratio of 5:1. The structure of the major epimer was assigned as **6a** and the minor epimer as **6b**, primarily on



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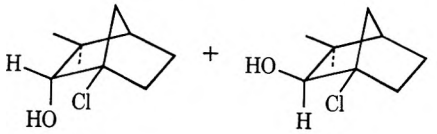
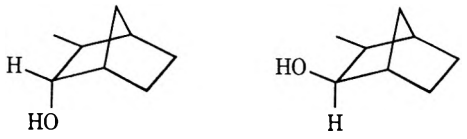


6a **6b**

the basis of the chemical shifts and multiplicities of the C-2 H which occurred at τ 6.42 and 6.90 for **6a** and **6b**, respectively. The resonance at τ 6.42 was a singlet while the resonance at 6.90 was a doublet, J = 2.0 Hz, as expected if the long range coupling to the 7-anti proton of **6b** were observed. The compounds **7a** (τ 6.43) and **7b** (τ 6.73) serve as good models for the chemical shifts of **6a** and **6b**.[26]

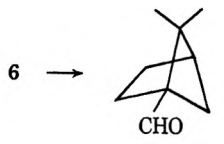


7a **7b**

Treatment of the mixture of chloro alcohols **6a** and **6b** with sodium hydroxide in DMF gave a mixture of products which could be analyzed by nmr and glpc. The composition of the mixture was dependent on the reaction time. Short reaction times, 2–3 hr, yielded an aldehyde (nmr signal τ 0.3, singlet) as well as starting material. When the reaction time was increased to 18 hr only small amounts of the aldehyde could be detected but three new products, an alcohol, an acid, and an ester, could be isolated. The aldehyde and the acid were identified as 5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde (**2**) and 5,5-dimethylbicyclo[2.1.1]hexane-1-carboxylic acid (**8**) by comparison of their nmr and ir spectra to the spectra of authentic samples.[4,27] Reduction of the aldehyde **2** gave a primary alcohol identical with the alcohol produced in the rearrangement, thus establishing that the alcohol was 5,5-dimethylbicyclo[2.1.1]hexyl-1-methanol (**9**). Reduction of the ester gave only the alcohol **9**, thus establishing that the ester was 5′,5′-dimethylbicyclo[2.1.1]hexane-1′-methyl 5,5-dimethylbicyclo[2.1.1]hexane-1-carboxylate (**10**). The alcohol **9**, the acid **8**, and the ester **10** were formed probably by a Cannizzaro or Tishchenko reaction. If the crude reaction mixture was reduced with $LiAlH_4$, alcohol **9** was obtained in 86% yield. The alcohol **9** could be readily oxidized with Jones reagent to the acid **8** in quantitative yield.

The mechanism of the ring contraction is assumed to be a pinacol-type trans-coplanar rearrangement where the leaving group is displaced in a concerted reac-

(25) J. A. Sousa and A. L. Bluhm, *J. Org. Chem.*, **25**, 108 (1960).
(26) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).
(27) We wish to express our thanks to Professor H. O. Larson for copies of the nmr and ir spectra of **2** and **8**.



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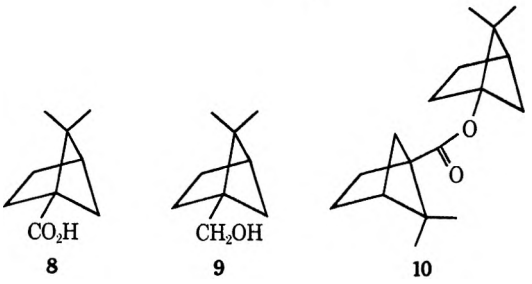

8 **9** **10**

tion.[28–30] The possibility of an SN1 process is clearly unreasonable on the basis of the known bridgehead reactivity.[31] The reaction is sensitive to the nature of the leaving group as well as solvent. We have prepared[21] and rearranged under much milder conditions 1-tosyloxy-3,3-dimethylbicyclo[2.2.1]-heptan-2-ol and obtained **2** as the major product. Rearrangement of **6** in refluxing hexane as solvent gave very different results. The only product of the reaction was a ketone which was identified as 3,3-dimethylbicyclo[2.2.1]heptan-2-one (**11**) by comparison to an

6 **11**

authentic sample. The process by which **11** is formed is still under investigation.

The overall sequence starting with *d*-camphor is very well adapted for large-scale preparation of **8** and **9** and proceeds in about 57% overall yield. While we believe the reaction to be general it is also clear that the rearrangement is very much dependent on reaction conditions.

Experimental Section[32]

1-Chloro-2-methylene-3,3-dimethylbicyclo[2.2.1]heptane (**4**). —A solution of 75.0 g (0.492 mol) of *d*-camphor in 34.2 ml of phosphorus trichloride was treated in portions with 110.0 g (0.618 mol) of phosphorus pentachloride heated at reflux for 6 hr, cooled, carefully poured into a beaker of ice, and extracted three times with 100-ml portions of pentane. The combined organic fractions were treated successively with 10% sodium bicarbonate solution and water, dried ($MgSO_4$), and concentrated under reduced pressure. A glpc chromatogram of this crude product showed only two components in about 1:4 ratio. The minor component, bp 103–110° (63.0 mm), exhibited the following spectral properties: ir (CCl_4) 3125, 3030, 877 cm^{-1}; nmr (CCl_4) τ 9.23 (s, 3, methyl), 9.15 (s, 3, methyl), 9.02 (s, 3, methyl), 9.0–8.0 (m, 4), 7.67 (d of d, 1, J_{12} = 4 Hz, bridge-

(28) M. Nussim and Y. Mazur, *Tetrahedron*, **24**, 5337 (1968).
(29) D. Redmore and C. D. Gutsche, *Advan. Alicycl. Chem.*, **3**, 1 (1971).
(30) J. V. Paukstelis and J.-L. Kao, *J. Amer. Chem. Soc.*, **94**, 4783 (1972).
(31) R. C. Fort, Jr., and P. v. R. Schleyer, *Advan. Alicycl. Chem.*, **1**, 283 (1966).
(32) All melting points were determined on a Kofler melting point apparatus and are corrected. All boiling points are uncorrected. All nmr spectra were recorded on Varian A-60, T-60, HA-100, or XL-100 nmr spectrometers in carbon tetrachloride or deuteriochloroform with TMS internal standard at τ 10.0 ppm. Ir spectra were recorded on a Perkin-Elmer spectrometer Model 137 or 357. All mass spectra were determined on an AEI MS-9 mass spectrometer and all microanalyses were performed by Mr. Moon-geu Kim at Department of Chemistry, Kansas State University.

head), 4.22 (d, 1, J = 4 Hz, olefinic); mass spectrum m/e (rel intensity) 172 (M^+, 20), 170 (M^+, 56), 157 (28), 155 (56), 144 (19), 142 (64), 135 (40), 129 (20), 127 (64), 119 (56), 107 (56), 93(40), 91 (100), 79 (32), 77 (47). The presence of three methyl groups in addition to the olefinic proton at τ 4.22 established the structure to be 1,7,7-trimethyl-2-chlorobicyclo[2.2.1]hept-2-ene.

The major and desired component was distilled: bp 83–86° (19.0 mm) [lit.[22] bp 74–75° (3.5 mm)]; 70% yield; ir (neat) 3090, 1667, 1385, 1366, 890 cm^{-1}; nmr (CCl_4) τ 8.92 (s, 6, *gem*-dimethyl), 8.4–7.8 (m, 7), 5.28 (s, 1, olefinic), 4.92 (s, 1, olefinic); mass spectrum m/e (rel intensity) 172 (M^+, 10), 170 (M^+, 30), 157 (3), 155 (10), 143 (7), 141 (19), 135 (25), 129 (33), 127 (100), 119 (23), 107 (19), 105 (20), 93 (25), 91 (65), 79 (26), 77 (30), 69 (30). The above data are in complete agreement with those reported for 1-chloro-2-methylene-3,3-dimethylbicyclo[2.2.1]-heptane.[22,33]

Ozonolysis of 1-Chloro-2-methylene-3,3-dimethylbicyclo-[2.2.1]heptane.—A solution of 6.0 g (35.0 mmol) of 1-chloro-2-methylene-3,3-dimethylbicyclo[2.2.1]heptane in 200 ml of methanol[23] was treated with ozone for 2.0 hr at −78°. The cold solution was purged with nitrogen for 0.5 hr and 1.0 g (25.6 mmol) of sodium borohydride dissolved in 10 ml of water was added.[25] The reaction was allowed to warm up to room temperature. The solvent was removed on a rotary evaporator, and the residue was acidified with 10% hydrochloric acid and extracted with ether three times. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was distilled, bp 58–59° (0.25 mm), to give 5.8 g (94% yield) of a mixture of two compounds in 87:13 ratio. The minor component was not isolated but was detected from the nmr of the crude reaction mixture by the presence of a resonance at τ 6.9. The major component, assigned to 1-chloro-3,3-dimethylbicyclo[2.2.1]heptan-*endo*-2-ol on the basis of the chemical shift of the methine proton on the carbon bearing oxygen, was collected by glpc: ir (neat) 3448 cm^{-1} (bonded OH); nmr (CCl_4) τ 9.1 (s, 3, methyl), 9.92 (s, 3, methyl), 8.7–7.6 (m, 8), 6.42 (s, 1, OCH); mass spectrum m/e (rel intensity) 176 (M^+, 27), 156 (9), 139 (25), 138 (100), 128 (77), 109 (28), 102 (40), 101 (37), 100 (50), 95 (73), 73 (56), 72 (43), 69 (98), 67 (89), 65 (37), 55 (43), 43 (90), 41 (98), 39 (69).

Anal. Calcd for $C_9H_{15}ClO$: C, 61.88; H, 8.66. Found: C, 61.80; H, 8.46.

1-Chloro-3,3-dimethylbicyclo[2.2.1]heptan-2-one.—A solution of 8.0 g (46.5 mmol) of 1-chloro-2-methylene-3,3-dimethylbicyclo[2.2.1]heptane in 150 ml of methanol was treated with ozone at −78° for 2 hr. The reaction mixture was purged with nitrogen for 0.5 hr and then treated with 40 ml of dimethyl sulfide.[24] The reaction mixture was allowed to warm up to room temperature and stirred overnight. The solvent and excess dimethyl sulfide were removed on a rotary evaporator and the residue was dissolved in hexane and washed with ether. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was distilled to give 6.7 g (84% yield) of 1-chloro-3,3-dimethylbicyclo[2.2.1]heptan-2-one: bp 65–67° (1.8 mm) (lit.[21] bp 193–197°); ir (neat) 1754 cm^{-1} (C=O), 1379, 1361, (*gem*-dimethyl); nmr (CCl_4) τ 8.99 (s, 3), 8.85 (s, 3), 8.20–7.60 (m, 7).

Reduction of 1-Chloro-3,3-dimethylbicyclo[2.2.1]heptan-2-one.—A solution of 2.0 g (11.6 mmol) of 1-chloro-3,3-dimethylbicyclo[2.2.1]heptan-2-one in 20 ml of THF was added to a slurry of 200 mg of $LiAlH_4$ in THF and refluxed for 1 hr. The excess $LiAlH_4$ was destroyed by careful successive addition of H_2O, 15% NaOH, and H_2O. The solid was removed by filtration and washed wth more THF, and the solvent was removed under reduced pressure. The residue was dissolved in ether, washed with water, dried ($MgSO_4$), and concentrated. The resulting liquid was distilled, bp 55–58° (0.25 mm), to give 1.7 g (85% yield) of a mixture of 1-chloro-3,3-dimethylbicyclo[2.2.1]-heptan-*endo*- and -*exo*-2-ols as determined by nmr.

Rearrangement of 1-Chloro-3,3-dimethylbicyclo[2.2.1]heptan-2-ol.—A solution of 1.00 g (5.7 mmol) of 1-chloro-3,3-dimethylbicyclo[2.2.1]heptan-2-ol in 10.0 ml of DMF was added dropwise with stirring to a slurry of 0.5 g of sodium hydride (50% in oil) previously washed with hexane four times. After the vigorous reaction subsided, the temperature was raised to and maintained at 85° overnight under nitrogen. The reaction mixture was cooled and treated with 5.0 ml of methanol, followed by 30.0 ml of water, extracted with ether, and dried ($MgSO_4$). Evaporation of the solvent gave 0.72 g of an oil which had two major components in glpc. The minor component was collected and shown to be an alcohol: mp 80–83°; ir (CCl_4) 3615 (free OH), 3400 (bonded OH), 1385, 1370 (*gem*-dimethyl), 1120, 1020, 1010 cm^{-1}; nmr (CCl_4) τ 9.22 (s, 3, C-5 *endo*-methyl), 9.16 (d, 1, J = 9 Hz, C-6 endo H), 8.83 (s, 3, C-5 *exo*-methyl), 8.6–7.9 (m, 7), 6.43 (s, 2, CH_2O–).

The other compound was shown to be an ester by the following data: ir (neat) 1725 (ester C=O), 1385, 1360 cm^{-1} (*gem*-dimethyl); nmr (CCl_4) τ 9.21 (s, 3, methyl), 9.11 (s, 3, methyl), 9.15 (d, 1, J = 7 Hz), 8.95 (d, 1, J = 7 Hz), 8.80 (s, 6), 8.7–7.6 (m, 12), 5.95 (s, 2, $-CH_2O-$).

If the reaction time was reduced to 2–3 hr a different product could be detected along with significant amounts of starting material. Glpc collection material indicated the presence of an aldehyde, $\nu_{max}^{CCl_4}$ 1710 cm^{-1}, nmr τ 0.3. The nmr and ir spectra were identical with spectra obtained from Larson[3,4,27] for 5,5-dimethylbicyclo[2.1.1]hexane-1-carboxaldehyde.

The aqueous layer was acidified with 10% hydrochloric acid, extracted with ether, dried ($MgSO_4$), and concentrated. Removal of the solvent gave 200 mg of an acid: mp 114–115° (lit.[3,4] mp 115–119°); ir (CCl_4) 2600 (bonded OH), 1690 (C=O), 1390, 1370 cm^{-1} (*gem*-dimethyl); nmr (CCl_4) τ 9.19 (s, 3, methyl), 8.86 (d, 1, J = 7.5 Hz), 8.72 (s, 3, methyl), 8.5–7.5 (m, 7), −2.15 (s, 1, acidic); mass spectrum m/e (rel intensity) 154 (M^+, 9), 139 (12), 112 (33), 109 (38), 95 (21), 69 (89), 67 (72), 41 (100), 39 (55). Comparison of the nmr and ir of the above acid with the spectra of 5,5-dimethylbicyclo[2.2.1]hexane-1-carboxylic acid kindly supplied by Larson indicated that the two were identical.

Reduction of 5′,5′-Dimethylbicyclo[2.1.1]hexane-1′-methyl 5,5-Dimethylbicyclo[2.1.1]hexane-1-carboxylate.—A solution of 700 mg (2.54 mmol) of 5′,5′-dimethylbicyclo[2.1.1]hexane-1-methyl 5,5-dimethylbicyclo[2.2.1]hexane-1-carboxylate in 10 ml of ether was added to a slurry of 500 mg of $LiAlH_4$ in ether and heated under reflux for 12 hr. Decomposition of $LiAlH_4$ with water, sodium hydroxide, and water was followed by filtration and extraction. The organic layer was dried ($MgSO_4$), and concentrated to give an oil from which 600 mg (85%) of a colorless solid, 5,5-dimethylbicyclo[2.1.1]hexane-1-methanol, could be obtained by sublimation (32°, 0.2 mm).

5,5-Dimethylbicyclo[2.1.1]hexane-1-methanol.—A solution of 7.0 g (40.0 mmol) of 1-chloro-3,3-dimethylbicyclo[2.2.1]heptan-2-ol in 50 ml of DMF was added to a slurry of 5.0 g of NaH as previously described. After 18 hr the reaction was made acid to congo red and extracted with ether. Drying the solution ($MgSO_4$) and addition of 2.0 (67 mmol) of $LiAlH_4$ over a period of minutes and allowing the reaction to stand for 6 hr before decomposition of the excess $LiAlH_4$ with water, extraction with ether, drying, and removal of the solvent gave 4.8 g (86%) of a solid, mp 79–83°, identified as 5,5-dimethylbicyclo[2.1.1]hexane-1-methanol.

Registry No.—**3**, 464-49-3; **4**, 4017-64-5; **5**, 37611-37-3; **6a**, 37611-38-4; **6b**, 37611-39-5; **9**, 37611-40-8; **10**, 37611-41-9; 1,7,7-trimethyl-2-chlorobicyclo[2.2.1]-hept-2-ene, 37681-82-6.

(33) G. H. Richey, Jr., T. J. Barbacik, D. L. Dull and J. E. Grant, *J. Org. Chem.*, **29**, 3095 (1964).

Reactions of 2,8-Dihalo-8-thiatricyclo[3.2.1.0^{3,6}]octane

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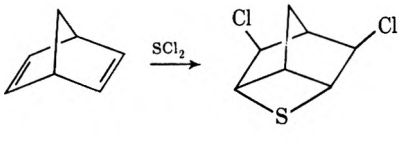
Carbonium ion, radical, or carbanion reactions of the halides of 2,8-dichloro- (1) or 2,8-dibromo-8-thiatricyclo[3.2.1.0^{3,6}]octane (3) involve participation by sulfur. Thus, treatment of the dichloro compound 1 with boron tribromide generates the dibromide 3 and with acetic acid the corresponding *exo,exo*-diacetate, whereas alane or cyanide ion produced *endo*-2,3-epithio-5-norbornene. Radical reactions initiated by tri-*n*-butyltin hydride or chromous acetate led only to a rearrangement product, nortricyclyl mercaptan. Finally, lithium dimethylcuprate produced *endo*-2-methylthio-*exo*-3-bromo-5-norbornene.

The addition of sulfur dichloride to norbornadiene proceeds exclusively and in high yield to produce 2,8-dichloro-4-thiatricyclo[3.2.1.0^{3,6}]octane (**1**).[1] This unusual reaction, whose high selectivity suggested the possibility of an episulfonium salt **2** as an intermediate,



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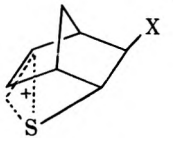
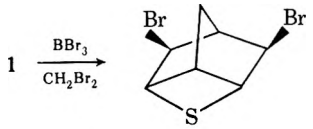


2

encouraged us to examine some of the chemistry of the adduct as a source of fascinating new reactions emanating from the flexible chemical reactivity of sulfur. Indeed, all reactions of the halides (carbonium ion, radical, carbanion) involve participation by sulfur.

If **2** is an intermediate in the addition reaction, ionization of **1** back to **2** in principle also should be possible. Although treatment with alane (AlH_3) failed to provide any support for such an ionization, boron tribromide[2] quantitatively replaced both chlorines with bromines. The assignment of the structure of the dibromide as **3** rather than as an alternative such as **4** was clearly



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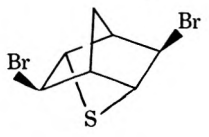

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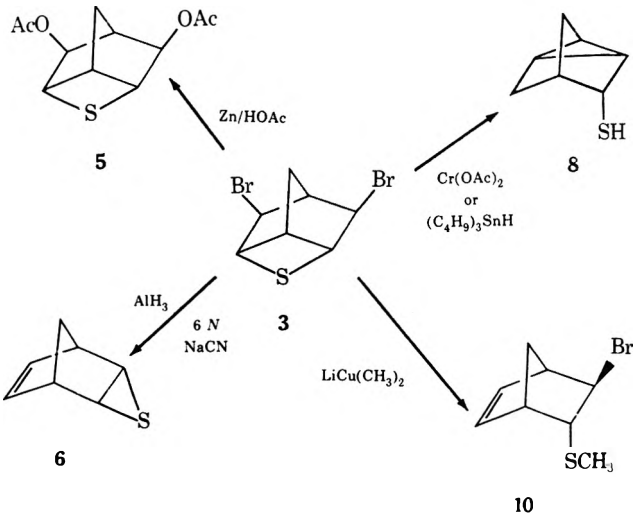
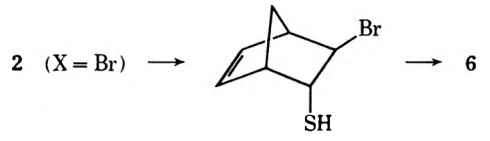
indicated by the nmr spectrum (see Experimental Section). The dibromide also ionizes readily to **2** (X = Br). Thus, attempted reduction of **3** with zinc in acetic acid only led to solvolysis and formation of diacetate **5** in 84% yield (see Scheme I). In contrast to the trapping of **2** (X = Br or Cl) at carbon with

Scheme I

Reactions of 2,8-Dibromo-4-thiatricyclo[3.2.1.0^{3,3}]octane



acetate or bromide as nucleophiles, hydride captures **2** (X = Br) at sulfur to give **7**. Thus, the product of



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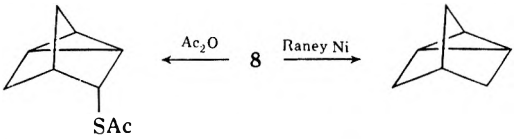
alane reduction, *endo*-2,3-epithio-5-norbornene (**6**), results upon subsequent cleavage of hydrogen bromide from this intermediate. Support for this interpretation arises from the inertness of dibromide **3** to refluxing lithium aluminum hydride, ruling out initiation of reaction by hydride attack on bromine. On the other hand, cyanide ion induces reduction of **3** to **6** in 84% yield, a process almost certainly involving initial reaction of cyanide at bromide.[3]

Attempts to replace bromine with hydrogen or alkyl groups led only to rearrangement products. Radical debrominations led to 2-nortricyclyl mercaptan (**8**).



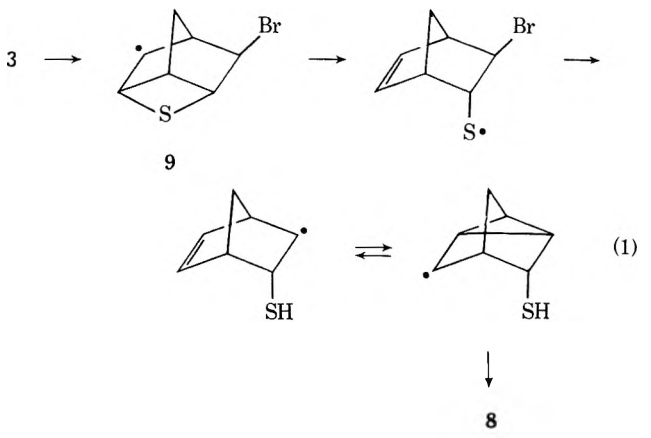
The structure of **8** was demonstrated by Raney nickel desulfurization to nortricyclene and acetylation to the

(1) (a) F. Lautenschlaeger, *J. Org. Chem.*, **31**, 1669 (1966); (b) *ibid.*, **34**, 3998 (1969).

(2) S. W. Tobey and R. West, *J. Amer. Chem. Soc.*, **88**, 2481 (1966).

(3) The similar reaction with dichloride **1** proceeded in 31% yield; see ref 1b.

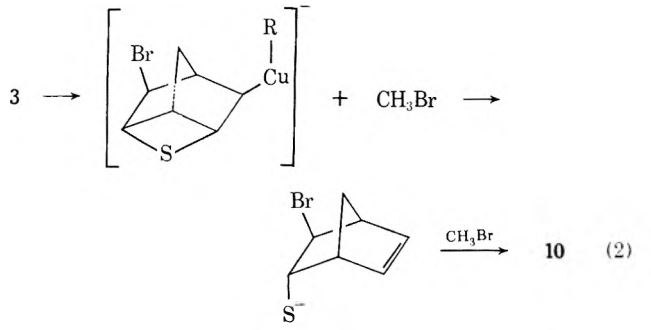
known thioacetate[4] as well as by spectral means. Equation 1 illustrates the probable pathway. In these



(1)

events, radical **9** undergoes elimination much faster than either hydrogen atom transfer in the tin hydride reduction or electron capture and protonation in the chromous ion reduction.[5,6] Identical behavior was observed with the dichloride **1** under these conditions.

Most surprising was the reaction of dibromide **3** with lithium dimethylcuprate. No products of C-alkylation were observed. The only product, isolated in 80% yield, was *exo*-2-bromo-*endo*-3-methylthio-5-norbornene. Equation 2 rationalizes its formation. Metal-



(2)

halogen exchange has been found in a few other cases of attempted alkylation with cuprates but usually when the alkyl group on copper is larger than methyl.[7]

Experimental Section[8]

Preparation of *exo,exo*-2,8-Dibromo-4-thiatricyclo[3.2.1.0^{3,6}]-octane (3).—*exo,exo*-2,8-Dichloro-4-thiatricyclo[3.2.1.0^{3,6}]octane (19.4 g, 0.10 mol) was dissolved in 100 ml of methylene bromide. The solution was cooled to −5° and 55.0 g (0.22 mol) of boron tribromide was added by syringe over a 15-min period. The reaction started immediately and was very exothermic. After addition, the reaction was stirred for 1 hr at 0° and then heated at 70° for 20 min. The mixture was then slowly added to 1 l. of water and 800 ml of carbon tetrachloride. After 3 × 500 ml water washes, the carbon tetrachloride layer was dried and evaporated to give 28.0 g of crude product. The product was recrystallized from hexane to give 26.5 g (94%) of gray-white crystals: mp 81–83°; nmr (CCl_4) τ 5.31 (s, 2 H), 6.0 (m, 1 H), 6.55 (d, J = 1 Hz, 1 H), 6.65 (s, 2 H), 7.72 (bs, 2 H); ir (CCl_4) 15.95 μ; mass spectrum m/e (rel intensity) 286 (9), 284 (18), 282 (9), 206 (60), 204 (60), 160 (18), 124 (41), 124 (37), 98 (30), 93 (45), 92 (100).

Anal. Calcd for $C_7H_8Br_2S$: C, 29.57; H, 2.82; Br, 56.33; S, 11.27. Found: C, 29.67; H, 2.85; Br, 56.37; S, 11.20.

Preparation of *exo,exo*-2,8-Diacetoxy-4-thiatricyclo[3.2.1.0^{3,6}]-octane (5).—A solution of 1.42 g (5.0 mmol) of *exo,exo*-2,8-dibromo-4-thiatricyclo[3.2.1.0^{3,6}]octane in 10 ml of glacial acetic acid was treated with 0.65 g (10 g-atom) of zinc dust. The mixture was heated to 80° and stirred for 24 hr. After the mixture was cooled, 25 ml of chloroform was added and the resultant slurry was filtered and washed with 2 × 50 ml of water. The chloroform layer was dried and the solvent was removed by evaporation. The crude product (1.01 g, 84% yield) was distilled to give 0.40 g (33%) of a colorless liquid, bp 113° (6.7 mm), which solidified upon standing: mp 46–48°; nmr (CCl_4) τ 4.68 (s, 2 H), 6.10 (m, 1 H), 6.98 (d, J = 4.0 Hz, 2 H), 7.05 (m, 1 H), 8.00 (s, 6 H), 8.17 (bs, 2 H); ir (CCl_4) 5.72 μ; mass spectrum m/e (rel intensity) 242 (14), 140 (15), 139 (7), 125 (5), 124 (7), 123 (5), 122 (7), 111 (11), 107 (7), 82 (13), 79 (14), 67 (10), 66 (12), 43 (100).

Anal. Calcd for $C_{11}H_{14}O_4S$: mol wt, 242.0612. Found: mol wt, 242.0579.

Reaction of *exo,exo*-2,8-Dibromo-4-thiatricyclo[3.2.1.0^{3,6}]octane (3) with Lithium Aluminum Hydride and Aluminum Chloride.—Lithium aluminum hydride (0.114 g, 3.0 mmol) and aluminum chloride (0.133 g, 1.0 mmol) were added to 10 ml of dry tetrahydrofuran. The suspension was stirred for 20 min and then 0.50 g (1.7 mmol) of *exo,exo*-2,8-dibromo-4-thiatricyclo[3.2.1.0^{3,6}]octane was added. The resultant slurry was refluxed for 24 hr. The solution was slowly hydrolyzed with a dilute sodium hydroxide solution. The aqueous layer was extracted with 2 × 50 ml of carbon tetrachloride. The combined carbon tetrachloride layers were dried and evaporated to give a viscous liquid. Flask distillation of this liquid in a Hickman still at 0.1 mm gave 0.036 g (17% yield) of a foul-smelling solid. The nmr and ir were identical with those of *endo*-2,3-epithio-5-norbornene:[1b] nmr (CCl_4) τ 4.35 (bs, 2 H), 6.84 (bs, 2 H), 7.02 (bs, 2 H), 7.98 (s, 2 H); ir (CCl_4) 6.10 μ; mass spectrum m/e (rel intensity) 126 (1), 125 (5), 124 (14), 123 (43), 98 (39), 92 (27), 91 (100), 79 (35).

Reaction of *exo,exo*-2,8-Dibromo-4-thiatricyclo[3.2.1.0^{3,6}]octane (3) with Sodium Cyanide.—*exo,exo*-2,8-Dibromo-4-thiatricyclo[3.2.1.0^{3,6}]octane (10.0 g, 0.035 mol) and 5.80 g (0.118 mol) of sodium cyanide were added to 105 ml of 85% ethanol. The reaction mixture was heated at 70° for 1 hr and then 100 ml of water was added to it. The aqueous phase was extracted with 2 × 50 ml of chloroform. The combined chloroform layers were dried ($MgSO_4$) and evaporated to give a yellow liquid. Distillation of the liquid gave 3.40 g (80% yield) of *endo*-2,3-epithio-5-norbornene, bp 68° (13 mm). The colorless liquid solidified to give a white, crystalline solid, mp 46–47° (lit.[1b] mp 45–47°).

Reaction of *exo,exo*-2,8-Dichloro-4-thiatricyclo[3.2.1.0^{3,6}]octane (1) with Chromous Acetate.[9]—To a solution of 175 ml of dimethylformamide, 26 ml of water, and 40 ml of ethylenediamine which was deoxygenated was added 36 g (0.192 mol) of chromous acetate monohydrate. The resultant solution was a dark purple-blue, indicating that the chromous ion–ethylenediamine complex had formed. The complex was cooled to 0° and stirred for 15 min. *exo,exo*-2,8-Dichloro-4-thiatricyclo-[3.2.1.0^{3,6}]octane (4.65 g, 0.024 mol) was dissolved in 10 ml of deoxygenated dimethylformamide and it was added all at once by syringe to the chromous solution. An immediate color change took place as the solution became reddish-purple. It was stirred at 0° for 10 min and then poured into 500 ml of water.

(4) T. V. van Auken and E. A. Rick, *Tetrahedron Lett.*, 2709 (1968).

(5) J. Kochi, D. M. Singleton, and L. J. Andrews, *Tetrahedron*, **24**, 3503 (1968).

(6) For the norbornenyl-nortricyclyl radical problem see S. J. Cristol and R. W. Gleason, *J. Org. Chem.*, **34**, 1762 (1969); D. I. Davies, J. N. Done, and D. H. Hey, *Chem. Commun.*, 725 (1966); C. R. Warner, R. J. Strunk, and H. G. Kuivila, *J. Org. Chem.*, **31**, 3381 (1966).

(7) E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 3911 (1967); **90**, 5615 (1968).

(8) Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. Infrared spectra were determined on a Beckman IR-8 spectrophotometer, and ultraviolet spectra were recorded on Cary Model 11 and Model 15 spectrophotometers. Nmr spectra were determined on a Varian Associates Model A-60A, HA-100, or XL-100 spectrometer fitted with a variable-temperature probe. Chemical shifts are given in parts per million relative to TMS as an internal standard. Mass spectra were taken on a CEC 103 C or a MS-902 mass spectrometer at an ionizing current of 40 mA and ionizing voltage of 70 V. Analyses were performed by Spang Microanalytical Laboratory and Micro-Tech Laboratories, Inc. Unless otherwise indicated, extractions were performed with chloroform, magnesium sulfate was employed as a drying agent, and all reactions were run under nitrogen. Vpc analyses were performed on an Aerograph Model 90P instrument.

(9) J. K. Kochi, D. M. Singleton, and L. J. Andrews, *Tetrahedron*, **24**, 3503 (1968).

The water layer was extracted with 3 × 100 ml of pentane. The combined pentane extracts were dried ($MgSO_4$) and evaporated to give a foul-smelling, viscous, colorless oil. Bulb-to-bulb distillation at 1 mm gave 0.486 g (16% yield) of a colorless liquid which was identified as tricyclo[2.2.1.$0^{2,6}$]-3-heptylthiol: nmr τ 7.25 (d, J = 7 Hz, 1 H), 8.17 (d, J = 7 Hz, 1 H), overlapping with 8.25 (b s, 1 H), 8.70 (b s, 3 H), 8.87 (m, 4 H); ir 3.25, 3.88 μ; mass spectrum m/e (rel intensity) 128 (5), 127 (5), 126 (60), 97 (19), 83 (95), 81 (100), 79 (25), 78 (15), 77 (65).

Anal. Calcd for $C_7H_{10}S$: C, 66.73; H, 8.06; S, 25.30. Found: C, 66.66; H, 7.94; S, 25.39.

Reaction of *exo,exo*-2,8-Dibromo-4-thiatricyclo[3.2.1.$0^{3,6}$]octane (3) with Tri-*n*-butyltin Hydride.—A dry 25-ml one-neck flask was equipped with a short path distillation head and receiver flask immersed in a −78° bath. In the flask was placed 1.42 g (5.0 mmol) of *exo,exo*-2,8-dibromo-4-thiatricyclo[3.2.1.$0^{3,6}$]octane and 8.73 g (0.03 mol) of freshly distilled tri-*n*-butyltin hydride. A trace of AIBN was added and the reaction was heated to 100° at a pressure of 15 mm. The reaction was kept at 100° for 2 hr. A distillate was collected and was identified by vpc, ir, and nmr as pure tricyclo[2.2.1.$0^{2,6}$]heptylthiol. The yield was 100 mg (31%).

Reaction of Tricyclo[2.2.1.$0^{2,6}$]heptyl-3-thiol (8) with Acetic Anhydride.—Tricyclo[2.2.1.$0^{2,6}$]heptylthiol (0.10 g, 0.79 mmol) and 0.0829 g (0.80 mmol) of acetic anhydride were dissolved in 2 ml of dry pyridine. The mixture was heated at 90° for 1 hr and then poured into 20 ml of water. The water was extracted with 2 × 5 ml of ether. The combined ether layers were dried ($MgSO_4$) and the ether was removed by evaporation. A clear liquid (0.140 g, 100% yield) was recovered and identified as 3-thiolacetoxytricyclo[2.2.1.$0^{2,6}$]heptane[10] by mixed injection with authentic material on vpc (8 ft × 0.25 in. column of 20% Dow 710 on Chromosorb P at 138°, retention time, 64 min) and by nmr analysis: nmr (CCl_4) τ 6.62 (s, 1 H), 7.78 (s, 3 H), 8.00 (bs, 1 H), 8.32–9.00 (m, 7 H); ir 3.22, 5.90 μ; mass spectrum m/e (rel intensity) 170 (1), 169 (2), 168 (34), 140 (8), 127 (4), 126 (15), 125 (50), 110 (18), 93 (100), 92 (32), 91 (80), 79 (17), 77 (50), 66 (44), 65 (20).

(10) T. van Auken and E. A. Rick, *Tetrahedron Lett.*, 2709 (1968).

Reaction of 2,8-Dibromo-4-thiatricyclo[3.2.1.$0^{3,6}$]octane (8) with Lithium Dimethylcuprate. A.—Tetrakis[iodo(tri-*n*-butylphosphene)copper(I)], 7.84 g (0.20 mol), was dissolved in 100 ml of dry ether. The mixture was stirred and cooled to −78°. Methyllithium (1.42 *M*, 0.05 mol, 28 ml) in ether was added by syringe to the cold solution over a 2-min period to generate the lithium dimethylcuprate. The colorless solution was then stirred for 10 min.

2,8-Dibromo-4-thiatricyclo[3.2.1.$0^{3,6}$]octane (2.84 g, 0.01 mol) was dissolved in 50 ml of dry ether and this solution was added all at once *via* syringe to the −78° lithium dimethylcurprate solution. The solution remained colorless. After the solution was stirred at −78° for 1 hr, 1.23 g (0.01 mol) of dry nitrobenzene was added all at once by syringe and the solution turned to a deep green color. The Dry Ice bath was removed and the solution was allowed to warm to 0°. The solution was then added to 250 ml of water and the water–ether mixture was filtered through Celite to remove insoluble copper salts. The ether layer was separated and washed with 3 × 100 ml of water, dried ($MgSO_4$), and evaporated. The resultant orange liquid was distilled to give 1.75 g (80% yield) of an orange liquid, bp 52° (0.1 mm). The product was identified as a new compound, *endo*-2-methylthio-*exo*-3-bromo-5-norbornene: nmr (CCl_4) τ 3.85 (m, 2 H), 6.48 (t, J = 2 Hz, 1 H), 6.68 (t, J = 2 Hz, 1 H), 6.94 (bs, 2 H), 7.81 (s, 3 H), 8.10 (m, 2 H); ir (CCl_4) 6.10, 14.50 μ; mass spectrum m/e (rel intensity) 220 (3), 218 (3), 154 (79), 152 (79), 141 (5), 140 (10), 139 (100), 124 (5), 123 (7), 92 (22), 91 (99), 73 (14).

Anal. Calcd for $C_8H_{11}BrS$: mol wt, 219.9745. Found: mol wt, 219.9710.

Registry No.—**1**, 6557-78-4; **3**, 37406-72-7; **5**, 37406-73-8; **6**, 22061-73-0; **8**, 37163-84-1; **10**, 37163-85-2; 3-thiolacetoxytricyclo[2.2.1.$0^{2,6}$]heptane, 37163-86-3.

Acknowledgment.—We wish to thank the National Science Foundation and the National Institutes of Health for their generous support of our program.

Aziridines. XXVI. Reactions of 1,3-Diazabicyclo[3.1.0]hex-3-enes

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The selective methylation and oxidation of 4-phenyl-6-*p*-nitrophenyl-3-diazabicyclo[3.1.0]hex-3-ene (**1a**) by trimethyloxonium tetrafluoroborate and *m*-chloroperbenzoic acid to form 2,2,3-trimethyl-4-phenyl-6-*p*-nitrophenyl-1-aza-3-azoniabicyclo[3.1.0]hex-3-ene tetrafluoroborate (**3**) and 2,2-dimethyl-4-phenyl-6-*p*-nitrophenyl-1,3-diazabicyclo[3.1.0]hex-3-ene 3-oxide (**11**), respectively, have been achieved. The addition of nucleophiles such as potassium cyanide and sodium borohydride to **3** as well as the reaction of **3** with diazomethane were studied. The cycloadditions of **11** to *N*-phenylmaleimide and diethyl azodicarboxylate were also investigated.

Three earlier papers in this series described the synthesis of the fused aziridines 1,3-diazabicyclo[3.1.0]hex-3-enes (**1**) and 1,4-diazabicyclo[4.1.0]hept-4-enes (**2**) and their thermal cycloadditions to alkenes, alkynes, and diethyl azodicarboxylate.[1-4] These thermal reactions of **1** and **2** were readily accounted for by carbon–carbon fission of the aziridine rings of **1** and **2** to form 1,3-dipolar intermediates (azomethine ylides) which subsequently added to the unsaturated substrates (Scheme I).

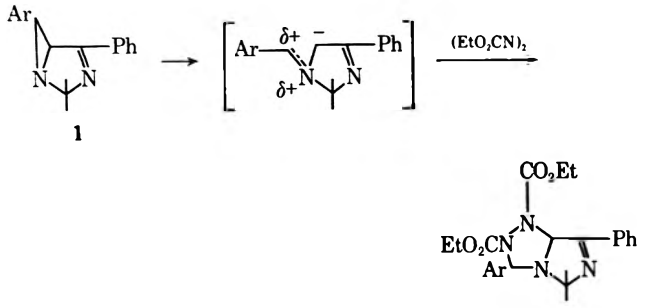
Recently the photolysis of **1** has been reported in detail[5-7] and the colored species produced have been identified also as 1,3 dipoles[7] which can be trapped with suitable 1,3 dipolarphiles.

The present paper describes the methylation and oxidation of **1** by trimethyloxonium tetrafluoroborate and *m*-chloroperbenzoic acid, respectively, and the chemical reactions of the resulting methylated and oxidized derivatives of **1**.

Treatment of a methylene chloride solution of 2,2-dimethyl-4-phenyl-6-*p*-nitrophenyl-1,3-diazabicyclo-

(1) H. W. Heine, R. W. Weese, R. A. Cooper, and A. J. Durbetaki, *J. Org. Chem.*, **32**, 2708 (1967).
(2) H. W. Heine, A. B. Smith III, and J. D. Bower, *ibid.*, **33**, 1097 (1968).
(3) H. W. Heine and R. P. Henzel, *ibid.*, **34**, 171 (1969).
(4) See also H. W. Heine, R. H. Weese, and R. A. Cooper, U. S. Patent 3,609,165 (Sept 28, 1971).
(5) A. Padwa, S. Clough, and E. Glazer, *J. Amer. Chem. Soc.*, **92**, 1778 (1970).
(6) T. DoMinh and A. M. Trozzolo, *ibid.*, **92**, 6997 (1970).
(7) T. DoMinh and A. M. Trozzolo, *ibid.*, **94**, 4046 (1972).

SCHEME I



[3.1.0]hex-3-ene (1a) with trimethyloxonium tetrafluoroborate formed compound **3** (Scheme II). That methylation had occurred at the N-3 position of **1a** was evident from the acid hydrolysis of **3** to the known *trans*-2-benzoyl-3-*p*-nitrophenylaziridine (**4**) and from the infrared spectrum of **3**, which exhibited a strong absorption band at 1631 cm^{-1} characteristic of ternary iminium salts.[8,9] Other evidence confirming the structure of **3** was the reactions of **3** with potassium cyanide to form **5** and with sodium borohydride to form **6**. These reactions are typical of ternary iminium salts.[10,11] Compound **6** was also obtained by treatment of **5** with sodium borohydride. The conversion of **5** to **6** is analogous to the reaction of 10-cyanoquinolizidine with lithium aluminum hydride to give quinolizidine.[11]

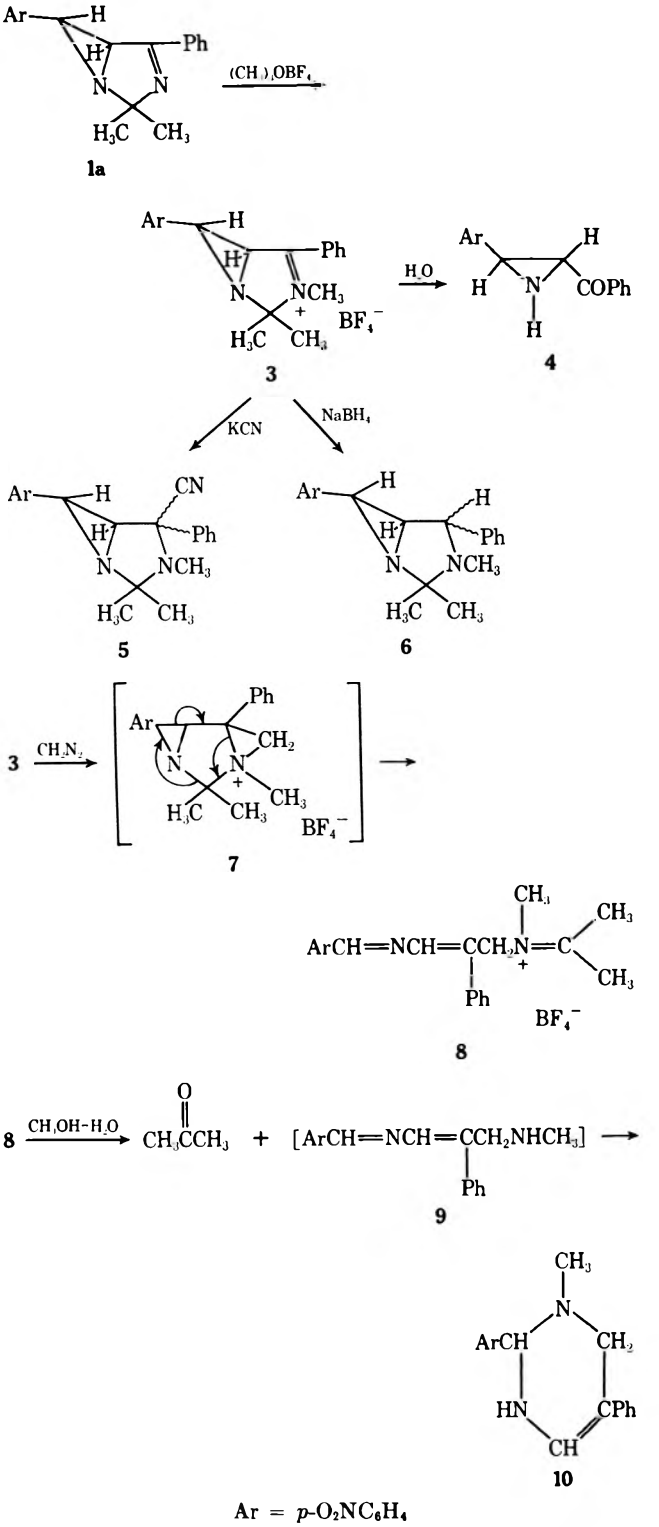
A most novel transformation occurred when **3** was treated with diazomethane. Compound **8** was formed, presumably through the intermediacy of the aziridinium ion **7** (Scheme II). An infrared spectrum of **8** exhibited a very broad absorption peak at approximately 1050 cm^{-1} which is characteristic of tetrafluoroborate salts and two absorption peaks at 1670 and 1598 cm^{-1} that were assigned to the iminium and imino groups, respectively. The nmr spectrum of **8** in CD_3CN at $-10°$ showed the typical splitting pattern of the *p*-nitrophenyl group at δ 8.20 (2 H) and 8.44 (2 H), the benzal proton as a singlet at 8.72, the vinylic proton and the phenyl protons coincidently absorbing as a single peak at 7.63 (6 H), the methylene group as a singlet at 5.58, the *N*-methyl moiety at 3.38, and the two remaining methyl groups as singlets at 2.67 and 2.43.

Compound **8** was further characterized by its hydrolysis in aqueous methanol to acetone (identified as a 2,4-dinitrophenylhydrazone) and **10**. The structure of **10** was confirmed by nmr and mass spectroscopy and by acid hydrolysis to *p*-nitrobenzaldehyde. The nmr spectrum of **10** established the presence of the XCH-NHCHY moiety and the absence of a benzal proton, signifying that the anticipated hydrolysis product of **8**, namely, **9**, spontaneously cyclized to **10** (Scheme II).

The suggested intermediacy of **7** in the reaction of **3** with diazomethane seems quite reasonable, since it is well known that addition of diazomethane to ternary iminium salts is a general method for the preparation of aziridinium salts.[12,13]

A benzene solution of **1a**, when treated with *m*-chloro-

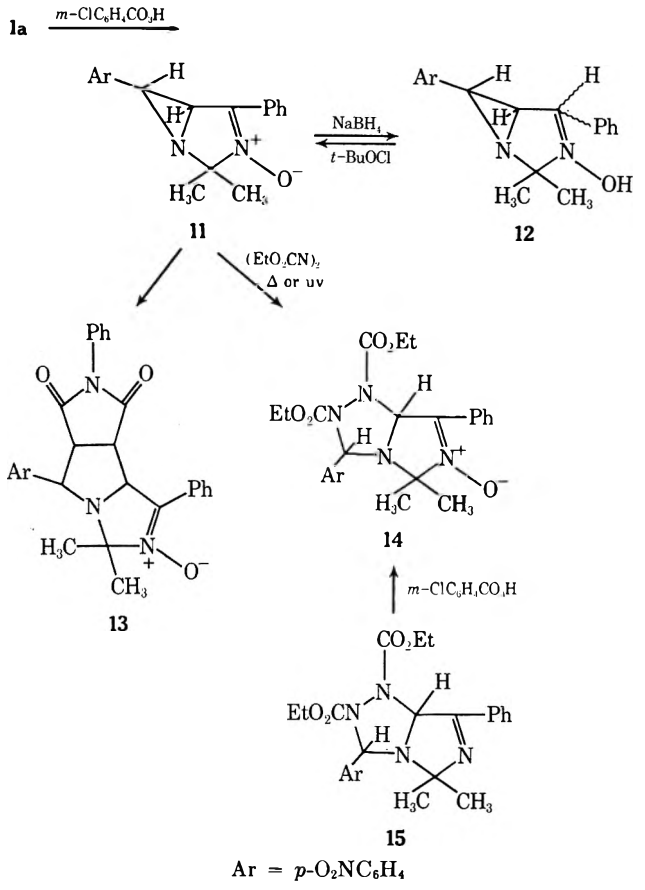
SCHEME II



perbenzoic acid at room temperature, gave the *N*-oxide **11** (Scheme III). The infrared spectrum of **11** exhibited strong absorption bands at 1250 cm^{-1}, the region that has been assigned to the N–O stretch of nitrones,[14] and at 1540 cm^{-1}, which is characteristic of nitrones such as Δ^1-pyrroline *N*-oxides.[14,15a,b] It was easy to reduce **11** with sodium borohydride to the *N*-

(8) N. J. Leonard and V. W. Gash, *J. Amer. Chem. Soc.*, **76**, 2781 (1954).
(9) N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 3021 (1963).
(10) N. J. Leonard, P. D. Thomas, and V. W. Gash, *J. Amer. Chem. Soc.*, **77**, 1552 (1955).
(11) N. J. Leonard and A. S. Hay, *ibid.*, **78**, 1984 (1956).
(12) N. J. Leonard and K. Jann, *ibid.*, **82**, 6418 (1960); **84**, 4806 (1962).
(13) N. J. Leonard, *Rec. Chem. Progr.*, **26**, 211 (1965).
(14) P. A. Smith and J. E. Robertson, *J. Amer. Chem. Soc.*, **84**, 1197 (1962).
(15) (a) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. J. Todd, *J. Chem. Soc.*, 2094 (1959); (b) M. C. Kloetzel, F. L. Chubb, R. Gobran, and J. L. Pinkus, *J. Amer. Chem. Soc.*, **83**, 1128 (1961).

SCHEME III



hydroxy compound **12** and to oxidize **12** to **11** with *tert*-butyl hypochlorite.

Compound **11**, like **1**, formed an azomethine ylide when heated. In refluxing toluene with *N*-phenylmaleimide and diethyl azodicarboxylate **11** gave the cycloadducts **13** and **14**, respectively. Interestingly, irradiation of a benzene solution of **11** and diethyl azodicarboxylate also gave **14** identical in all respects with **14** obtained from the thermolysis reaction. The structure of **14** was determined by elemental analyses and nmr spectroscopy and by an independent synthesis involving the oxidation of the known bicyclic compound **15**[2] with *m*-chloroperbenzoic acid. The nmr spectrum of **14** showed the two methine protons as singlets at δ 6.65 and 6.83, as would be expected if cleavage of the carbon–carbon bond of the aziridine ring of **11** had occurred in the reaction.

We have assigned a cis configuration to **14**. The starting aziridine **1a** had been shown earlier to have a trans configuration[1] and the same stereochemistry is present in **11**, since oxidation of the imino nitrogen should not alter the spatial relationship of the ring hydrogens. On the basis of orbital symmetry rules trans **11** would undergo conrotatory opening to a syn 1,3-dipolar intermediate. Capture of the syn 1,3 dipole by diethyl azodicarboxylate should yield *cis*-**14**. Huisgen and coworkers have verified conrotatory ring openings for other ground-state aziridine systems[16] and DoMinh and Trozzolo reported similar conclusions[7] for aziridine **1a**. It has also been observed that the thermal and photolytic cycloaddition of **1a** to TCNE or dimethyl acetylenedicarboxylate gave cycloadducts having identical stereochemistry. It was suggested that the photoinduced reaction involved electronically excited states which internally convert to vibrationally excited states.[7] Presumably a similar situation arises in the photolytic cycloaddition of **11** to diethyl azodicarboxylate, since both the thermal and photolytical processes yield identical **14**.

(16) R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.*, **89**, 1753 (1967).

Experimental Section

Compound 3.—To a stirred solution of 500 mg (1.62 mmol) of **1a** in 35 ml of anhydrous CH_2Cl_2 under nitrogen was added 250 mg of freshly prepared trimethyloxonium tetrafluoroborate. After 6 hr the reaction mixture was filtered to give 620 mg (93%) of crude **3**. Five recrystallizations from absolute ethanol gave **3**, mp 190–191°.

Anal. Calcd for $C_{19}H_{20}N_3O_2BF_4$: C, 55.77; H, 4.93; N, 10.27. Found: C, 55.50; H, 4.73; N, 10.16.

Conversion of 3 to 4.—A suspension of 300 mg (0.733 mmol) of **3** in 200 ml of Et_2O and 150 ml of H_2O was stirred for 8 hr. The ether layer was removed and dried over $MgSO_4$. The solvent was evaporated to give 105 mg (53%) of **4**.[1]

Reaction of 3 with KCN.—A suspension of 425 mg (1.03 mmol) of **3** in 10 ml of Et_2O was shaken vigorously with 500 mg of KCN in 20 ml of H_2O. The ether layer was washed with three 50-ml portions of H_2O and dried over $MgSO_4$. Evaporation of the ether layer gave 300 mg (84%) of **5**, which melted at 151–153° after three recrystallizations from hexane.

Anal. Calcd for $C_{20}H_{20}N_4O_2$: C, 68.97; H, 5.97; N, 16.08. Found: C, 69.17; H, 5.92; N, 15.94.

Reaction of 3 with $NaBH_4$.—A mixture of 920 mg (2.24 mmol) of **3** and 320 mg of $NaBH_4$ in 45 ml of absolute ethanol was stirred vigorously for several hours. The EtOH was evaporated and 50 ml of H_2O was added to the residue. The solution was neutralized with glacial acetic acid and then extracted with Et_2O. The ether layer was separated and dried over $MgSO_4$. The ether was evaporated and the yellow, oily residue was slurried with petroleum ether (bp 30–60°). The solvent was evaporated and fresh petroleum ether was added and evaporated. After this procedure was repeated several times 629 mg (87%) of **6** precipitated and was filtered. Recrystallization from petroleum ether gave **6** melting at 105–107°.

Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.86; H, 6.63; N, 13.23.

Conversion of 5 to 6.—To a solution of 820 mg (2.35 mmol) of **5** in 45 ml of absolute EtOH was added 320 mg of $NaBH_4$. The reaction mixture was stirred overnight and the solvent was evaporated. The residue was slurried with 50 ml of H_2O and the solution was neutralized with glacial acetic acid. The solution was extracted with Et_2O and the ether extract was dried. The Et_2O was evaporated and the 500 mg (66%) of **6** that was obtained was purified as described above.

Conversion of 3 to 8.—Employing the usual precautions involved in the preparation of diazomethane, a solution of 500 mg of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide in 20 ml of Et_2O was added to a 125-ml distilling flask that was connected to a condenser delivering into two receiving flasks in series and both cooled in ice. The first receiver contained a magnetic stirring rod and 10 ml of Et_2O and the second receiver contained 20 ml of ether and the inlet tube dips below the surface of the solvent. To the cooled solution was added 10 ml of 95% EtOH in which two pellets of KOH had previously been dissolved. The diazomethane was distilled and to the distillate was added 8 ml of CH_3CN containing 409 mg of **3**. Evolution of nitrogen occurred immediately. The reaction mixture was stirred for 1 hr. If no solid had precipitated, small portions (3–5 ml) of dry Et_2O were added to the mixture over a period of 0.5 hr. The crystalline **8** was filtered and purified by dissolving it in a minimum of acetone and reprecipitating it by the addition of dry Et_2O. Compound **8** was obtained in 48–73% yields and melted at 121–122°. It was placed in a desiccator and stored in a refrigerator.

Anal. Calcd for $C_{20}H_{22}BF_4N_3O_2$: C, 56.75; H, 5.25; N, 9.93. Found: C, 56.48; H, 5.39; N, 10.01.

Hydrolysis of 8.—To a well-stirred solution of 20 mg of NaOH in 8 ml of H_2O was suspended 200 mg of **8**. Methanol (6 ml) was immediately added, and the suspension was stirred overnight and then filtered to give 125 mg (90%) of **10**. The filtrate was added to 10 ml of a 1% ethanolic solution of 2,4-dinitro-

phenylhydrazine containing 100 mg of HCl and the mixture was refluxed overnight. Filtration gave 65 mg (55%) of acetone 2,4-dinitrophenylhydrazone, mp 122–124°

Compound 10 melted at 130–138°: molecular ion *m/e* 194; nmr (DMSO-d_6) δ 2.32 (s, 3, NCH_3), 3.23 (s, 2, CH_2), 4.88 (d, 1, -NCHN-), 6.27 (t, 1, NH), 7.00 (d, 1-CH=C-), 7.66 (d, 2, aromatic), 8.17 (d, 2, aromatic). Deuteration caused the peak at δ 6.27 to disappear and the peaks at 4.88 and 7.00 to become singlets.

Acid Hydrolysis of 10.—Compound 10 (125 mg) was suspended in a vigorously stirred solution of 10 ml of 10% HCl. The orange color of 10 gradually turned to a pale yellow or sometimes tan color. The reaction mixture was filtered to give 50 mg (78%) of *p*-nitrobenzaldehyde.

Conversion of 1a to 11.—To a solution of 540 mg (1.75 mmol) of 1a in 50 ml of C_6H_6 was added 1 g of 85% *m*-chloroperbenzoic acid. The mixture was kept at room temperature for 2 days and then it was washed several times with a saturated solution of Na_2CO_3. The benzene layer was dried and filtered. Evaporation of the C_6H_6 gave 260 mg (45%) of 11. Several recrystallizations from methanol gave 11, mp 161–163°.

Anal. Calcd for $C_{18}H_{17}N_3O_3$: C, 66.88; H, 5.30; N, 12.99. Found: C, 67.10; H, 5.30; N, 12.69.

Reduction of 11 to 12.—To 646 mg (1.99 mmol) of 11 in 40 ml of a 1:1 mixture of absolute ethanol and 2-propanol was added 1 g of $NaBH_4$. The reaction mixture was stirred at 40° overnight. The solvents were evaporated and water and $CHCl_3$ were added to the residue. The chloroform layer was separated and dried over $MgSO_4$. Evaporation of the $CHCl_3$ and recrystallization of the residue from CCl_4 gave 412 mg (60%) of 12, mp 165–166°.

Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.03; H, 5.68; N, 12.71.

Conversion of 12 to 11.—To a mixture of 108 mg of 12 in 30 ml of C_6H_6 was added 36 mg of *tert*-butyl hypochlorite. The reaction mixture was stirred for 15 min. The solvent was evaporated to give a 97% yield of 11.

Reaction of 11 with *N*-Phenylmaleimide.—A mixture of 270 mg (0.832 mmol) of 11 and 144 mg (0.831 mmol) of *N*-phenylmaleimide in 12 ml of dry toluene was refluxed for 2.5 hr. Evaporation of the solvent and recrystallization of the residue from 2-propanol gave 267 mg (65%) of 13, mp 257–259°.

Anal. Calcd for $C_{28}H_{24}N_4O_5$: C, 67.07; H, 4.97; N, 11.51. Found: C, 67.28; H, 5.01; N, 11.55.

Reaction of 11 with Diethyl Azodicarboxylate (Method A).—A mixture of 356 mg (1.10 mmol) of 11 and 187 mg (1.07 mmol) of diethyl azodicarboxylate in 12 ml of toluene was refluxed for 2 hr. Evaporation of the solvent and recrystallization from 1-propanol gave 422 mg (79%) of 14, mp 155–157°.

Anal. Calcd for $C_{24}H_{27}N_5O_7$: C, 57.93; H, 5.46; N, 14.06. Found: C, 57.98; H, 5.58; N, 14.08.

Conversion of 11 to 14 (Method B).—A mixture of 452 mg of 11 and 244 mg of diethyl azodicarboxylate in 150 ml of C_6H_6 was irradiated for 2 hr. Evaporation of the solvent and slurrying the residue in a small quantity of C_2H_5OH gave 447 mg of 14. The melting points and infrared spectra of 14 obtained by methods A and B were identical. A control run of 220 mg of 11 and 140 mg of diethyl azodicarboxylate was allowed to stand for 20 hr at room temperature. Evaporation of the solvent and slurrying the residue in EtOH resulted in the recovery of 183 mg of 11.

Oxidation of 15 to 14.—A mixture of 350 mg of 15 and 743 mg of 85% *m*-chloroperbenzoic acid in 15 ml of C_6H_6 was allowed to stand at room temperature for 15 hr. The benzene layer was washed twice with Na_2CO_3 solution and twice with H_2O and dried over $MgSO_4$. The C_6H_6 was evaporated and the glassy residue was slurried with a small quantity of EtOH. The EtOH was evaporated and a small quantity of EtOH was again added. Constant scratching of the walls of the container with a glass rod gave 62 mg of 14, mp 152–154°, having the same ir spectrum as 14 obtained from methods A and B above.

Registry No.—1a, 13591-65-6; 3, 37500-32-6; 5, 37488-69-0; 6, 37488-70-3; 8, 37488-71-4; 10, 37488-72-5; 11, 37528-70-4; 12, 37488-73-6; 13, 37488-74-7; 14, 37500-33-7; diazomethane, 334-88-3.

Acknowledgment.—We thank Drs. William Vanden-Heuvel and Byron A. Arison for discussions on the mass spectrum and nmr spectrum of compound 11 and Dr. Anthony Trozzolo for some stimulating conversations. Acknowledgment is made to the National Institutes of Health for Grant CA-10015.

Polycyclic Aziridines. 1-Alkyl-6-keto-1,1a,6,6a-tetrahydro-1a-phenylindeno[1,2-*b*]azirines

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A previously reported investigation[2b] of the reaction of 2,3-dibromo-3-phenylindanone with cyclohexyl and methyl amines, respectively, to form 1-alkyl-6-(alkylimino)-1,1a,6,6a-tetrahydro-1a-phenylindeno[1,2-*b*]-azirines (3) has been extended to include similar reactions with other primary amines. Schiff base formation in this series is catalyzed by the presence of the amine hydrobromide salt. Hydrolysis of the Schiff bases to the previously unknown tricyclic aziridinyl ketones (8) can be accomplished on a silica gel column. The aziridinyl ketones undergo thermal valence tautomerism and yield 1,3-dipolar cycloaddition products similar to those observed with the analogous Schiff bases.

The reactions of the bromine derivatives of cyclic α,β-unsaturated ketones with primary and secondary amines have been the subjects of previous investigations in this laboratory.[1] Aziridinyl ketones are the usual products when primary amines are employed. It has been shown that 2,3-dibromo-3-phenylindanone (1) and 2-bromo-3-phenylindenone (2) react with cyclohexyl or methyl amine to give the Schiff base derivative (3a,b) of the expected aziridinyl ketone.[2] Previous attempts to obtain the aziridinyl ketone from its Schiff base by partial hydrolysis have resulted in ring opening and formation of either the diketone 4 or the α-aminoindenone 5.[2b]

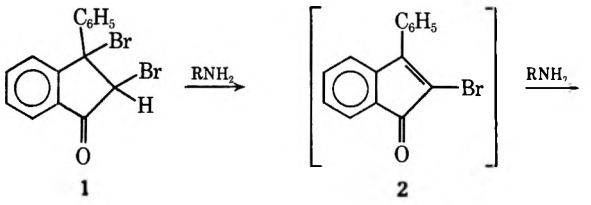
This paper reports the characterization of additional aziridinyl Schiff bases in the 3-phenylindenone-1 system and an unexpectedly simple method of obtaining the corresponding aziridinyl ketones.

(1) (a) N. H. Cromwell and R. D. Campbell, *J. Org. Chem.*, **22**, 520 (1957), and previous papers in the series; (b) A. Hassner and N. H. Cromwell, *J. Amer. Chem. Soc.*, **80**, 901 (1958); (c) E. M. Wu, Ph.D. Thesis, University of Nebraska, 1966; (d) B. D. Pearson, R. P. Ayer, and N. H. Cromwell, *J. Org. Chem.*, **27**, 3038 (1962).

(2) (a) A. E. Pohland, M. C. McMaster, R. C. Badger, and N. H. Cromwell, *J. Amer. Chem. Soc.*, **87**, 2510 (1965); (b) N. H. Cromwell and M. C. McMaster, *J. Org. Chem.*, **32**, 2145 (1967).

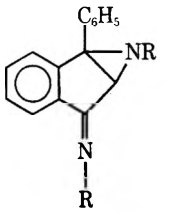
Results and Discussion

Schiff Base Formation.—2,3-Dibromo-3-phenylindanone (1) reacts readily at room temperature with benzyl, cyclohexyl,[2b] ethyl, isopropyl, and methyl[2b] amines to yield the appropriate 1-alkyl-6-(alkylimino)1,1a,-6,6a-tetrahydro-1a-phenylindeno[1,2-*b*]azirines (**3a–e**). All except the ethyl derivative have been obtained as white or nearly white crystalline solids by direct or fractional crystallization from benzene–petroleum ether (bp 60–70°) solutions. The ethyl derivative has been obtained only as a yellow-orange colored oil, identified through ample spectral and chemical evidence. Reaction of **1** with *tert*-butylamine resulted only in dehydrohalogenation to 2-bromo-3-phenylindenone (**2**). No trace of the anticipated Schiff base or of any aziridine was detected in the *tert*-butylamine reaction mixture, even when elevated temperatures, excessive amounts of the amine, or sealed tube techniques were employed. This must be attributed to the steric bulk of the *tert*-butyl group, particularly in light of the fact that benzylamine, a weaker base, did react readily to produce an aziridinyl Schiff base.



1 2

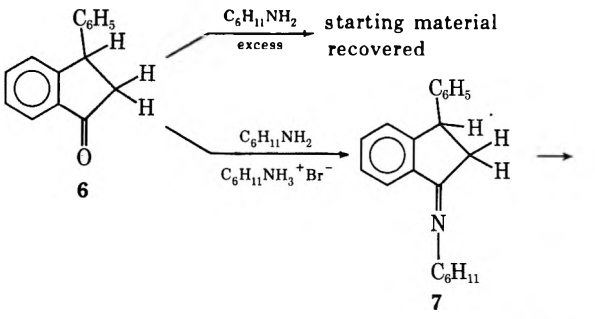
a, R = C_6H_{11}
b, R = CH_3
c, R = CH_2CH_2
d, R = $CH(CH_3)_2$
e, R = $CH_2C_6H_5$



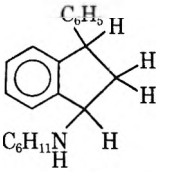
3

Identification of these aziridine systems is simplified by the characteristic medium to intense C=N absorption in the infrared spectrum near 1660 cm^{-1}. Integration of the pmr spectrum clearly indicates the presence of two alkyl groups. The presence of the aziridine ring is revealed by a characteristic singlet due to the bridgehead proton at τ 6.8. Mass spectral and ultraviolet data are in all cases consistent with the reported structures. Further evidence for the established structural assignments is provided by the hydrolysis of **3** to the diketone **4** using concentrated sulfuric acid.

The above reaction proceeds *via* dehydrohalogenation of the dibromide to the α-bromo-α,β-unsaturated ketone, which then undergoes addition of the amine to form the α-bromo-β-amino ketone.[2b] In the case of primary amines, ring closure to form the aziridine ring with loss of HBr can occur. The sequential step of Schiff base formation remains uncertain, but experiments indicate that it occurs after the initial dehydrohalogenation of the dibromide. Formation of the Schiff base is catalyzed by the presence of the amine hydrobromide salt in the reaction mixture. The reaction of 3-phenylindanone-1 (**6**) with cyclohexylamine resulted in 90% recovery of unreacted starting material, whereas the same reaction run in the presence of cyclohexylamine hydrobromide gave a 71% yield of the Schiff base, 1-cyclohexylimino-3-phenylindan (**7**). Thus the hydrobromide salt appears necessary for Schiff base formation to proceed. This is further supported by the fact that nearly quantitative yields of the 2-bromo-3-phenylindenone can be recovered immediately following addition of the amine to the dibromide solution, with no evidence for the existence of either the Schiff base or the aziridine in the reaction mixture.

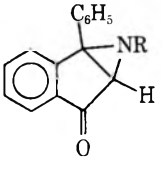


6 7

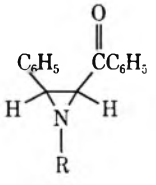


11

Hydrolysis.—During the course of study of this new aziridinyl Schiff base system, it was desired to obtain the corresponding ketones **8** for comparison with their acyclic analogs **9**, to see whether they might be involved in the reported rearrangement of *cis*-1-cyclohexyl-2-phenyl-3-benzoylethylenimine to 2-cyclohexylamino-3-phenylindenone (**5a**).[2a]



8

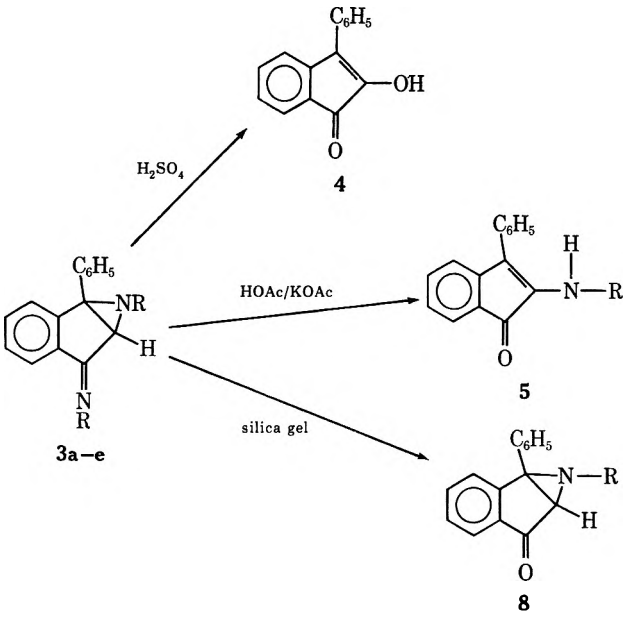


9

Methods which may be used for the hydrolysis of the imino group are severely limited by the reactivity and facile opening of the aziridine ring and the ability of the system to undergo a valence tautomerism to an isoquinolinium imine[3] at elevated temperatures. In addition, the Schiff base seems to exhibit a marked degree of stability not always associated with imines, owing to conjugation with the phenyl ring of the indanone system.[4]

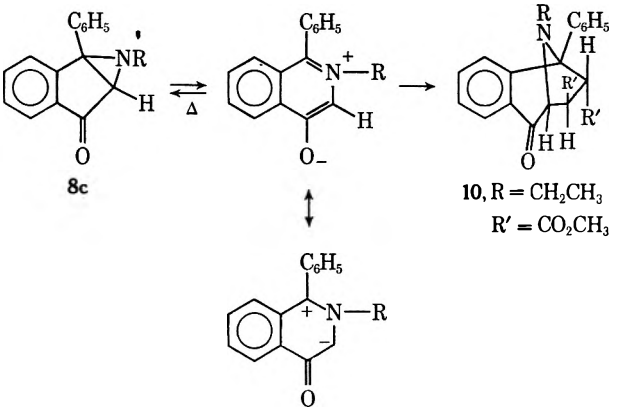
The equilibrium involving Schiff base formation for the indanone system lies almost completely to the side of the imine, and attempts to force the reaction in the reverse direction were initially unsuccessful. Schiff base **3a** would not react with water either with or without the presence of the amine hydrobromide salt to yield any trace of the ketone. Acid hydrolysis had already been shown to lead to other products.[2b]

(3) (a) J. W. Lown and K. Matsumoto, *Chem. Commun.*, 692 (1970); (b) *J. Org. Chem.*, **36**, 1405 (1971).
(4) J. Lown and K. Matsumoto, *Can. J. Chem.*, **49**, 3443 (1971).



When attempts to crystallize the ethyl derivative **3c** from its reaction mixture were unsuccessful, column chromatography on silica gel produced a nearly quantitative conversion of the aziridinyl Schiff base to the corresponding aziridinyl ketone (**8c**, R = Et). The cyclohexyl, methyl, and ethyl aziridinyl ketones (**8a–c**), crystallized from methanol–water, have been obtained as solids to date from the hydrolysis of the corresponding Schiff bases on silica gel columns. This class of ketones is characterized by great instability to air and light, turning from colorless to pale yellow during attempts at recrystallization, or upon standing at room temperature. The structural assignments are supported by ir, pmr, mass, and uv spectroscopy. Hydrolysis on silica gel columns may provide a new method for the hydrolysis of Schiff bases in the presence of other reactive functional groups. The pmr spectra are nearly identical with those of the Schiff bases, except for the absence of one alkyl group and slight shifts in the positions of the bridgehead proton. Nitrogen inversion was observed at room temperature for the methyl aziridinyl ketone **8b**. Nitrogen inversion was not observed in the corresponding Schiff base **3b**, suggesting that the presence of the imino alkyl group may, through steric hindrance, lock the *N*-alkyl group of the aziridine into a preferred conformation. Further evidence for the assigned structures is provided by hydrolysis to the diketone **4** with concentrated sulfuric acid. Column chromatography on alumina gave similar results, although with lesser efficiency.

Valence Tautomerism.—Lown and Matsumoto have reported the thermally disallowed valence tautomerization of the iminoaziridines to isoquinolinium imines[3] and an analogous tautomerism for the isoelectronic epoxyindanone system.[4] We wish to report that our new ethyl aziridinyl ketone **8c** also undergoes a thermally disallowed valence tautomerization, as shown by trapping of the carbonyl ylide in a 1,3-dipolar cycloaddition with dimethylfumarate. A mixture of isomers is obtained in which the endo product **10** appears to predominate. Further studies are underway to establish the course of similar cycloadditions to the valence tautomer. The intermediate qualifies as an *azomethine ylide* 1,3 dipole without a double bond but with internal octet stabilization.[5]



The reduction of the C=N bond in 1-cyclohexylimino-3-phenylindan (**7**) to 1-cyclohexylamino-3-phenylindan (**11**) with sodium borohydride was readily accomplished, but a similar reaction attempt with the aziridinyl Schiff base **3a** gave an impure product.

Experimental Section[6]

3,3-Diphenylpropionic Acid.[7]—3,3-Diphenylpropionic acid was prepared in 98% yield according to the method of Pfeiffer and de Waal.

3-Phenyl-1-indanone.[8]—3-Phenyl-1-indanone was prepared by the method of Kohler in 92% yield.

2,3-Dibromo-3-phenylindanone[9] **(1).**—2,3-Dibromo-3-phenylindanone was prepared in 92% yield according to the method of Weisz and Luft.

1-Cyclohexyl-6-(cyclohexylimino)-1,1a,6,6a-tetrahydro-1a-phenylindeno[1,2-*b*]azirine (3a).[2b]—This compound was prepared as described by Cromwell and McMaster.

1-Methyl-6-(methylimino)-1,1a,6,6a-tetrahydro-1a-phenylindeno[1,2-*b*]azirine (3b).[2b]—This compound was prepared as described by Cromwell and McMaster.

1-Ethyl-6-(ethylimino)-1,1a,6,6a-tetrahydro-1a-phenylindeno-[1,2-*b*]azirine (3c).—A 5-g (0.0137 mol) sample of the dibromo ketone **1** was dissolved in 75 ml of dry ether, to which was added 4.5 ml (0.0685 mol) of $EtNH_2$. After 3 days of stirring in a foil-wrapped flask at room temperature, 3.30 g (96.3%) of ethylamine hydrobromide was filtered from the solution. The filtrate was washed with water and dried over $CaSO_4$, and solvent was evaporated to leave a brown-orange colored oil which could be neither decolorized with charcoal nor crystallized: $\nu_{C=N}^{CCl_4}$ 1660 cm^{-1}; pmr τ 2.23–2.93 (9 H, aromatic multiplet), 6.12–6.76 (2 H, $=NCH_2$ multiplet), 6.81 (1 H, bridgehead singlet), 7.43–8.18 (2 H, aziridine NCH_2 multiplet), and 8.54–9.09 (6 H, two CH_3 groups, overlapping triplets).

1-Isopropyl-6-(isopropylimino)-1,1a,6,6a-tetrahydro-1a-phenylindeno[1,2-*b*]azirine (3d).—A 5-g (0.0137 mol) sample of the dibromo ketone **1** was dissolved in 50 ml of dry benzene, to which was added 6 ml (0.704 mol) of isopropylamine. After 3 days of stirring in a foil-wrapped flask at room temperature, 125 ml of dry ether was added to precipitate 3.5 g (91.2%) of the isopropylamine hydrobromide, mp 162–164°. Filtration gave a brown-colored solution, which was washed with water and dried over $CaCl_2$, and the solvent was evaporated to leave a brown, sticky oil which crystallized after standing in the freezer for 2 days with occasional stirring. Recrystallization from petroleum ether (bp 60–70°) gave 3.0 g of **3d** (72.0%) as a white, crystalline solid:

(5) (a) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963); (b) P. B. Woller and N. H. Cromwell, *J. Org. Chem.*, **35**, 888 (1970).

(6) Infrared spectra were obtained in carbon tetrachloride solutions using a Perkin-Elmer 237 instrument, unless otherwise noted. Pmr spectra were obtained using a Varian A-60 instrument. Ultraviolet spectra were obtained in isooctane using a Cary 14 spectrophotometer. Melting points were determined using the Mel-Temp apparatus.

(7) P. Pfeiffer and H. L. de Waal, *Justus Liebigs Ann. Chem.*, **520**, 185 (1935).

(8) E. P. Kohler, *Amer. Chem. J.*, **31**, 649 (1904).

(9) R. Weisz and S. Luft, *Monatsh. Chem.*, **48**, 338 (1927).

mp 91–92°; molecular ion *m/e* 304; ir $\nu_{C=N}^{CCl_4}$ 1646 cm^{-1}; uv λ_{max} 252 mμ (ε 19,500); pmr τ 2.14–2.86 (9 H, aromatic multiplet), 5.71–6.29 (1 H, C=NCH), 6.80 (1 H, singlet, bridgehead), 7.68–8.38 (1 H, aziridinyl methine multiplet), and 8.62–9.22 (12 H, multiplet of overlapping doublets from 4 CH_3).

Anal. Calcd for $C_{21}H_{24}N_2$: C, 82.89; H, 7.96; N, 9.21. Found: C, 82.87; H, 7.60; N, 9.51.

1-Benzyl-6-(benzylimino)-1,1a,6,6a-tetrahydro-1a-phenylindeno[1,2-*b*]azirine (3e).—A 5-g (0.0137 mol) sample of the dibromoindanone 1 was dissolved in 30 ml of dry benzene, to which was added 8 ml (0.0720 mol) of benzylamine. After stirring for 3 days in the dark at room temperature, 100 ml of dry ether was added and 4.8 g (93.3%) of benzylamine hydrobromide was filtered off, mp 204–210°. After washing with water, drying over $CaCl_2$, and solvent removal, a brown oil remained which was crystallized from benzene–petroleum ether to yield 2.32 g (42.4%) of **3e**: mp 88–89°; ir $\nu_{C=N}^{CCl_4}$ 1659 cm^{-1}; uv λ_{max} 254 mμ (ε 14,400); pmr τ 1.84–2.86 (19 H, aromatic multiplet), 5.10–5.25 (2 H, C=NCH$_2$–), 6.37–6.66 (2 H, aziridinyl methylene), and 6.60 (1 H, bridgehead).

Anal. Calcd for $C_{29}H_{24}N_2$: C, 86.97; H, 6.04; N, 7.00. Found: C, 87.14; H, 6.06; N, 7.08.

Reaction of 1 with *tert*-Butylamine.—A 3-g (0.00820 mol) sample of the dibromoindanone 1 was dissolved in 11.7 ml of dry benzene to which 4.25 ml (0.0406 mol) of *tert*-butylamine was added. After stirring in the dark at room temperature for 23 days, addition of 50 ml of anhydrous ether precipitated 1.26 g of *tert*-butylamine hydrobromide (99.8% yield for removal of only one bromine atom). The filtrate was washed with water and dried over $CaSO_4$, and solvent was removed to yield 1.80 g (77%) of 2-bromo-3-phenylindenone (**2**), mp 113–114° after recrystallization from MeOH.

This same reaction, attempted with larger excesses of amine, at elevated temperatures, and in a sealed tube resulted in similarly high yields of the same product.

Reaction of 1 with Ammonia.—A 5-g (0.0137 mol) sample of the dibromo-3-phenylindanone 1 was dissolved in 300 ml of anhydrous ether and saturated with NH_3 gas. After stirring for 5 days in the dark at room temperature, 1.2 g of ammonium bromide was filtered from the reaction mixture (89% yield for removal of only one Br atom). Solvent removal left 3.20 g (81.8%) of 2-bromo-3-phenylindenone (**2**), mp 113–114° after recrystallization from MeOH.

1-Cyclohexylimino-3-phenylindan (7).—A 16-g (0.0769 mol) sample of 3-phenylindanone-1 (**6**), 17.6 ml (0.1538 mol) of cyclohexylamine, and 13.8 g (0.0769 mol) of cyclohexylamine hydrobromide were placed in 160 ml of dry benzene and allowed to stir at room temperature in the dark for 4 days. Addition of 480 ml of dry ether precipitated 98.9% of the hydrobromide salt. After filtration and solvent removal, the Schiff base **7** was crystallized from *n*-hexane to yield 15.8 g (71.1%): mp 97–98°; $\nu_{C=N}^{CDCl_3}$ 1648 cm^{-1}; pmr τ 2.17–3.19 (9 H, aromatic multiplet), 5.49–5.75 (1 H, methylene quartet), 6.50–7.55 (2 H, methylene multiplet), and 8.00–9.17 (11 H, cyclohexyl multiplet); uv λ_{max} 248 mμ (ε 17,510), 279.5 (34,800), 287 (46,800), and 297 (43,900).

Anal. Calcd for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.84. Found: C, 87.00; H, 8.06; N, 4.79.

An identical control experiment in which the cyclohexylamine hydrobromide was not included in the reaction mixture resulted in 90% recovery of unreacted starting materials.

Attempted Reaction of 3a with Water.—A 0.1-g (0.00261 mol) sample of **3a** and 0.096 g (0.00051 mol) of cyclohexylamine hydrobromide were dissolved in a mixture of 20 ml of benzene, 10 ml of ether, and 1 ml of water and stirred in the dark at room temperature for 2 days. The reaction was diluted with 50 ml of ether, washed three times with 25-ml portions of water, and dried over $CaCl_2$. Solvent removal left a yellow oil, recrystallized from petroleum ether to yield 95% of unreacted starting material **3a**. The infrared spectrum of the yellow oil was superimposable on that of the starting material, with only an extremely weak C=O absorption. An identical experiment, conducted without the cyclohexylamine hydrobromide, gave the same results.

1-Ethyl-6-keto-1,1a,6,6a-tetrahydro-1a-phenylindeno[1,2-*b*]azirine (8c).—A 3.78-g (0.0137 mol) sample of **3c** was placed on a silica gel column and eluted with successively increasing portions of ether in petroleum ether. A 3.31-g (0.0133 mol) sample of **8c** was obtained (97% yield) as a colorless oil which rapidly turned yellow on exposure to air and light. Recrystallization from MeOH–H_2O gave a pale yellow solid: mp 57–58°; ir $\nu_{C=O}^{CCl_4}$ 1721 cm^{-1}; mass spectrum molecular ion *m/e* 249; pmr τ 2.33–3.00 (9 H, aromatic multiplet), 7.02 (1 H, singlet, bridgehead), 7.17–7.83 (2 H, methylene multiplet), and 8.72–9.13 (3 H, methyl triplet); uv λ_{max} 229 mμ (ε 18,800), 240 (14,400), and 270–280 (3200–2240).

Anal. Calcd for $C_{17}H_{15}NO$: C, 81.89; H, 6.06; N, 5.62. Found: C, 81.87; H, 6.10; N, 5.59.

Hydrolysis of 8c.—A 1.0-g (0.00402 mol) sample of **8c** was dissolved in 50 ml of concentrated H_2SO_4 to give a dark red-brown solution, which was poured into 400 ml of water at 70° and allowed to stir overnight. Filtration yielded 0.73 g (0.00330 mol) of 2-hydroxy-3-phenylindenone (**4**) as a red-brown solid, mp 140–144° (82%). The infrared spectrum was superimposable on that for an authentic sample of the diketone.[10]

1-Cyclohexyl-6-keto-1,1a-6,6a-tetrahydro-1a-phenylindeno-[1,2-*b*]azirine (8a).—A 0.118-g (0.00307 mol) sample of **3a** was placed on a silica gel column and eluted with successively increasing portions of ether in petroleum ether. The product **8a** was obtained as 0.088 g (95%) of a colorless oil which rapidly turned yellow on exposure to air or light. Crystallization from MeOH–H_2O gave a pale yellow solid: mp 103–105°; ir $\nu_{C=O}^{CCl_4}$ 1710 cm^{-1}; mass spectrum molecular ion *m/e* 303; pmr τ 2.27–2.90 (9 H, aromatic multiplet), 7.05 (1 H, bridgehead singlet), and 7.88–9.35 (11 H, cyclohexyl multiplet).

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.00; H, 7.44; N, 4.26.

1-Methyl-6-keto-1,1a,6,6a-tetrahydro-1a-phenylindeno[1,2-*b*]-azirine (8b).—A 0.512-g (0.00207 mol) sample of **3b** was placed on a silica gel column and eluted with successively increasing portions of ether in petroleum ether. The product **8b** was obtained as 0.292 g (60%) of a colorless oil which rapidly turned yellow on exposure to air or light. Crystallization from MeOH–H_2O gave a white solid: mp 109–110°; ir $\nu_{C=O}^{CCl_4}$ 1718 cm^{-1}; mass spectrum molecular ion *m/e* 235; pmr τ 2.17–2.76 (9 H, aromatic multiplet), 6.95 (1 H, bridgehead singlet), and 7.70 (3 H, methyl protons, doublet at room temperature due to nitrogen inversion, singlet upon heating).

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 82.00; H, 5.51; N, 5.78.

Hydrolysis of 8a and 8b.—Compounds **8a** and **8b** were hydrolyzed to **4** in the same manner as **8c** above.

Thermal Valence Tautomerism and Dipolar Cycloaddition to 8c.—A 3-g (0.00121 mol) sample of **8c**, 0.174 g (0.00121 mol) of dimethyl fumarate, and 10 ml of dry toluene were placed in a sealed tube under a nitrogen atmosphere and heated to 135° (oil bath) for 12 hr. Solvent removal, followed by trituration with petroleum ether, gave a purple colorled solution and a brown colored gum, separated by decantation. Solvent removal gave a purple colored gum which was crystallized from MeOH–H_2O to yield 0.1035 g (21.8%) of the dipolar cycloaddition product **10**: mp 110–111°; $\nu_{C=O}^{CDCl_3}$ 1740–1680 cm^{-1} (unresolved); mass spectrum molecular ion *m/e* 393; pmr τ 2.17–3.48 (9 H, aromatic), 5.33–5.57 (2 H), 6.19 (3 H), 6.56 (3 H), 6.19–6.56 (1 H), 7.72–7.95 (2 H), and 9.0–9.21 (3 H).

Anal. Calcd for $C_{23}H_{23}NO_5$: C, 70.20; H, 5.75; N, 3.57. Found: C, 70.40; H, 5.85; N, 3.73.

1-Cyclohexylamino-3-phenylindan (11).—A 1.5-g (0.00519 mol) sample of **7** was dissolved in 50 ml of dry EtOH and allowed to stir in the dark at room temperature with 0.2 g (0.00529 mol) of $NaBH_4$. After stirring for 3.75 hr, a large amount of a white flocculent precipitate had formed and effervescence had ceased. The mixture was poured into 50 ml of ice water, extracted with 250 ml of ether (in three portions), and washed with two 50-ml portions of water, and the ether layer was dried over $CaSO_4$. Solvent removal left 0.879 g (59%) of a white solid, recrystallized from benzene–petroleum ether: mp 116–117.5°; ir 3450 cm^{-1} (weak, NH, very broad), no C=O or C=N bands present; mass spectrum, parent ion *m/e* 291; pmr τ 2.50–3.16 (9 H, aromatic multiplet), 5.49–6.04 (2 H, multiplet), 6.76–7.50 (2 H, multiplet), and 7.83–9.17 (12 H, multiplet).

Anal. Calcd for $C_{21}H_{25}N$: C, 86.59; H, 8.59; N, 4.81. Found: C, 86.58; H, 8.93; N, 4.74.

Registry No.—**1**, 37528-66-8; **2**, 19772-61-3; **3a**, 1981-53-9; **3b**, 13118-16-6; **3c**, 37528-67-9; **3d**, 37666-

(10) C. F. Koelsch, *J. Amer. Chem. Soc.*, **58**, 1321 (1936).

06-1; 3e, 37528-68-0; 4, 1713-37-7; 6, 16618-72-7; 7, 37488-35-0; 8a, 37488-36-1; 8b, 37488-37-2; 8c, 37488-38-3; 10, 37500-24-6; 11, 37488-39-4; isopropylamine hydrobromide, 29552-58-7; benzylamine hydrobromide, 37488-40-7.

Acknowledgment.—This work was supported in part by Grant CA-02931 from the National Cancer Institute of the U. S. Public Health Service and by a grant from the Damon Runyon Memorial Fund for Cancer Research.

Ionization in Liquid Ammonia of Methyl and Amino Groups Bonded to Pyridine and Pyrazine. A Method of Determining Their pK_a Values[1]

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Proton magnetic resonance spectra of ionized 2-methyl and 2-amino derivatives of pyridine and pyrazine along with spectra of 2-pyridone and 2-pyrazinone in liquid ammonia are reported. Changes in chemical shifts produced by ionization of the pyridines are linearly related to those for the pyrazines. Competition experiments show that 2-methyl- is less acidic than 4-methylpyridine; estimates of the pK_a values for these two acids are given. It is suggested that the results provide a basis for determining the equilibrium acidities of weak heterocyclic acids.

The acidities of heterocyclic molecules containing carbon or nitrogen side chains having pK_a values >20 are largely undetermined.[3,4] Liquid ammonia is an attractive solvent for the determination of pK_a values of these weak acids. Ammonia has long been used to study the kinetic acidities of weak acids, both carbocyclic and heterocyclic.[3,7] Its very low self-ionization constant (pK = 32.5 at −33°)[8] allows high concentrations of the conjugate bases of the weak acids to be formed. The recent determination of pK_a values for a few carbocyclic nitrogen and carbon acids in ammonia by means of potentiometry, nmr, and ultraviolet spectroscopy[9] encouraged us to study weak heterocyclic acids.

We have found nmr to be a useful way to study the ionization of pyridines and pyrazines in ammonia and report results dealing with the ionization of methyl and amino groups bonded to these heterocyclic rings. That simple ionization takes place in the presence of amide ion was established by consideration of nmr spectra and by a correlation involving changes in chemical shifts resulting from the deprotonation of these weak acids and the more readily ionizable compounds 2-pyridone and 2-pyrazinone.[10] Our results pave the way for the determination of pK_a values for these and many more weakly acidic heterocyclic molecules in ammonia. They also provide the first reliable estimates of the pK_a values for 2- and 4-methylpyridines.

Results and Discussion

Pyridines.—Addition of 2-methylpyridine to an excess of KNH_2 in ammonia gives a highly colored solution. Its nmr spectrum shows at −40° no evidence of unreacted starting material or any other component in addition to ionized substrate. Chemical shifts and coupling constants are given in Table I. The ring protons of the anion are shielded by 1.6, 1.7, 2.3, and 1.3 ppm for the 3, 4, 5, and 6 positions, respectively, relative to the starting carbon acid in ammonia. The methylene group shows a clear AB pair of doublets at −40°, τ 7.4 and 7.55 (J = 3.2 Hz). These shifts are very similar to that of the methyl group, τ 7.5. No change in the spectrum could be detected after the sample stood for 1 week at room temperature, indicating a surprising stability. The large shielding values and the nonequivalent methylene protons indicate that a largely ionic compound is formed;[13] charge delocalization into the ring leads to double-bond character and restricted rotation about the methylene–ring bond. When the carbon acid is incompletely neutralized, signals for both the acid and its conjugate base are present. There is no evidence of signal averaging. This is to be expected.[16]

The nmr spectrum of this 2-pyridylmethylpotassium in ammonia is very similar to that of 2-pyridylmethyllithium in tetrahydrofuran.[17] The shielding of ring and methylene protons of the sample in ammonia is no greater than 12 Hz; coupling constants for ring protons

(1) Presented in part at the Gordon Conference on Heterocyclic Chemistry, New Hampton, N. H., June 26–30, 1972.

(2) To whom correspondence should be addressed.

(3) N. N. Zatsepina, A. V. Kirova, and I. F. Tupitsyn, *Org. Reactiv. (USSR)*, **5**, 70 (1968).

(4) In marked contrast, considerable effort has been applied to the determination of pK_a values for weakly acidic aromatic hydrocarbons.[5,6]

(5) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965; A. Streitwieser, Jr., and J. H. Hammons, *Progr. Phys. Org. Chem.*, **3**, 41 (1965).

(6) H. Fischer and D. Rewicki, *Progr. Org. Chem.*, **7**, 116 (1967).

(7) A. I. Shatenshtein and I. O. Shapiro, *Russ. Chem. Rev.*, **37**, 845 (1968); A. I. Shatenshtein, *Advan. Phys. Org. Chem.*, **1**, 156 (1963); *Tetrahedron*, **18**, 95 (1962); N. N. Zatsepina, I. F. Tupitsyn, A. V. Kirova, and A. I. Belyashova, *Org. Reactiv. (USSR)*, **8**, 787 (1971).

(8) L. V. Coulter, J. R. Sinclair, A. G. Cole, and G. C. Roper, *J. Amer. Chem. Soc.*, **81**, 2986 (1959).

(9) J. J. Lagowski, *Pure Appl. Chem.*, **25**, 429 (1971).

(10) Anions of the type considered here can be trapped by electrophiles in ammonia; the reactions are of preparative value.[11,12]

(11) H. C. Brown and W. A. Murphy, *J. Amer. Chem. Soc.*, **73**, 3308 (1951).

(12) W. Schwaiger and J. P. Ward, *Recl. Trav. Chim. Pays-Bas*, **90**, 513 (1971); S. V. Kannan and H. Pines, *J. Org. Chem.*, **36**, 2304 (1971); G. W. H. Cheeseman and E. S. G. Werstiuk, *Advan. Heterocycl. Chem.*, **14**, 99 (1972).

(13) It is expected that ion pairing will be important in ammonia for this and the other compounds considered here.[9,14,15] Hence, pK_a values are ion-pair values.[6]

(14) M. Fisher and M. Szwarc, *Macromolecules*, **3**, 23 (1970); M. Schlosser, *Angew. Chem., Int. Ed. Engl.*, **3**, 287 (1964); "Ions and Ion Pairs in Organic Reactions," Vol. 1, M. Szwarc, Ed., Wiley-Interscience, New York, N. Y., 1972.

(15) J. H. Takemoto and J. J. Lagowski, *J. Amer. Chem. Soc.*, **91**, 3785 (1969).

(16) T. Birchall and W. L. Jolly, *ibid.*, **87**, 3007 (1965).

(17) K. Konishi, K. Takahashi, and R. Asami, *Bull. Chem. Soc. Jap.*, **44**, 2281 (1971).

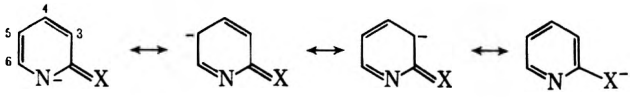
TABLE I
CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR IONIZED 2-SUBSTITUTED PYRIDINES IN AMMONIA

X	3	4	5	6	J, Hz 3,4	3,5	3,6	4,5	4,6	5,6
I, CH_2	4.51	3.93	5.23	3.00	9.0	1.3	1.0	6.0	2.0	4.8
NH	4.24	3.34	4.54	2.55	8.5	1.5	1.0	6.5	2.0	5.0
O	3.98	2.89	4.03	2.26	8.5	1.2	1.0	6.5	2.5	5.0

differ by less than 0.7 Hz. (The methylene group was said to be broad.[17]) Because the material in ammonia is largely ionic and because the spectra of the two salts in the two solvents are so similar, it seems likely that the lithium compound also is largely ionic.

The nmr spectra of ionized 2-aminopyridine and 2-pyridone in ammonia also were obtained. Since 2-methylpyridine is completely ionized by an excess of amide ions, the more acidic amino and oxy compounds also must undergo total ionization in the presence of excess amide ions. Again, deprotonation brings about shielding of the ring protons but shielding factors are smaller than those for methyl group ionization, being in the range 0.3–1.1 ppm. Unlike the carbon acid just considered, separate signals for these acids and their conjugate bases are not expected, owing to rapid proton exchange.[16]

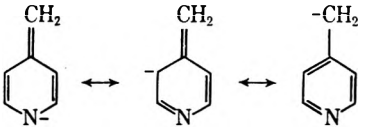
Comparison of the three isoelectronic conjugate bases, Table I, reveals that coupling constants are virtually identical. Chemical shifts vary in an understandable way. As more negative charge resides on the side chain in the order expected from atom electronegativity considerations, *i.e.*, X = CH_2, NH, and O, respectively, in I, smaller shielding factors result for the ring protons. Indeed, the spectral similarities firmly support the idea that the three pyridines only undergo simple ionization in the presence of amide ions to give charge-delocalized ion I.



I, X = CH_2, NH, O

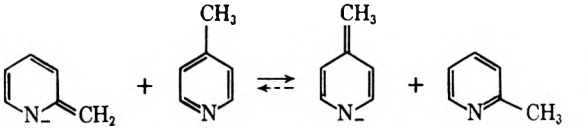
The nmr spectrum of the anion of 2-pyridone in D_2O has been reported.[18] Comparison of the spectra obtained from ammoniacal and aqueous solutions indicates that there are only minor differences in coupling constants (<0.5 Hz) but there are large differences in chemical shifts, those protons for the sample in ammonia all being shielded. Differences are 24 (H-3), 20 (H-4), 28 (H-5), and 6 Hz (H-6). Differences are likely to be due to solvation of the anion. It would appear from these large differences in chemical shifts that this anion could be useful in solvation studies.

4-Methylpyridine reacts completely with excess KNH_2 at −40° to give its conjugate base II. The AA′XX′ spectrum consists of a broadened doublet at τ 3.3 for the H-2,6 protons; the H-3,5 signals at τ 4.55 consist of a pair of doublets with small wing peaks. The separation of the main (outer) doublet peaks is 5.5 Hz. The methylene singlet is at τ 7.3 while the methyl group of starting material is at τ 7.7 Again, when the acid is incompletely converted to its conjugate base in the presence of a deficiency of amide ion, no signal averaging of the acid and its conjugated base are apparent.



II

A comparison of the relative acidities of 2- and 4-methylpyridines revealed that the 2-methyl- is a weaker acid than the 4-methylpyridine. Two types of experiments were performed. A mixture of 2-methylpyridine and its conjugate base was prepared using a deficiency of amide ion. This then was added to excess 4-methylpyridine. Analysis of the resultant mixture (−40°) indicated that no conjugated base of 2-methylpyridine was present; instead the conjugated base of 4-methylpyridine was formed.[19] This result clearly indicates that 2-methyl- is a weaker carbon acid than 4-methylpyridine (eq 1).



(1)

In other experiments a mixture of 2- and 4-methylpyridines was allowed to compete for a deficiency of amide ion in ammonia. No ionized 2-methylpyridine could be detected in the presence of both ionized and un-ionized 4-methylpyridine and of un-ionized 2-methylpyridine. This is consistent with the result given in eq 1. From the concentrations obtained by integration and the assumption that no more than 1% of the conjugate base of 2-methylpyridine was present in the mixture, it may be calculated that the ionization constant, K_a, for the 4-methyl compound must be at least 75 times greater than that for 2-methylpyridine. The acidifying effect of the para annular nitrogen atom is considerably greater than that of the ortho annular nitrogen atom.

A comparison between the acidity of the methylpyridines and ammonia may be made by using the shape of the ammonia solvent peak to provide an estimate of the amide ion concentration.[20,21] When both 4-methylpyridine and its conjugate base are present in ammonia at −40° in a 1:1 ratio, the solvent peak is a partially collapsed triplet rather than a singlet. This means that the amide ion catalyzed hydrogen exchange of ammonia is slow because the amide ion concentration in the carbon acid buffer mixture is low. The

(18) R. H. Cox and A. A. Bothner-By, *J. Phys. Chem.*, **73**, 2465 (1969).

(19) Experiment kindly performed by T. M. Oestreich.

(20) R. A. Ogg, Jr., *Discuss. Faraday Soc.*, **17**, 215 (1954); J. D. Roberts, "Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, Chapter 4.

(21) T. J. Swift, S. B. Marks, and W. G. Sayre, *J. Chem. Phys.*, **44**, 2797 (1966); D. R. Clutter and T. J. Swift, *J. Amer. Chem. Soc.*, **90**, 601 (1968).

amide ion concentration may be estimated from the coupling constant for ammonia (44 Hz) and the rate constant for hydrogen exchange ($1.7 \times 10^6\ M^{-1}\ \text{sec}^{-1}$ at $-40°$[21]). Hence $[NH_2^-] \sim 44\pi/(\sqrt{2} \times 1.7 \times 10^6)$ or $[NH_2^-] \sim 6 \times 10^{-5}\ M$. Use of this estimate, the carbon acid buffer ratio, and the known ionization constant for ammonia (pK_{NH_3}[8] = 33.2 at $-40°$) allows an estimate of the ionization constant of the carbon acid to be made (eq 2).

$$\frac{[PyCH_3][NH_2^-]}{[PyCH_2^-]} = \frac{10^{-33.2}}{K_a} \qquad (2)$$

The pK_a value of 4-methylpyridine at $-40°$ is ~29. It is fortuitous that the amide ion concentration is such that the solvent signal is a partially collapsed triplet. This is an ideal situation for the accurate determination of the amide ion concentration by means of a computer-assisted line-shape analysis. It appears that a more refined pK_a value could be obtained from studies involving various ratios of acid to conjugate base and an accurate line-shape determination of the amide ion concentration. Such a study is highly desirable not only because a more refined pK_a value would be obtained but also because this value could then serve as a reference value. Comparisons with other acids in competition experiments of the type employed with the two methylpyridines then lead to pK_a values for other compounds.

When both 2-methylpyridine and its conjugate base are present in ammonia at $-40°$ in a 3:1 ratio, the solvent peak is a broadened singlet. Before this information can be used to estimate a lower limit of the amide ion concentration and of the pK_a of the carbon acid, it must be established that the triplet to singlet conversion of the solvent signal by proton exchange is catalyzed only by amide ion; *i.e.*, the possibility of catalysis by the 2-pyridylmethyl anion (general base catalysis) must be eliminated. This possibility can be dismissed because it has been reported that a mixture of this carbon acid and its conjugate base in ND_3 slowly undergoes H–D exchange in the side chain. Although the carbon base must dedeuterate the solvent in the course of H–D exchange, the pseudo-first-order constant[22] for this process is only $<10^{-6}\ \text{sec}^{-1}$ at $-45°$. This is much too slow to bring about collapse of the triplet solvent signal which requires a pseudo-first-order rate constant of $\sim 44\ \pi/\sqrt{2}$ or $\sim 10^2\ \text{sec}^{-1}$ at $-45°$. Clearly, then, collapse of the solvent triplet is essentially catalyzed by amide ion and the shape of the solvent peak provides a valid estimate of the amide ion concentration. Hence $[NH_2^-] > 6 \times 10^{-5}\ M$. From eq 2, the pK_a of 2-methylpyridine at $-40°$ is likely to be >29. That this acid is completely ionized by amide ion means $pK_a < 33.2$. In other words the pK_a is >29 but <33. Moreover, consideration of the results of the competition experiment, eq 1, and of the estimated pK_a of 4-methylpyridine allows an estimate of ~31 to be made for the pK_a of 2-methylpyridine. The pK_a values for 2- and 4-methylpyridines are similar, for example, to the pK_a[15] (28.6) of di(4-methoxyphenyl)methane in ammonia at $-34.5°$.

(22) N. N. Zatsepina, I. F. Tupitsyn, A. V. Kirova, and A. I. Belyashova, *Org. Reactiv. (USSR)*, **6**, 257 (1969). The fractional amount of substrate in the anion form is ~0.2.

The pK_a values for the methylpyridines are the first reliable estimates of the acidities of these two carbon acids. Other values based upon the rates of hydrogen–deuterium exchange in ethanol-*O*-*d* and an assumed Brønsted relationship[3] are known to be incorrect.[23]

Toluene, the deaza analog of the methylpyridines, does not undergo detectable ionization in the presence of amide ion.[11,24] Clearly, the acidifying effect of the annular nitrogen atom in the heterocyclic compounds is enormous.

Pyrazines.—The identity of the product resulting from the reaction of 2-methylpyrazine with amide ion is of special interest. Pyrazine itself (but not pyridine) reacts with amide ion to give an anionic σ complex, III.[25] It therefore becomes of interest to learn whether addition or ionization is the preferred reaction of 2-methylpyrazine.

In the presence of excess KNH_2 at $-40°$ no unreacted 2-methylpyrazine could be detected. Instead the spectrum (Table II) of a single substance was evi-

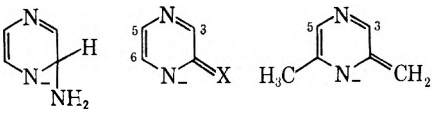
TABLE II
CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR IONIZED 2-SUBSTITUTED PYRAZINES IN AMMONIA

	τ			J, Hz	
X	3	5	6	3,6	5,6
IV, CH_2	3.13	4.14	3.25	1.5	3.0
HN	2.80	3.40	2.80	*a*	2.7
O	2.48	2.77	2.31	1.2	2.7

[a] Signal overlap prevents accurate analysis.

dent. The large shielding and the presence of an AB pair of doublets at τ 7.22 and 7.35 (J = 2.8 Hz) provide evidence that 2-methylpyrazine undergoes deprotonation to give charge-delocalized anion IV, X = CH_2, rather than addition of amide ion to give an anionic σ complex. The latter complex would be expected to show a singlet for the methyl group.

Signal assignments were aided by a consideration of the spectrum of ionized 2,6-dimethylpyrazine in ammonia. Monoanion V is formed and has the following characteristics: τ 3.27 (H-3), 4.23 (H-5), 7.21, 7.39 (CH_2), and 8.41 (CH_3). The methylene protons are nonequivalent at $-40°$, J = 2.5 Hz. Since the ring protons in V appear as singlets, meta spin coupling ($J_{3,5}$) is insignificant. Hence, the significant couplings in the monomethyl anion can only be $J_{5,6}$ and $J_{3,6}$. The assumption that ortho ($J_{5,6}$) is larger than para coupling ($J_{3,6}$) allows all the signal assignments in IV to be made. The H-3 and H-5 protons of IV and V have consistent assignments.



III IV V

Although pyrazine reacts with amide ion to give III, methylpyrazines undergo deprotonation to give delocalized carbanions IV, X = CH_2, and V. This suggests that such aromatic anions are lower in energy

(23) A. Streitwieser, Jr., W. B. Hollyhead, G. Sonnichsen, A. H. Pudjaatmaka, C. J. Chang, and T. L. Kruger, *J. Amer. Chem. Soc.*, **93**, 5096 (1971).

(24) T. Birchall and W. L. Jolly, *ibid.*, **88**, 5439 (1966).

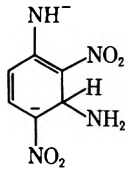
(25) J. A. Zoltewicz and L. S. Helmick, *ibid.*, **94**, 682 (1972).

than carbon-methylated derivatives of nonaromatic ion III. This conclusion is of special interest in that heteroaromatic molecules containing a methyl group bonded to an annular carbon atom often show a greatly diminished reactivity in the Chichibabin amination reaction. This was interpreted to mean that the methyl group underwent ionization under the conditions of the amination and thereby hindered the addition of amide ion to an annular carbon atom, a necessary first step in the Chichibabin reaction.[26] Our results provide the first direct evidence to support this suggestion. Since a number of methylated heterocyclic compounds show diminished reactivity[26] in the amination reaction, ionization often must be preferred over addition.

Again the nmr spectra of amino and oxy acid analogs were obtained. The spectral properties of the conjugate bases of 2-aminopyrazine and 2-pyrazinone are given in Table II. Coupling constants for the three isoelectronic pyrazine bases are very similar. Ionization of the pyrazine acids result in smaller shielding factors for the anions having the more electronegative nitrogen and oxygen side chains, just as in the pyridine series.

The nmr spectrum of the anion of 2-pyrazinone in methanol has been reported.[18] Comparison of this with that obtained using ammonia solvent shows minor differences in coupling constants but greater shielding (5–12 Hz) in ammonia. As in the 2-pyridone case, solvation differences probably are responsible.

We find no evidence of dianion formation of the type reported for 2,4-dinitroaniline in ammonia containing amide ion. This aniline undergoes both ionization (amino group) and addition reactions with amide ion to give VI.[24]



VI

Correlation of Chemical-Shift Changes Resulting from Ionization.—The effect of ionization on the chemical shifts of the ring protons (shielding factors) is given by the difference in shift between an ion and its conjugate acid. For the pyridine and pyrazine series the position (H-5) para to the side chain has the largest shielding factor; usually, but not always, the shielding factor for the ortho position (H-3) is larger than that for a meta position (H-6). The factors generally are larger in the pyrazine series. When the factors for the 3, 5, and 6 positions of the pyrazine family of acids are plotted against those for the corresponding pyridine acids, a linear relationship (Figure 1) is obtained. The least-squares line (correlation coefficient 0.988) is given by eq 3 where SF is shielding factor.

$$\text{pyrazine SF} = 1.01\ \text{pyridine SF} + 0.135\ \text{ppm} \qquad (3)$$

It should be noted that the chemical shifts of 2-pyridone and 2-pyrazinone could not be employed in

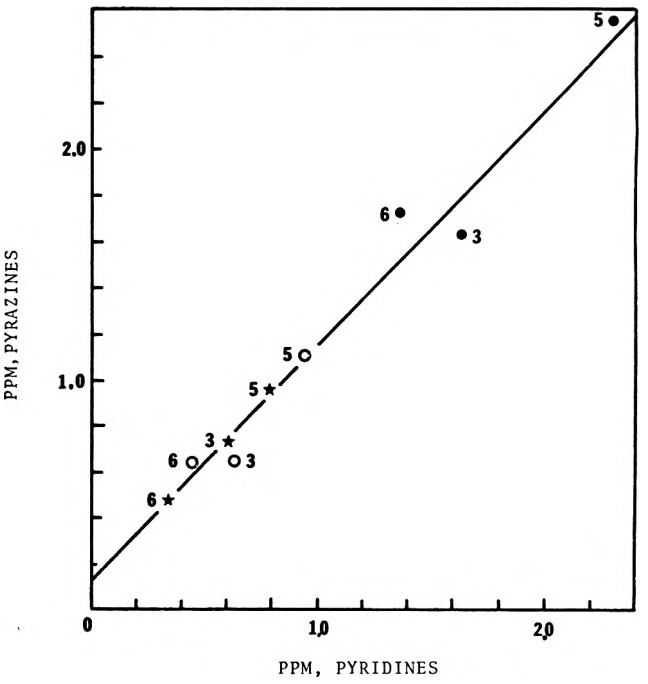
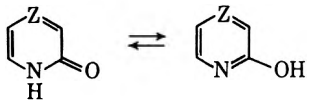


Figure 1.—Plot of the change in chemical shift resulting from the ionization of pyrazines *vs.* that for the ionization of pyridines in ammonia. The change is given by the difference between the shift of an ion and its conjugate acid. Filled circles refer to methyl, open circles to amino, and stars to oxy compounds. The proton positions are indicated.

making this correlation because these compounds are not analogous structurally to the methyl and amino acids. The hydroxy tautomer is the appropriate structural analog. Unfortunately, nmr spectra of the hydroxy compounds are unavailable because the molecules exist largely in tautomeric forms having the proton bonded to nitrogen rather than to oxygen,[27] VII.



VII, Z = CH, N

To overcome this limitation the nmr spectra of methoxy compounds were employed as models of the hydroxy compounds. Since the nmr spectra of the un-ionized compounds are not significantly dependent on solvent, chemical shifts obtained using DMSO solvent were employed.[28]

The shielding factors may be correlated in other ways. For example, the shielding factors for H-5 of the three acids are linearly related to those for H-3, pyridines and pyrazines showing the same correlation.

These correlations can be understood in familiar, general terms. As a position carries a greater fraction of the negative charge, larger shielding factors are observed. The presence of a second annular nitrogen atom in the pyrazine series provides additional (inductive) stabilization of the negative charge, leading to a larger fraction of the charge on the ring positions.

(26) F. W. Bergstrom, *J. Amer. Chem. Soc.*, **53**, 3027, 4065 (1931); *J. Org. Chem.*, **3**, 233 (1938).

(27) A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.*, **1**, 339 (1963).

(28) G. S. Marx and P. E. Spoerri, *J. Org. Chem.*, **37**, 111 (1972). R. H. Cox and A. A. Bothner-By, *J. Phys. Chem.*, **72**, 1646 (1968).

These correlations provide additional support for the nmr assignments as well as further support for our claim that only ionization of acids is being observed.

In conclusion, we have established that some pyridine and pyrazine carbon and nitrogen acids in ammonia containing amide ion only undergo simple deprotonation reactions. Competitive ionization experiments which are expected to provide relative pK_a values were shown to be possible. Solvent line-shape analysis could provide an accurate pK_a value for 4-methylpyridine, a compound which can then serve as a reference standard.

At this early stage in the development of acidity scales using liquid ammonia as a solvent, it is imperative that independent approaches be developed to verify the validity of the pK_a values.[5,6] Our method makes possible the establishment of an acidity scale for ammonia solutions which is independent of other scales. It extends from very weak acids such as 2-methylpyridine to moderately strong acids such as 2-pyrazinone.[29] This scale could easily be related to the newly reported one[9,30] and thereby establish whether both scales provide the same pK_a values for the same compounds in ammonia. It should be noted that many more compounds will have to be added to our list in order to carry out competition experiments to cover a wide pK_a range.

It is expected that our method will make possible the determination of pK_a values for many weak heterocyclic acids. The information obtained from these acidity studies would greatly add to our understanding of the effects of structure on the acidity of weak acids, now largely based on studies of hydrocarbons.[5]

Experimental Section

Materials.—All compounds are commercially available; they were used as received. The sodium salt of 2-pyrazinone was used directly.

General Procedure for Obtaining Nmr Spectra of Ammonia–Amide Ion Reaction Mixtures.—The apparatus consisted of a 25-ml, three-neck round-bottom flask, to which was added a 2-mm ground glass stopcock near the bottom, and 7- and 10-ml calibration lines. The flask was fitted with a stopper, a septum through which liquids were added by syringe, and a Dry Ice–acetone condenser with attached drying tube ($CaCl_2$). A glass-enclosed stirring bar was used for magnetic stirring. The stopcock was connected to a glass capillary tube by a 1-cm piece of Tygon tubing. The capillary was tapered so that it would fit into a standard nmr tube.

The apparatus was flame dried under a slow stream of dried nitrogen. Ammonia then was condensed into the flask. Potassium amide was generated by the addition of a pin-head size piece of $Fe(NO_3)_3 \cdot 9H_2O$ catalyst and potassium metal; 1 to 3 hr are required for amide ion formation, as evidenced by a change from a blue to a gray color.

A weighed amount of heterocyclic substrate was added to the flask or to an nmr tube. Ammonia solution then was drained through the capillary tube into an nmr tube immersed in a Dry Ice–acetone bath. The tube was then capped. The substrate concentration was $\sim 0.5\ M$.

Trimethylamine (τ 7.87) or benzene (2.60) internal standard were added to the nmr tube. In the case of trimethylamine, 2 ml of vapor were removed by syringe from a flask cooled to 0° and fitted with a septum. The vapor was injected into the tube at a level below that of the cooling bath.

The tube was sealed with a torch. The contents of the tube were mixed by inverting the tube; the tube was cooled in the bath every few seconds to maintain a low temperature. However, the heterocycle dissolves more readily at higher temperatures.

For low temperature nmr work, the level of liquid NH_3 should be below the spinner; otherwise poor cooling may result. This, in turn, may give pressures high enough to explode the tube and damage the probe. Standard thin wall (0.4-mm thickness) nmr tubes may be used safely to 0° or even 25°. For higher temperatures medium wall (0.75 mm) tubes should be employed. When possible, it is desirable to test the seals of the tubes by immersion into baths at temperatures at or above probe temperatures.

Spectra were obtained with a Varian A-60A spectrometer equipped with a V-6040 variable-temperature controller.

Competion Experiments Involving 2- and 4-Methylpyridines.—Two different experiments were employed. (a) A mixture of ionized and un-ionized 2-methylpyridine was prepared by adding excess 2-methylpyridine to KNH_2–NH_3. A portion of this solution was taken to confirm that the carbon acid and its conjugate base were present. The mixture then was added to an nmr tube cooled in acetone–Dry Ice containing excess 4-methylpyridine. The temperature of the mixture was raised to 0° for <1 min before a spectrum was obtained at −40°. No ionized 2-methylpyridine could be detected, only ionized 4-methylpyridine. (b) The KNH_2 was added to a cooled nmr tube containing both 2- and 4-methylpyridine.

Registry No.—Pyridine, 110-86-1; pyrazine, 290-37-9.

Acknowledgment.—This work was kindly supported by the National Science Foundation (GP 25500).

(29) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, Washington, D. C., 1965.

(30) J. H. Takemoto and J. J. Lagowski, *Inorg. Nucl. Chem. Lett.*, **6**, 315 (1970).

Pyrolysis of Phenylalanine, 3,6-Dibenzyl-2,5-piperazinedione, and Phenethylamine

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Phenylalanine and its low-temperature pyrolysis products, 3,6-dibenzyl-2,5-piperazinedione and phenethylamine, were found to undergo pyrodegradation and pyrosynthesis reactions at 650 and 850°. While the pyrolysates obtained from the three substances contained the same kinds of compounds, variations in quantities were observed. The chief constituent (650°) of the phenylalanine and dibenzylpiperazinedione pyrolysates was toluene, while that of the phenethylamine pyrolysate was styrene. Other substances found in moderate quantities were bibenzyl, biphenyl, stilbene, phenanthrene–anthracene, and benzene. Dibenzylpiperazinedione pyrolysate contained, in addition, moderate amounts of benzonitrile and phenylacetonitrile. Hydrogen cyanide was produced in all pyrolyses. At the higher pyrolysis temperatures yields of fluorene, pyrene, and phenanthrene–anthracene increased while yields of bibenzyl and stilbene diminished or fell to zero. These data suggest that both simultaneous and nonsimultaneous multiple bond cleavages are competitive in the thermally induced breakdown of phenylalanine and that at higher temperatures the simultaneous multiple processes become more prominent.

The thermolysis of complex plant materials, such as tobacco, gives rise to a wide variety of organic substances,[1] most of which are produced through the processes of pyrodegradation and pyrosynthesis. Experiments in which individual components of the plant, such as proteins[2] and amino acid,[2,3] have been pyrolyzed show that pyrolysis mixtures of similar composition are produced. The low-temperature pyrolysis of amino acids to give amines and nitriles[4-7] by decarboxylation and piperazinedione by cyclodehydration[4-8] suggests that these substances may be primary pyrolysis products at higher temperatures. The investigation described here was conducted to determine, by examination of pyrolysate composition, in what way the high-temperature pyrolysis of these intermediates contributes to the pyrolysate composition of phenylalanine.

Phenylalanine, phenethylamine, and 3,6-dibenzyl-2,5-piperazinedione (I) were pyrolyzed under the same conditions at 650 and 850° in a nitrogen atmosphere. The results are reported in Tables I, II, and III. Another possible breakdown pathway involves deamination of phenylalanine to cinnamic acid. Products arising from the thermolysis of cinnamic acid previously described by Jones and Schmeltz[9] are included for comparison.

Evidence that these probable primary pyrolysis products, or their precursors, are involved at least to some extent in the thermolytic decomposition of phenylalanine in the present experiments was provided by the isolation of the intermediates. Thus phenethylamine was isolated from 450 and 650° pyrolysis experiments in 6.9 and 0.5% yields, respectively, and 3,6-dibenzyl-2,5-piperazinedione (I) was isolated from a 850° pyrolysis experiment. Only trace quantities of cinnamic acid were found in 450 and 650° pyrolysis experiments. In spite of the relatively high stability of cinnamic acid (Jones and Schmeltz[9] recovered 42% cinnamic acid on pyrolysis at 700°) only very small amounts of total acid fraction (0.05–0.06%) were produced in the pyrolysis of phenylalanine at 450–850°. Because of these observations it appears that the deamination of phenylalanine probably represents a very minor decomposition pathway in the thermolysis of the amino acid.

The production of the gases HCN, NH_3, CO, and CO_2 during each of the pyrolyses is consistent with the formation of the possible intermediates, but this production, with the exception of HCN formation, does not allow distinction between the paths followed. The low ammonia yields observed do not provide a reliable indication of the fraction of reaction occurring by a deamination pathway (of phenylalanine or phenethylanime) since ammonia is known to dissociate almost completely to nitrogen and hydrogen at *ca.* 625°.[10]

Although CO_2 yields were expected to be relatively large in view of the ease with which amino acids decarboxylate at low temperatures, especially in the presence of radicals,[6] the low CO_2 yields do not rule out this path. Carbon dioxide is readily reduced to carbon monoxide by carbon at 1000°[11] or by hydrogen at 600–1000°.[12] In the experiments reported here, it is likely that the CO_2 is not significantly reduced by carbon, since no reduction of CO_2 was observed when the gas passed over carbonized amino acid in the pyrolysis apparatus at 850°. Some additional contribution to the CO_2 and CO yields could have arisen from the thermal decomposition of cinnamic acid, the deamination product of phenylalanine, since conjugated unsaturated acids have been reported to produce CO_2 and CO in ratio of *ca.* 1–2:1 at 500°.[13] In view of the CO_2:CO ratio observed in the present experiments and of the stability of cinnamic acid under pyrolytic conditions,[6] this path is probably a minor one. The quantities of carbon monoxide and carbon dioxide produced in the present experiments suggest that some of the carbon monoxide arises from interaction of water with carbon, carbon radicals, or alkanes.

The intermediacy of 3,6-dibenzyl-2,5-piperazinedione

(1) R. Stedman, *Chem. Rev.*, **68**, 153 (1968).
(2) E. B. Higman, I. Schmeltz, and W. S. Schlotzhauer, *J. Agr. Food Chem.*, **18**, 636 (1970).
(3) J. M. Patterson, M. L. Baedecker, R. Musick, and W. T. Smith, Jr., *Tobacco Sci.*, **13**, 26 (1969); J. M. Patterson, W. Y. Chen, and W. T. Smith, Jr., *ibid.*, **15**, 98 (1971).
(4) E. Waser, *Helv. Chim. Acta*, **8**, 758 (1925).
(5) J. Vollumin, P. Kriemler, I. Omura, J. Seibl, and W. Simon, *Microchem. J.*, **11**, 73 (1966).
(6) G. Chatelus, *Bull. Soc. Chim. Fr.*, 2523 (1964); 929 (1965).
(7) G. P. Shulman and P. G. Simmonds, *Chem. Commun.*, 1040 (1968).
(8) S. W. Fox, *Science*, **132**, 200 (1960).
(9) T. C. Jones and I. Schmeltz, *J. Org. Chem.*, **34**, 645 (1969).
(10) N. V. Sidgwick, "The Chemical Elements and Their Compounds," Vol. I, Pergamon Press, Oxford, 1950, p 658.
(11) I. G. Petrenko, *Khim. Tekhnol. Topl. Masel*, 15 (1957); *Chem. Abstr.*, **51**, 17366 (1957).
(12) W. M. Graven and F. J. Long, *J. Amer. Chem. Soc.*, **76**, 2602 (1954), and references cited therein.
(13) R. L. Forman, H. M. Mackinnon, and R. D. Ritchie, *J. Chem. Soc.*, 2013 (1968).

TABLE I

RELATIVE CONCENTRATIONS OF COMPONENTS[a] PRODUCED IN THE PYROLYSIS OF PHENYLALANINE AND ITS PRIMARY PYROLYSIS PRODUCTS, 3,5-DIBENZYL-2,5-PIPERAZINEDIONE, PHENETHYLAMINE, AND CINNAMIC ACID

	Phenylalanine		Dibenzylpiperazinedione[b]		Phenethylamine		Cinnamic acid[c]	
Component	650°	850°	650°	850°	650°	850°	700°	900°
Acenaphthylene						0.1		0.2
Aniline	<0.1	0.1	<0.1	0.1	<0.1	0.1		
Benzene	2.1	7.6	4.8	13.0	0.5	0.8	<0.1	0.8
Benzonitrile	0.2	1.9	1.9	5.0	0.2	3.1		
Bibenzyl	13.5		2.5		9.9			
Biphenyl	<0.1	1.6	0.4	1.7	0.1	2.4	<0.1	0.6
9,10-Dihydrophenanthrene	1.4		0.5					
Diphenylmethane	<0.1	0.7	0.4	0.2	7.5		<0.1	0.1
Ethylbenzene	3.4		1.6		4.1		0.2	0.6
Fluoranthene		0.5		2.7		0.7		<0.1
Fluorene	0.5	1.6	0.6	0.8	1.9	1.4	0.2	0.8
Indene and *m*-tolunitrile	0.2	0.9	0.6	1.1		1.2	0.7[d]	0.7[d]
Indole and cinnamonitrile	0.7	1.0	2.9	1.4	1.8	0.4		
Isoquinoline	0.9	0.6	1.7	1.6	0.4	0.1		
m-Methylbiphenyl		0.5	1.0	0.7		1.2		
p-Methylbiphenyl		1.4		0.6		0.4		
1-Methylindole	0.2				<0.1			
2- and 3-Methylindole	<0.1		0.1					
2-Methylquinoline		<0.1	<0.1	<0.1				
3-Methylquinoline		<0.1	<0.1					
α-Methylstyrene	0.3	0.1	0.1		0.3			
β-Methylstyrene					0.2			
m- and *p*-Methylstyrene				<0.1				
Naphthalene	0.2	1.2	0.9	1.9	0.1	2.5	0.3	2.5
1-Naphthonitrile				0.2				
2-Naphthonitrile						<0.1		
Phenanthrene and anthracene	5.1	9.3	7.1	9.1	5.6	6.0	0.9[e]	2.6[e]
Phenanthridine		0.1	<0.1	0.4		0.1		
Phenethylamine	0.6				13.8			
Phenylacetonitrile	0.3	0.3	3.7	0.8	0.4	0.3		
Phenylacetylene		0.5		<0.1				
1-Phenylnaphthalene			<0.1				0.8	1.5
2-Phenylnaphthalene	4.6	1.6	1.1	1.8	0.1	0.6		
Pyrene		0.5		0.1		0.1		<0.1
Quinoline	0.1	0.7	0.8	2.3	0.4	0.1		
trans-Stilbene	5.5	1.7	3.8	0.5	10.2		1.3	2.3
Styrene	8.2	7.5	6.1	1.3	19.5	0.1	21.3	26.8
Toluene	20.6	21.8	30.6	8.9	7.3	3.2	0.6	0.9
o-Toluidine				<0.1				
o-Tolunitrile		0.3	0.3	0.5		0.1		
p-Tolunitrile						0.4		
m-Xylene		0.1		<0.1				

[a] Reported in grams component produced per mole of substance pyrolyzed. [b] Values of grams/mole divided by 2. [c] Values calculated from ref 9. [d] Reported as indene only, ref 9. [e] Reported as phenanthrene only, ref 9.

TABLE II

YIELDS[a] OF GASES OBTAINED ON THE PYROLYSIS OF PHENYLALANINE, 3,6-DIBENZYL-2,5-PIPERAZINEDIONE, AND PHENETHYLAMINE

	Phenylalanine		3,6-Dibenzyl-2,5-piperazinedione		Phenethylamine	
Product	650°	850°	650°	850°	650°	850°
CO_2	3.6	5.8	8.1	12.9		
CO	*c*	98.7	39.7[b]	77.0[b]		
HCN	0.3	17.2	25.3[b]	29.5[b]	8.2	50.0
NH_3	2.7	0.3	*c*	*c*	1.2	0.5

[a] Moles of gas per mole of substance pyrolyzed × 100. [b] Moles of gas per mole of substance pyrolyzed × 50. [c] Found but not determined quantitatively.

TABLE III

WEIGHTS OF PYROLYSATES AND MAJOR FRACTIONS OF THE PYROLYSATE

Compd pyrolyzed	Temp, °C	Weight pyrolyzed, g	Weight of pyrolysate, g	Weight of neutrals, g	Weight of bases, g
Phenylalanine	650[a]	93.0	71.0	41.6	2.4
Phenylalanine	850[a]	94.0	68.0	36.9	1.3
Dibenzylpiperazinedione	650[a]	65.0	36.0	29.2	1.3
Dibenzylpiperazinedione	850[a]	41.0	24.5	13.9	1.6
Phenethylamine	650	51.7	44.6	24.2	7.4
Phenethylamine	850	36.3	27.7	11.2	0.2

[a] Trace amounts of phenols were also obtained.

provides an attractive explanation for the formation of both HCN and CO. The propensity of nitrogen heterocycles,[14-16] including piperazinedione, to form HCN is well known and in the present work considerable quantities of HCN and CO were obtained on the pyrolysis of dibenzylpiperazinedione. Possible decom-

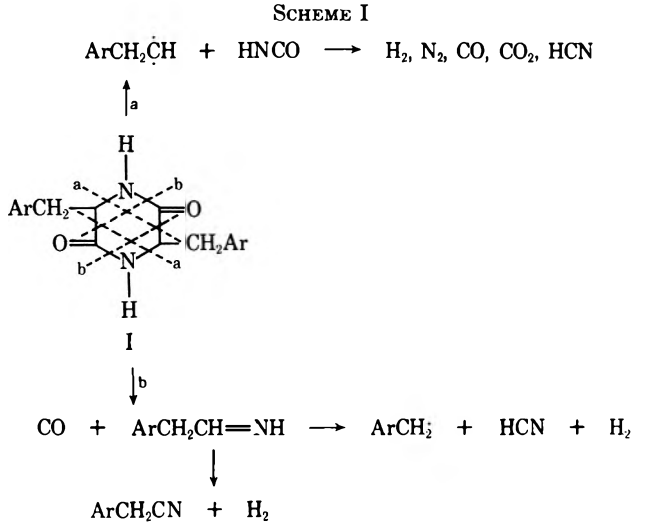
(14) C. D. Hurd, A. R. Macon, J. I. Simon, and R. V. Levetan, *J. Amer. Chem. Soc.*, **84**, 4509 (1962).

(15) J. M. Patterson, A. Tsamasfyros, and W. T. Smith, Jr., *J. Heterocycl. Chem.*, **5**, 727 (1968).

(16) W. R. Johnson and J. G. Kang, *J. Org. Chem.*, **36**, 189 (1971).

position modes of the piperazinedione I which produce HCN and CO are summarized in Scheme I.

SCHEME I



Mode a produces benzylcarbene and isocyanic acid with the isocyanic acid further decomposing (500–700°) to H_2, N_2, CO_2, CO, and HCN,[17] while mode b produces carbon monoxide and phenylethylidenimine, which in turn produces phenylacetonitrile or HCN, H_2, and benzyl radical. Since the HCN yield from phenylalanine (pyrolyzed at 650°) is only 0.3% while under the same conditions the yield from piperazinedione is 25%, it is concluded that piperazinedione formation is minimal during the pyrolysis of phenylalanine. At 850° piperazinedione formation may be involved to a greater extent, but it seems more likely that at this temperature the HCN is formed from phenethylamine or its radical precursor II formed by decarboxylation. Under similar conditions (800°) trimethylamine

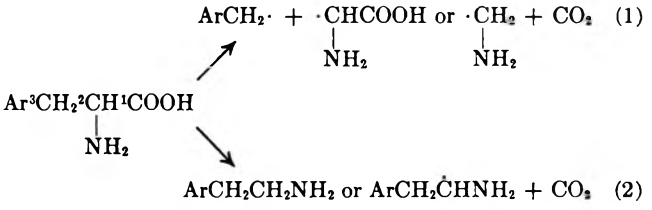
$$\mathrm{ArCH_2\dot{C}HNH_2}$$
II

is converted into HCN in 98% yield.[18] The interaction of ammonia with carbon to form HCN and H_2 does not appear to be involved to any great extent in these pyrolyses, since the conversion to HCN at 800° was only 2%.[18]

The pyrolyses products observed can be explained in terms of an initial benzylic bond cleavage followed by additional competitive paths in which reactive intermediates (phenyl and benzyl radicals, carbenes) and thermally unstable molecules (styrene) are formed. The ways by which these reactive species produce pyrolysis products have been described previously.[9,19,20]

Although the pyrolysate compositions obtained from the compounds studied show qualitative similarities, the quantitative differences imply that there is a relationship between the structure of the substance pyrolyzed and the makeup of its pyrolysate. It is suggested that these quantitative differences arise from variations in reactive intermediate concentrations which in turn are related to the structure of the substance pyrolyzed.

The yields of HCN, toluene, and styrene, and the fact that amino acids undergo a facile radical-catalyzed decarboxylation,[6] suggest that phenylalanine decomposes by two competing paths: one involving a concerted or nearly concerted rupturing of bonds at positions 1 and 2 (eq 1) and the other involving



decarboxylation followed by decomposition of the phenethylamine or its radical precursor (eq 2).

Benzyl C–C bond cleavage appears to be a major decomposition pathway in the decomposition of dibenzylpiperazinedione in view of the high yields of toluene produced. Thermal scission of the ring (Scheme I) by modes a and/or b probably also contributes to benzyl radical formation. The benzylcarbene formed in the mode a cleavage can dissociate into benzyl radical and methine or dimerize to form a dibenzylethylene and then decompose.[9] The higher yields of benzene (relative to those obtained from phenethylamine or phenylalanine) could also have arisen from the benzylcarbene by dissociation into phenyl and vinyl radicals (eq 3) or from its dimer by

$$\mathrm{ArCH_2\dot{C}H\cdot \longrightarrow Ar\cdot + CH_2{=}CH\cdot} \qquad (3)$$

subsequent decomposition. This species (benzylcarbene) could also be one of the precursors of styrene (eq 4).

$$\mathrm{ArCH_2\dot{C}H\cdot \xrightarrow{H\cdot} ArCH_2\dot{C}H_2 \xrightarrow{-H\cdot} ArCH{=}CH_2} \qquad (4)$$

In the pyrolysis of phenethylamine, the initial benzylic C–H and C–C cleavages result in the formation of phenethylamine radical and benzyl radical, respectively. The phenethylamine radical, in turn, eliminates amino radical, producing styrene or undergoes cleavage, producing phenylcarbene and methylamine radical.

At 850°, random bond cleavage occurs to a greater extent in the phenylalanine pyrolysis and participation of the decarboxylation intermediate becomes less important. Formation of a greater abundance of phenyl and benzyl radicals is reflected in the increases in yields of benzene, biphenyl, benzonitrile, toluene, and diphenylmethane. The pyrolyses of dibenzylpiperazinedione and phenethylamine at 850° likewise produce increased phenyl radical concentrations which are responsible for increases in yields of benzene, benzonitrile, and biphenyl. These increases in yields also may be due, in part at least, to the fact that substances formed from these radicals at 650° such as bibenzyl,[21] *trans*-stilbene,[9] and diphenylmethane[21] are not stable at 850°.

The absence of bibenzyl from the pyrolytic products of the three compounds at 850° may be attributed to the relative ease with which bibenzyl undergoes either cleavage at the carbon–carbon single bond or dehydro-

(17) R. A. Back and J. Childs, *Can. J. Chem.*, **46**, 1023 (1968).
(18) G. A. Voerkelius, *Chem.-Ztg.*, **33**, 1078, 1090 (1909); *Chem. Abstr.*, **4**, 1653 (1910).
(19) G. M. Badger in "Progress in Physical Organic Chemistry," Vol. 3, S. G. Cohen, A. Streitwieser, and R. W. Taft, Ed., Interscience, New York, N. Y., 1965, pp 1–40.
(20) F. R. Mayo, *J. Amer. Chem. Soc.*, **90**, 1289 (1968).
(21) J. W. Sweeting and J. R. Wilshire, *Aust. J. Chem.*, **15**, 89 (1962).

genation to *trans*-stilbene. The observation that the decrease in the yield of *trans*-stilbene at 850° in the phenylalanine, dibenzylpiperazinedione, and phenethylamine experiments is accompanied by an increase in the yield of phenanthrene is in accord with the observations of previous researchers that *trans*-stilbene may act as a precursor of phenanthrene at high temperatures.[9]

Consistent with the low yield of styrene from phenethylamine and dibenzylpiperazinedione at 850° is the production of fluoranthene and the higher yield of 2-phenylnaphthalene as compared with the yield at 650°. At 850°, styryl radicals may be more abundantly formed and formation of $C_6H_5CH{=}CH(C_6H_5)\text{-}\dot{C}\dot{C}H_2$ from two styryl radicals can explain the formation of 2-phenylnaphthalene, especially since the high yield of 2-phenylnaphthalene cannot be accounted for by the reaction of naphthyl radicals and phenyl radicals.[22] On the other hand, formation of a distyryl type intermediate, $C_6H_5\dot{C}HCH{=}CH\dot{C}HC_6H_5$, can give rise to 1-phenylnaphthalene, which has been shown to cyclodehydrogenate to fluoranthene.[22]

The formation of acenaphthylene, fluoranthene, and pyrene at 850° only and the higher yield of naphthalene at 850° as compared with the yield at 650° (in all three cases) are consistent with the decrease in the yield of styrene or of compounds that could give rise to styrene upon pyrolysis (such as bibenzyl[21] and *trans*-stilbene[9]), with the mechanisms of formation of these compounds from styrene moieties,[19] and with the evident increase in the production of gases made up of two carbon fragments at 850° as compared with 650°. The absence of acenaphthylene, fluoranthene, and pyrene from the products at 650° is in agreement with earlier observations that these compounds are not formed in the pyrolysis of styrene at 700°.[3]

Experimental Section

Ultraviolet spectra were measured in cyclohexane using a Perkin-Elmer Model 202 spectrophotometer, and infrared spectra were measured in chloroform or carbon tetrachloride using a Beckman IR-8 spectrophotometer equipped with a mirror beam condenser. Glpc retention times were measured and separation of the pyrolysate constituents was carried out on an F & M Model 810 gas chromatograph.

Materials.—Phenylalanine and phenethylamine were commercially available samples and were used as received. 3,6-Dibenzyl-2,5-piperazinedione was prepared from DL-phenylalanine by the method of Akimova[23] and recrystallized from dimethylformamide after washing with ethanol, mp 297–299° (uncorrected). The pure cis and trans isomers are reported[24] to melt at 311–312 and 289–291°, respectively. The product gave a satisfactory elemental analysis, a correct molecular weight (mass spectrum), and an infrared spectrum consistent with the piperazinedione structure.

Pyrolyses.—The pyrolyses were carried out in the apparatus previously described[15] using 20–30 ml of Berl saddles and a nitrogen flow of 100 ml/min for phenylalanine and dibenzylpiperazinedione pyrolyses and of 60 ml/min for phenethylamine pyrolyses.

The liquid products were collected in two traps, each of which was cooled in a Dry Ice–chloroform–carbon tetrachloride mixture. Gases which were not condensed by these traps were examined by infrared spectroscopy using a 100-mm gas cell. Identifications were based upon comparisons of the absorption bands observed with those reported in the literature[25] and with those obtained from authentic samples.

Quantitative gas analyses were carried out in separate experiments in which the compounds under investigation (10–20 g) were pyrolyzed under the conditions previously described. The gases were directed through a series of traps. Carbon dioxide and hydrogen cyanide were absorbed in 2 *M* KOH and ammonia in 3.5 *M* H_2SO_4. Carbonate was precipitated with barium nitrate solution and determined gravimetrically, and checked by titration with hydrochloric acid to a methyl red end point. Cyanide was determined on the filtrate from the carbonate determination using the Liebig–Deniges method.[26] The ammonia collected in the sulfuric acid trap was distilled into boric acid solution after basification and titrated potentiometrically with hydrochloric acid. The yield of carbon monoxide relative to carbon dioxide was determined by gas chromatography using a 4 ft × 0.25 in. silica gel (100–120 mesh) column at 25°. The moles of carbon monoxide produced was calculated from electronic integration data after correction for thermal conductivity differences and from the moles of carbon dioxide found by gravimetric analysis. The data are summarized in Table II.

The pyrolysate was heated in a water bath at 100° (the gases evolved were analyzed by infrared spectroscopy) and the distillate was collected. The residue was extracted with ether and the ether-soluble material was separated into acidic, neutral, and basic fractions by extraction with successive portions of 5% HCl and 5% NaOH, each saturated with NaCl. The neutral fraction was further separated into "volatile" and "nonvolatile" neutrals by distillation under reduced pressure (0.1 mm; maximum bath temperature, 150°). The compounds pyrolyzed along with the weights of the major fractions obtained are reported in Table III.

Separation and Identification of Components.—Components of the neutral and basic fractions were separated by glpc using a 30 ft × 0.375 in. 20% Apiezon L column (Anakrom 50/60 U) heated at 75° for 8 min and then programmed at 2°/min to 280°. The final temperature was maintained for an extended period to ensure elution of high-boiling components. In some experiments neutrals were also separated on a 20 ft × 0.375 in. 20% polyphenyl ether column and on a 30 ft × 0.375 in. 20% Apiezon W column. The bases were also separated on a 20 ft × 0.375 in. 20% SE-30 column.

Identifications of components are based on comparisons of glpc retention times, ultraviolet spectra, and infrared spectra with those obtained from authentic samples. Estimation of relative abundances of constituents are based on area per cent values obtained from glpc. The results are reported in Table I.

Registry No.—Phenylalanine, 63-91-2; 3,6-dibenzyl-2,5-piperazinedione, 2308-61-4; phenethylamine, 64-04-0; cinnamic acid, 621-82-9.

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(22) K. F. Lang and J. Buffleb, *Chem. Ber.*, **95**, 1049 (1962).

(23) L. N. Akimova, *Zh. Obshch. Khim.*, **27**, 1294 (1957); *Chem. Abstr.*, **52**, 4497*h* (1958).

(24) R. Brown, C. Kelley, and S. F. Wiberley, *J. Org. Chem.*, **30**, 277 (1965).

(25) R. H. Pierson, A. N. Fletcher, and E. S. C. Gantz, *Anal. Chem.*, **28**, 1218 (1956).

(26) I. M. Kolthoff and V. A. Stenger, "Volumetric Analysis," Vol. II, Interscience, New York, N. Y., 1947, pp 282, 283.

Reactions of Pyrrole with Isothiocyanates. Preparation and Reactions of *N*-Ethoxycarbonylpyrrole-2-thiocarboxamide and 2-Thiopyrrole-1,2-dicarboximide

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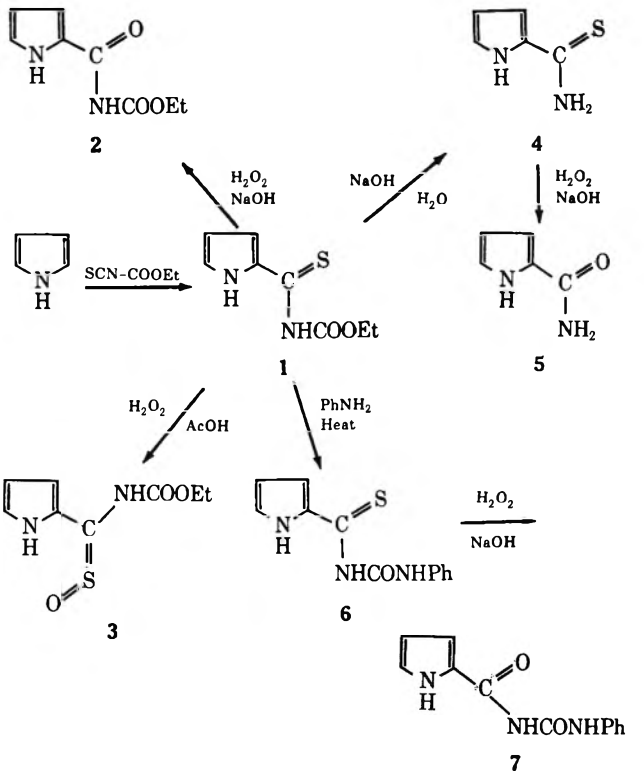
The reaction of pyrrole with ethoxycarbonyl isothiocyanate yields *N*-ethoxycarbonylpyrrole-2-thiocarboxamide (**1**), which is converted to 2-thiopyrrole-1,2-dicarboximide (**14**) by treatment with hot quinoline. Starting with pyrrolylpotassium, *N*-ethoxycarbonylpyrrole-1-thiocarboxamide (**24**) and 1-thiopyrrole-1,2-dicarboximide (**34**) are similarly obtained. Compounds **1**, **14**, and **24** are convenient and versatile sources of a variety of monocyclic and bicyclic thioamides, thioamide *S*-oxides, and amidines of pyrrole.

Nitrogen-substituted pyrrole-2-carboxamides[1] and thioamides[2] are useful synthetic intermediates because they allow formation of a new heterocyclic ring fused to the original pyrrole ring.[3,4] To supplement the results of a recent study of the preparation and reactions of *N*-ethoxycarbonylpyrrole-2-carboxamide and pyrrole-1,2-dicarboximide,[4] an investigation of the corresponding thio derivatives of pyrrole was undertaken.

N-Ethoxycarbonylpyrrole-2-thiocarboxamide (**1**) is obtained in high yield when pyrrole is allowed to react with ethoxycarbonyl isothiocyanate. The structure assignment is supported by the ir spectrum of the product, which shows absorption due to NH at 3350 and 3325 cm^{-1}, carbonyl at 1765 and 1740 cm^{-1},[5] and thiocarbonyl at 1120 cm^{-1}.[6] In agreement, the nmr spectrum displays three one-proton multiplets centered at δ 6.2, 6.8, and 7.0, characteristic of 2-substituted pyrrole derivatives of this type,[4,7] as well as two singlets at δ 8.7 and 9.9 for the imide and pyrrole NH protons, respectively. Oxidation of **1** with alkaline hydrogen peroxide yields the expected *N*-ethoxycarbonylpyrrole-2-carboxamide (**2**),[4] but treatment with hydrogen peroxide in acetic acid leads to *N*-ethoxycarbonylpyrrole-2-thiocarboxamide *s*-oxide (**3**). The ir spectrum of this compound lacks the C=S absorption band at 1120 cm^{-1} and displays, instead, a strong *S*-oxide band at 960 cm^{-1}.[8]

Compound **1** shows considerable reactivity toward nucleophilic reagents at both carbonyl and thiocarbonyl groups. Thus, heating with aqueous sodium hydroxide hydrolyzes the ester group with loss of CO_2 and formation of pyrrole-2-thiocarboxamide (**4**) in excellent yield. Brief boiling with aniline results in substitution at the carbonyl and yields *N*-phenylcarbamoylpyrrole-2-thiocarboxamide (**6**), which is readily oxidized to the known *N*-phenylcarbamoylpyrrole-2-carboxamide (**7**)[4] by hydrogen peroxide. On the other hand, prolonged standing at room temperature of a mixture of **1** and aniline leads to reaction at the thiocarbonyl with elimination of H_2S and formation of *N'*-ethoxycarbonyl-*N*-phenylpyrrole-2-carboxamidine (**8**). The ir spectrum of this compound contains C=O and C=N stretching bands at 1630 and 1570 cm^{-1}, respectively. In view of the low-frequency carbonyl absorption, the α,β-unsaturated ester structure **8** is likelier than that of the tautomeric carbamate.[9] This conclusion is supported by an inspection of the ir spectrum of the corresponding morpholine derivative **9** (obtained when **1** is boiled briefly with ethanolic morpholine) for which similar tautomerism is not possible. In this case the C=O band appears at 1650 cm^{-1} and the C=N band at 1570 cm^{-1}. The formation of *N*-ethoxycarbonylpyrrole-2-carboxamide (**2**) upon hydrolysis of either **8** or **9** by dilute hydrochloric acid is consistent with the structures formulated for these compounds.



It is interesting to note that a different product is obtained when hydrolysis of **8** is attempted by treatment with hot, aqueous NaOH, followed by acidification. This compound, which also results from the thermal decomposition of **8**, may be recrystallized unchanged from benzene or toluene, but is converted to an isomer upon recrystallization from methanol or ethanol. Either of the two isomers is hydrolyzed

(1) A. Treibs and W. Ott, *Justus Liebigs Ann. Chem.*, **577**, 119 (1952).

(2) E. Bullock and R. J. Abraham, *Can. J. Chem.*, **37**, 1391 (1959).

(3) (a) E. P. Papadopoulos and H. S. Habiby, *J. Org. Chem.*, **31**, 327 (1966); (b) E. P. Papadopoulos, *ibid.*, **31**, 3060 (1966).

(4) E. P. Papadopoulos, *ibid.*, **37**, 351 (1972).

(5) In chloroform solution, the two bands merge into one, at 1760 cm^{-1}, with a weak shoulder at 1730 cm^{-1}.

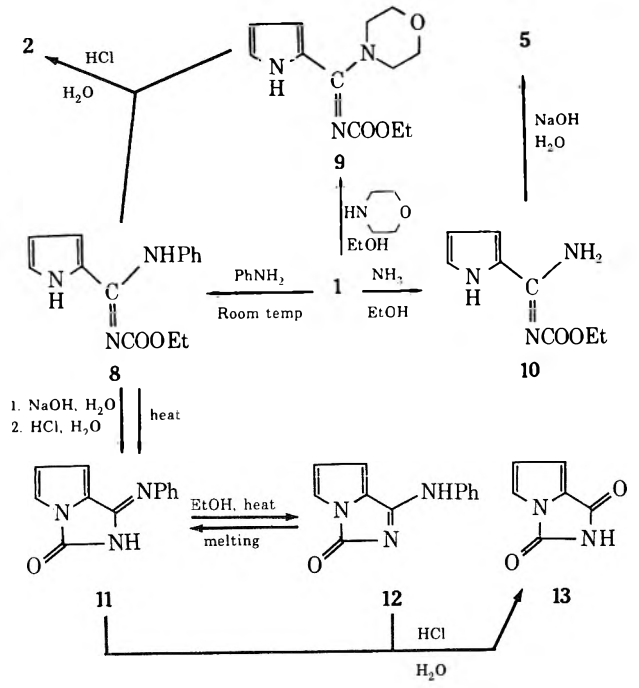
(6) E. Spinner, *J. Chem. Soc.*, 1237 (1960).

(7) L. R. Smith, A. J. Speziale, and J. E. Fedder, *J. Org. Chem.*, **34**, 633 (1969).

(8) W. Walter and H. P. Kubersky, *Justus Liebigs Ann. Chem.*, **694**, 70 (1966).

(9) Compare with C=O stretching frequencies in carbamates: 1720 cm^{-1} in PhNHCOOEt, 1740 and 1765 in **1**, 1770 cm^{-1} in **2**.

readily to pyrrole-1,2-dicarboximide (**13**) by hot, dilute hydrochloric acid.

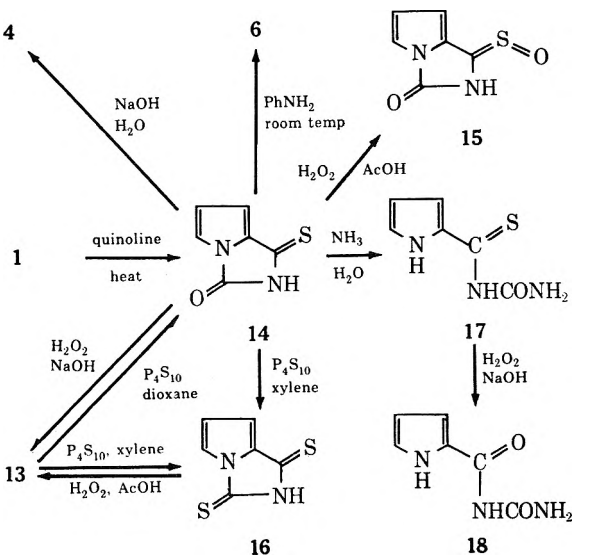


On the basis of ir spectral data, the structure of 1-phenyliminopyrrolo[1,2-*c*]imidazol-3(2*H*)-one (**11**) has been assigned to the initial hydrolysis product, and that of the tautomeric phenylamino derivative **12** to the isomerization product. The ir spectrum of **11** indicates absorption due to C=O at 1780 cm^{-1},[10] and to C=N at 1670 cm^{-1}. In the spectrum of **12**, the corresponding bands appear at 1720 and 1640 cm^{-1}. The lower frequency bands in the case of the latter tautomer are consistent with the conjugation of C=O, as well as the endocyclic position of C=N.[11] In support, the ir spectrum of the analogous morpholine derivative **19**, in which the C=N is by necessity endocyclic, exhibits a C=O band at 1730 cm^{-1} and a C=N band at 1600 cm^{-1}. Of the two tautomer, **11** appears to be the more stable one, because melting converts **12** into **11** but leaves **11** unchanged. Similarly, **12** is converted into **11** upon dissolution in chloroform. This is indicated by the fact that both tautomers give the same ir spectrum in $CHCl_3$ solution showing absorption due to C=O and C=N at 1780 and 1680 cm^{-1}, respectively. There is excellent agreement between the above considerations concerning the structures and ir spectra of tautomers **11** and **12** and the analogous observations made in the cases of 2-iminopyrrolidin-5-ones and 2-amino-Δ^1-pyrrolin-5-ones.[12]

The action of ammonia on **1** is similar to that of aniline and morpholine. Heating of **1** with ethanolic ammonia yields *N'*-ethoxycarbonylpyrrole-2-carboxamidine (**10**). Both ir (C=O at 1680 and C=N at 1620 cm^{-1}) and nmr (broad singlet for $-NH_2$ at δ 8.9) spectra of this compound are fully consistent with the structure assigned to it. Although it resists acid hydrolysis, **10** is readily converted to pyrrole-2-carboxamide (**5**) by hot, aqueous NaOH.

In analogy with the earlier observed behavior of **2**,[4] when **1** is heated with quinoline it undergoes cyclization resulting in elimination of EtOH and formation of 2-thiopyrrole-1,2-dicarboximide (**14**). The ir spectrum of this compound contains carbonyl and thiocarbonyl bands at 1760 and 1150 cm^{-1}, respectively. Its nmr spectrum displays multiplets centered at 6.6, 7.0, and 7.4, for the pyrrole ring protons, and a very broad signal centered at δ 12.3 for the NH proton. The structure formulated for **14** finds support in its formation from pyrrole-1,2-dicarboximide (**13**) by treatment with phosphorus pentasulfide, as well as in its oxidation to **13** by alkaline hydrogen peroxide. By the action of hydrogen peroxide in acetic acid, **14** is converted into 2-thiopyrrole-1,2-dicarboximide *S*-oxide (**15**). An inspection of the ir spectra shows that the spectrum of **15** retains the C=O band at 1770 cm^{-1}, but displays an *S*-oxide band at 1020 cm^{-1}, instead of the C=S band at 1150 cm^{-1} in the spectrum of **14**. Prolonged treatment with P_4S_{10} in refluxing xylene converts both **13** and **14** into pyrrole-1,2-dithiodicarboximide (**16**). The ir spectrum of this compound is characterized by a strong C=S band at 1130 cm^{-1} and the absence of any bands in the carbonyl region. As expected, its nmr spectrum corresponds very closely to that of **14**. Treatment with hydrogen peroxide in acetic acid oxidizes **16** to the dicarboximide **13**.

Nucleophilic reagents attack **14** at either the carbonyl or the thiocarbonyl group. In the first instance, the thiohydantoin ring opens between carbonyl and pyrrole nitrogen, yielding derivatives of pyrrole-2-thiocarboxamide, in complete analogy with the behavior of pyrrole-1,2-dicarboximide (**13**).[4] Thus, treatment with aqueous NH_3 converts **14** to *N*-carbamoylpyrrole-2-thiocarboxamide (**17**). The identification of this compound is based on its spectra (ir, C=O at 1730 cm^{-1}, C=S at 1130 cm^{-1}; nmr, $-NH_2$ at δ 7.8 and 9.1, imide NH at δ 10.8, pyrrole NH at δ 11.7) and its oxidation to the known *N*-carbamoylpyrrole-2-carboxamide (**18**)[4] by hydrogen peroxide. In a similar manner, the action of an excess of aniline on **14** leads to *N*-phenylcarbamoylpyrrole-2-thiocarboxamide (**6**). The analogous ring opening caused by aqueous NaOH proceeds with loss of CO_2 and yields pyrrole-2-thiocarboxamide (**4**). Reac-



(10) Compare with the following C=O stretching frequencies: 1760 cm^{-1} in **14**, 1795 in **13**.

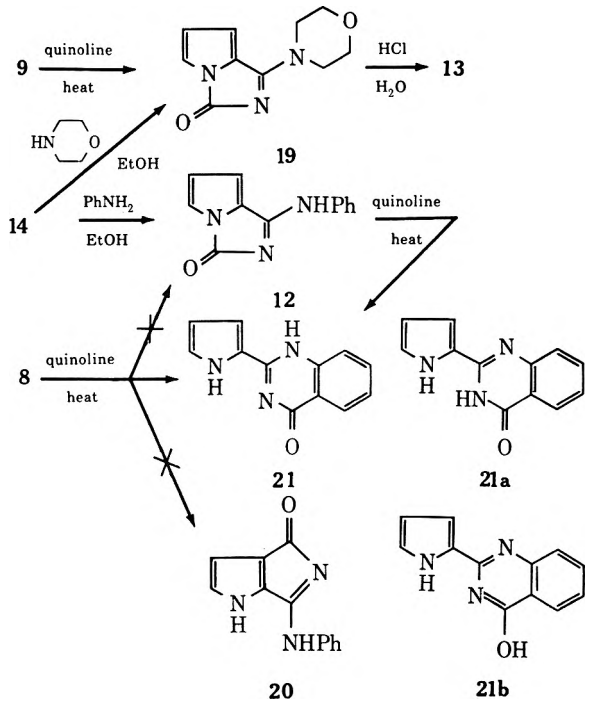
(11) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1962, p 269.

(12) A. Foucaud and P. Plusquellec, *Bull. Soc. Chim. Fr.*, 3813 (1968).

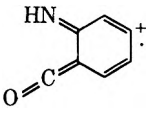
tion at the thiocarbonyl is observed when **14** is treated with a dilute solution of a primary or secondary amine in ethanol and results in replacement of sulfur by an imino group. In this way, treatment with ethanolic aniline yields 1-phenylaminopyrrolo[1,2-*c*]imidazol-3-one (**12**), which, as seen earlier, is also obtained by hydrolysis of the amidine **8**.

A similar reaction between **14** and morpholine in dilute ethanolic solution gives 1-morpholinopyrrolo-[1,2-*c*]imidazol-3-one (**19**). Like **12**, this compound is hydrolyzed by hot, dilute hydrochloric acid to pyrrole-1,2-dicarboximide (**13**).

A cyclization analogous to that involved in the formation of **14** from **1** is observed when the morpholine derivative **9** is heated with quinoline to form **19**. It is of interest to note that the same treatment with hot quinoline fails to convert amidine **8** to **11** or **12**. Instead, an isomer is obtained for which structure **20** or **21** (or a tautomer of either) may reasonably be suggested. The ir spectrum of the product, displaying a sharp NH band at 3420 cm^{-1}, a carbonyl band at 1680 cm^{-1}, and a C=N band at 1600 cm^{-1}, does not allow a choice to be made. However, the presence in it of a



band at 770 cm^{-1}, which is absent from the spectrum of **8**, may be taken to indicate an ortho-disubstituted benzene ring. The nmr and mass spectra, on the other hand, support the structure of 2-(2-pyrrolyl)quinazolin-4(1*H*)-one (**21**) or its 3-H tautomer **21a**.[13] In the nmr spectrum, in addition to two one-proton multiplets centered at δ 6.4 and 7.2, a third multiplet is sufficiently discernible at δ 7.5 (among the signals of the benzene ring protons) to establish the pattern which is characteristic of 2-monosubstituted pyrroles. Furthermore, two multiplets adding up to one proton and centered at δ 8.2 and 8.3 indicate a benzene proton peri to a carbonyl.[14a] There is no evidence for the presence of a significant amount of tautomer **21b**. The mass spectrum exhibits peaks at *m/e* 39 ($C_3H_3^+$), 66 (pyrrolyl ion), 92 (cyanopyrrole ion), and 119 (i), which are consistent

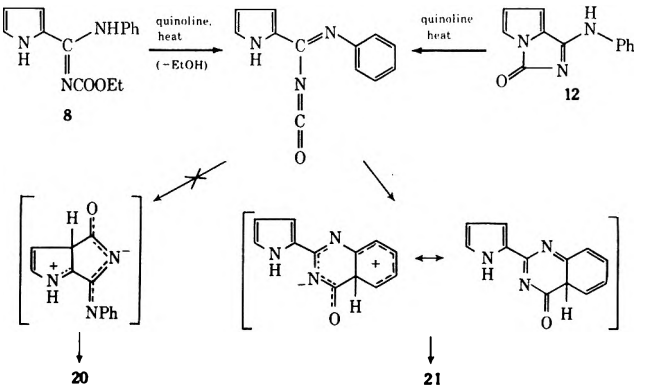


i

with structure **21**, but not with **20**.[14b] Noteworthy is the absence of a peak at *m/e* 77 (phenyl ion), which is prominent in the spectrum of the isomeric phenylamino derivative **12**.

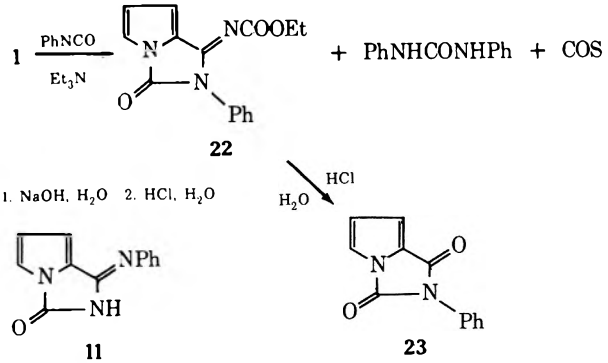
As shown in Scheme I, the formation of quinazolinone **21** from carboxamidine **8** may be accounted for by a re-

SCHEME I



action path in which initial loss of ethanol, resulting in formation of an isocyanate group, is followed by cyclization. Such a path is supported by the observation that **21** is also formed when **12** is heated with quinoline. The fact that electrophilic attack by the isocyanate group on the benzene ring (leading to **21**) is preferred over attack on the pyrrole ring (leading to **20**) may be attributed to the greater stability of the intermediate formed in the former case.

In earlier work,[4] it was found that *N*-ethoxycarbonylpyrrole-2-carboxamide (**2**) reacts with phenyl isocyanate, in the presence of triethylamine, to yield *N*-phenylpyrrole-1,2-dicarboximide (**23**). When the thio



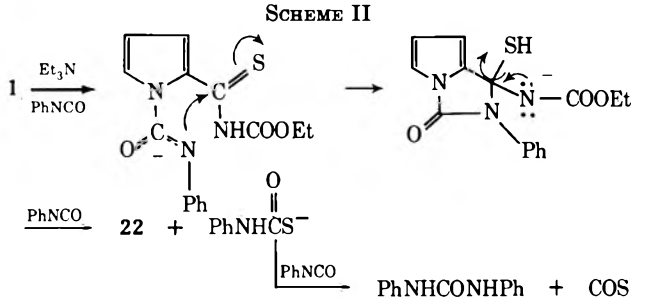
derivative **1** is treated similarly, it reacts in a different manner to form 1-ethoxycarbonylimino-2-phenylpyr-

(13) The formation of quinazolin-4(3*H*)-ones by thermal decomposition of amidines analogous to **8** is a known reaction: (a) R. Shah and M. B. Ichaporia, *J. Chem. Soc.*, 431 (1936); (b) R. Gompper, H. E. Noppel, and S. Schaefer, *Angew. Chem., Int. Ed. Engl.*, **2**, 686 (1963).

(14) (a) S. C. Pakrashi, J. Bhattacharyya, L. F. Johnson, and H. Budjiekiewicz, *Tetrahedron*, **19**, 1011 (1963). (b) Q. N. Porter and J. Baldas, "Mass Spectrometry of Heterocyclic Compounds," Wiley-Interscience, New York, N. Y., 1971, pp 325–333, 482.

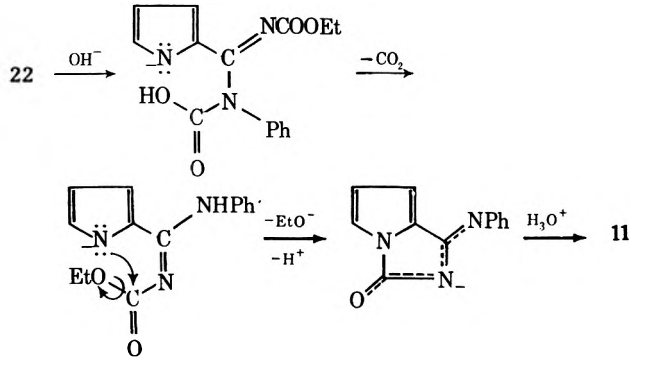
rolo[1,2-c]imidazol-3-one (22), together with *N,N'*-diphenylurea and carbonyl sulfide. The formation of these products may be accounted for by the reaction path shown in Scheme II.

SCHEME II



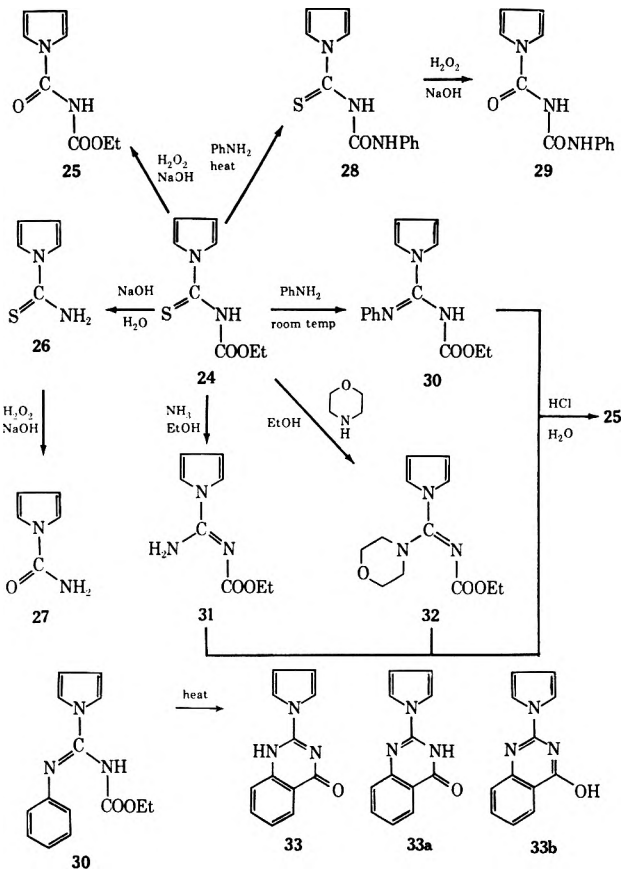
The structure assigned to compound 22 is consistent with its ir spectrum, which displays two carbonyl bands, at 1780 and 1700 cm^{-1}. The nmr spectrum confirms the retention of the ethoxycarbonyl group with typical triplet and quartet signals at δ 1.3 and 4.4. It further exhibits the characteristic pyrrole CH multiplets at δ 6.9, 7.2 and 8.0, as well as a singlet at δ 7.8 for the phenyl protons. Additional support for structure 22 is found in the formation of *N*-phenylpyrrole-1,2-dicarboximide (23) upon hydrolysis with hot, concentrated hydrochloric acid. It is interesting to note that hydrolysis of 22 by hot aqueous NaOH yields the phenylimino derivative 11. It appears that an initial ring opening is followed by loss of CO_2 and a new ring closure, as shown in Scheme III.

SCHEME III



As expected,[3,4] treatment of the potassium salt of pyrrole with ethoxycarbonyl isothiocyanate leads to reaction at the ring nitrogen and formation of *N*-ethoxycarbonylpyrrole-1-thiocarboxamide (24). In many respects, the reactivity of this compound parallels that of its isomer 1. Thus, it is oxidized readily to *N*-ethoxycarbonylpyrrole-1-carboxamide (25)[4] by hydrogen peroxide, although it fails to be converted to an *S*-oxide analogous to 3. Its alkaline hydrolysis proceeds with decarboxylation to yield pyrrole-1-thiocarboxamide (26), which is oxidized to pyrrole-1-carboxamide (27)[4] by hydrogen peroxide. Momentary boiling with aniline converts 24 into *N*-phenylcarbamoylpyrrole-1-thiocarboxamide (28), identified by its oxidation to the known *N*-phenylcarbamoylpyrrole-1-carboxamide (29).[4] Treatment with aniline, at room temperature, or with hot ethanolic ammonia or morpholine gives the corresponding pyrrole-1-carboxamidine derivatives 30, 31, and 32 which are hydrolyzed by dilute hydrochloric acid to *N*-ethoxycarbonylpyrrole-1-carboxamide (25). Ir and nmr spectra of 24–32 (Scheme IV) are fully

SCHEME IV

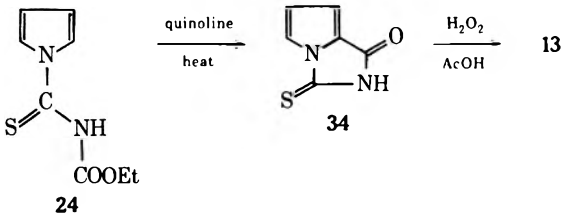


consistent with their proposed structures. For the product of the reaction with aniline at room temperature, the relatively high C=O stretching frequency (1725 cm^{-1}, Nujol mull) supports the structure of *N*-ethoxycarbonyl-*N'*-phenylpyrrole-1-carboxamidine (30), rather than that of the tautomeric α,β-unsaturated ester. The opposite must be true for this compound in solution, because the carbonyl band of the spectrum in $CHCl_3$ appears at 1650 cm^{-1}. For the earlier considered, isomeric pyrrole-2-carboxamidine derivative 8, in contrast, the C=O band appears at the same position (1630 cm^{-1}) both in emulsion and in solution spectra.

When heated 20–30° above its melting point, compound 30 loses ethanol and yields 2-(1-pyrrolyl)-quinazolin-4(1*H*)-one (33) or its 3-H tautomer 33a. This remarkably easy and clean transformation is analogous with the formation of the isomeric quinazolinone 21, when 8 is boiled with quinoline, but contrasts with the conversion of 8 into 11 by simple thermal decomposition.

Compared with the ir spectrum of 21, that of 33 lacks a strong, sharp NH band, but retains the C=O and C=N bands at essentially the same positions (1675 and 1615 cm^{-1}, respectively). The nmr spectrum of 33 displays two triplets at δ 6.4 and 7.8, which are characteristic of 1-monosubstituted pyrroles, as well as two multiplets, centered at δ 8.1 and 8.2, which indicate a benzene proton peri to a carbonyl.[14a] There is only a weak, diffuse signal, centered at about δ 12.5, for the NH proton. As in the case of 21, there is no evidence

supporting the presence of a significant amount of tautomer **33b**.



Rather unexpectedly, brief boiling of **24** with quinoline causes ring closure at position 2 of the pyrrole ring and yields 1-thiopyrrole-1,2-dicarboximide (**34**). The elimination of EtOH is indicated by the nmr spectrum of the product, which displays only three one-proton multiplets (centered at δ 6.6, 6.9, and 7.6) for the ring protons, in addition to a very broad signal (centered at δ 12.5) for the NH proton. The ir spectrum contains a carbonyl band at 1750 cm^{-1} and a thiocarbonyl band at 1140 cm^{-1}. Oxidation of this compound with hydrogen peroxide in acetic acid gives pyrrole-1,2-dicarboximide (**13**). No *S*-oxide analogous to **15** is isolated.

Experimental Section[15]

***N*-Ethoxycarbonylpyrrole-2-thiocarboxamide** (**1**).—A mixture of 16.8 g (0.25 mol) of pyrrole and 32.8 g (0.25 mol) of ethoxycarbonyl isothiocyanate,[16] both ice-cold, was swirled occasionally and cooled as needed to prevent its temperature from rising above 40°. Within about 1 hr the mixture had solidified, whereupon it was allowed to stand overnight. Following repeated washing of the product with petroleum ether (bp 60–90°), there was obtained 46.2 g (93%) of **1**, mp 95–98°. Recrystallization from aqueous ethanol gave the pure compound in the form of yellow crystals: mp 98.5–99.5°; ir 3350, 3325, 1765, 1740, 1535, 1510, 1340, 1210, 1120, 1070, 1025, 900, 870, 750, 695, and 620 cm^{-1}; nmr ($CDCl_3$) δ 1.3 (t, 3, J = 7 Hz, $-CH_3$), 4.2 (q, 2, J = 7 Hz, $-OCH_2-$), 6.2 (m, 1, pyrrolyl CH), 6.8 (m, 1, pyrrolyl CH), 7.0 (m, 1, pyrrolyl CH), 8.7 (s, 1, imide NH), and 9.9 (s, 1, pyrrolyl NH).

Anal. Calcd for $C_8H_{10}O_2N_2S$: C, 48.46; H, 5.08; N, 14.13. Found: C, 48.65; H, 5.20; N, 13.92.

Oxidation of 1 to *N*-Ethoxycarbonylpyrrole-2-carboxamide (**2**).—To an ice-cold solution of 0.50 g of **1** in 5 ml of absolute ethanol was added 1.0 g of anhydrous sodium carbonate and 5 ml of hydrogen peroxide (30%). The mixture was kept in an ice–water bath for 15 min, and at room temperature for a further 2 hr. Dilution with water and filtration yielded 0.25 g of **2**, mp 136–137°, raised to 138–140° by recrystallization from CH_2Cl_2 (lit.[4] mp 140–141°).

***N*-Ethoxycarbonylpyrrole-2-thiocarboxamide *S*-Oxide** (**3**).—Hydrogen peroxide (30%, 10 ml) was added in portions to an ice-cold mixture of 3.0 g of **1**, 3.0 g of sodium acetate, and 20 ml of acetic acid. When the resulting solution was allowed to stand at room temperature, a precipitate was formed within a few minutes. Dilution with water and filtration gave 3.0 g (94%) of **3**, mp 124.5–125.5° dec. An analytical sample was obtained by recrystallization from ethyl acetate as yellow crystals: mp 125–126° dec; ir 3240, 3150, 1720, 1560, 1525, 1400, 1270, 1240, 1140, 1080, 1040, 1000, 960, 860, 835, 750, 660, 600, and 470 cm^{-1}; nmr δ 1.3 (t, 3, J = 7 Hz, $-CH_3$), 4.4 (q, 2, J = 7 Hz, $-OCH_2-$), 6.6 (m, 1, pyrrolyl CH), 7.5 (m, 2, pyrrolyl CH), 10.8 (s, 1, NH), and 13.2 (s, 1, NH).

Anal. Calcd for $C_8H_{10}O_3N_2S$: C, 44.85; H, 4.71; N, 13.07. Found: C, 44.66; H, 4.72; N, 13.22.

(15) Melting points were determined in a Thomas-Hoover apparatus with use of a calibrated thermometer. A Perkin-Elmer Model 337 infrared spectrophotometer was used to take infrared spectra in Nujol. Nmr spectra were obtained on a Varian A-60A spectrophotometer using solutions in hexadeuteriodimethyl sulfoxide (unless otherwise indicated) with tetramethylsilane as internal standard. Known compounds were identified by comparison of their ir and nmr spectra with those of authentic samples, as well as by mixture melting point determination.

(16) R. W. Lamon, *J. Heterocycl. Chem.*, **5**, 837 (1968).

Pyrrole-2-thiocarboxamide (**4**). **A. By Hydrolysis of 1.**—A solution of 2.0 g of **1** in 10 ml of 10% aqueous sodium hydroxide was heated on the steam bath for 10 min. Cooling and filtration yielded 1.2 g (92%) of **4**, as pale yellow crystals: mp 161–162, raised to 162–164° by recrystallization from toluene (lit.[17] mp 162–164°); ir 3340, 3280, 3170, 1625, 1530, 1420, 1310, 1110, 1090, 1060, 970, 890, 880, 845, 750, 700, 600, 580, and 445 cm^{-1}; nmr δ 6.2 (m, 1, CH), 7.0 (m, 2, CH), 9.1 (s, 2, $-NH_2$), and 10.0–11.7 (very broad s, 1, pyrrolyl NH).

B. By Hydrolysis of 14.—Upon dissolution of 0.50 g of **14** in 5 ml of 10% aqueous sodium hydroxide, a solid started precipitating almost at once. Filtration, after 15 min, yielded 0.35 g (85%) of **4**, mp 160–162° raised to 161–163° by recrystallization from toluene.

Oxidation of 4 to Pyrrole-2-carboxamide (**5**).—To an ice-cold suspension of 0.50 g of **4** in 5 ml of 20% aqueous sodium hydroxide was added gradually 5 ml of hydrogen peroxide (30%) and the resulting mixture was kept in an ice–water bath for 10 min. When the reaction flask had been allowed to stand at room temperature for a few minutes, a vigorous reaction took place with evolution of gas and formation of a white precipitate. A cooling treatment followed by filtration yielded 0.30 g of **5**, mp 173–176° (lit.[18] mp 176.5°).

***N*-Phenylcarbamoylpyrrole-2-thiocarboxamide** (**6**). **A. From 1.**—A mixture of 1.0 g of **1** and 5 ml of aniline was boiled for about 1 min and the resulting solution was cooled and then filtered. Following washing of the precipitate with carbon tetrachloride, there was obtained 1.1 g (92%) of **6**, mp 211–212°. Recrystallization from ethanol yielded the pure compound in the form of yellow crystals: mp 213–214°; ir 3380, 3225, 3150, 1700, 1600, 1560, 1330, 1230, 1110, 1060, 980, 890, 860, 750, 690, 565, 520, and 505 cm^{-1}; nmr δ 6.3 (m, 1, pyrrolyl CH), 7.0–7.7 (m, 7, phenyl and pyrrolyl CH), 11.2 (s, 1, NH), 11.8 (sharp s superimposed on broad signal, 2, NH).

Anal. Calcd for $C_{12}H_{11}ON_3S$: C, 58.75; H, 4.52; N, 17.14. Found: C, 58.92, H, 4.42; N, 17.00.

B. From 14.—A mixture of 1.0 g of **14** and 5 ml of aniline was allowed to stand at room temperature for 18 hr. Dilution with carbon tetrachloride and filtration yielded 0.80 g (50%) of **6**, mp 207–209°, raised to 212–214° by recrystallization from ethanol.

Oxidation of 6 to *N*-Phenylcarbamoylpyrrole-2-carboxamide (**7**).—Hydrogen peroxide (30%, 3 ml) was added to 0.20 g of **5** and two crushed pellets of sodium hydroxide in 10 ml of ethanol, and the resulting mixture was allowed to stand in an ice–water bath for 1 hr. Following addition of another 3 ml of hydrogen peroxide, the reaction mixture was kept cold for a further 2 hr. It was then diluted with water, acidified, and filtered. There resulted 0.10 g of **7**, mp 250–252°. After recrystallization from ethanol, the melting point became 256–257° (lit.[4] mp 257–257.5°).

***N'*-Ethoxycarbonyl-*N*-phenylpyrrole-2-carboxamidine** (**8**).—A solution of 10 g of **1** in 30 ml of aniline was stirred magnetically, at room temperature, for 6 days. Removal of the excess of aniline by evaporation in a current of air and recrystallization of the residue from aqueous ethanol yielded 8.3 g (91%) of **8**, mp 98–100°. The pure compound was obtained as colorless crystals by further recrystallization from aqueous ethanol: mp 99.5–100.5°; ir 3250–3125, 1630, 1570, 1320, 1260, 1230, 1130, 1100, 1050, 930, 910, 880, 810, 750, 700, 690, and 605 cm^{-1}; nmr δ 1.1 (distorted t, 3, J = 7 Hz, $-CH_3$), 4.0 (distorted q, 2, J = 7 Hz, $-OCH_2-$), 6.2 (m, 1, pyrrolyl CH), 6.5–6.7 (m, 1, pyrrolyl CH), 7.0–7.5 (m, 6, phenyl and pyrrolyl CH), 9.3 and 9.8 (s, 1, PhNH–), and 11.5 (s, 1, pyrrolyl NH).

Anal. Calcd for $C_{14}H_{15}O_2N_3$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.50; H, 5.91; N, 16.51.

Hydrolysis of 8 to 2.—A mixture of 0.50 g of **8** and 5 ml of dilute hydrochloric acid was heated on the steam bath for 0.5 hr. Cooling of the product in an ice–water bath caused the precipitation of 0.20 g of **2**, mp 136–138°. Recrystallization from CH_2Cl_2 raised the melting point to 139–141°.

***N'*-Ethoxycarbonyl-*N*,*N*-oxybisethylenepyrrole-2-carboxamidine** (**9**).—A solution of 2.0 g of **1** and 5 ml of morpholine in 10 ml of absolute ethanol was boiled for 3 min and, after it had been cooled, it was diluted with cold water and the inner surface of the flask was scratched with a glass rod to induce crystallization.

(17) T. P. Sycheva, Z. A. Pankina, and M. N. Shchukina, *Zh. Obshch. Khim.*, **33**, 3654 (1963); *Chem. Abstr.*, **60**, 8012*h* (1964).

(18) E. Fischer and D. D. Van Slyke, *Chem. Ber.*, **44**, 3166 (1911).

Filtration yielded 1.8 g (72%) of **9**, mp 148–150°, and recrystallization from benzene gave the pure compound in the form of colorless crystals: mp 149–150°; ir 3200, 1650, 1570, 1300, 1260, 1210, 1180, 1125, 1110, 1040, 945, 900, 890, 870, 850, 805, 730, 610, and 510 cm^{-1}; nmr δ 1.0 (t, 3, J = 7 Hz, $-CH_3$), 3.4 (m, 4, morpholine $-CH_2NCH_2-$), 3.7 (m, 4, morpholine $-CH_2OCH_2-$), 3.9 (q, 2, J = 7 Hz, $-OCH_2-$), 6.2 (m, 1, pyrrolyl CH), 6.3 (m, 1, pyrrolyl CH), 6.9 (m, 1, pyrrolyl CH), and 11.3 (s, 1, NH).

Anal. Calcd for $C_{12}H_{17}O_3N_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.38; H, 6.94; N, 16.65.

Hydrolysis of 9 to 2.—A mixture of 0.30 g of **9** and 3 ml of dilute hydrochloric acid was heated on the steam bath for 25 min. Chilling of the product yielded 0.10 g of **2**, mp 138–140°.

***N'*-Ethoxycarbonylpyrrole-2-carboxamidine (10).**—A solution of 2.0 g of **1** in 10 ml of absolute ethanol saturated with ammonia at 0° was placed in a pressure bottle and heated on the steam bath for 1 hr. It was then cooled, diluted with water, and extracted with ether. Following a drying treatment ($MgSO_4$), evaporation of the ether solution to dryness yielded 1.6 g (89%) of **10**, mp 129–133°. The pure compound was obtained by recrystallization from water as light tan crystals: mp 136–137°; ir 3320, 3200, 1680, 1620, 1575, 1510, 1300, 1260, 1210, 1140, 1110, 1100, 1040, 970, 950, 890, 810, 750, 595, and 530 cm^{-1}; nmr δ 1.2 (t, 3, J = 7 Hz, $-CH_3$), 4.1 (q, 2, J = 7 Hz, $-OCH_2-$), 6.2 (m, 1, pyrrolyl CH), 7.0 (m, 1, pyrrolyl CH), 7.1 (m, 1, pyrrolyl CH), 8.9 (s, 2, $-NH_2$), and 11.6 (s, 1, pyrrolyl NH).

Anal. Calcd for $C_8H_{11}O_2N_3$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.23; H, 6.14; N, 23.11.

Hydrolysis of 10 to Pyrrole-2-carboxamide (5).—A mixture of 0.50 g of **10** and 10 ml of 10% aqueous sodium hydroxide was boiled for 15 min. A cooling treatment followed by filtration yielded 0.20 g of **5**, mp 173–175°, raised to 175–176° by recrystallization from aqueous ethanol.

1-Phenyliminopyrrolo[1,2-*c*]imidazol-3(2*H*)-one (11). A. By Hydrolysis of 8.—A mixture of 2.0 g of **8** and 10 ml of 10% aqueous sodium hydroxide was boiled until initial dissolution of the solid had been followed by formation of a new precipitate (about 1 min). The resulting mixture was cooled, then diluted with water and filtered. The solid material thus obtained was suspended in a small amount of water and acidified with dilute hydrochloric acid. A new filtration yielded 1.3 g (81%) of **11**, mp 165–166°, and recrystallization from benzene afforded the pure compound as pale yellow crystals: mp 168–168.5°; ir 1780, 1670, 1590, 1430, 1330, 1225, 1180, 1070, 1045, 910, 780, 735, 695, 625, 515, and 510 cm^{-1}; nmr δ 5.6 and 6.8 (m, 1, 3-pyrrolyl CH), 6.4 (m, 1, 4-pyrrolyl CH), 7.0–7.6 (m, 6, phenyl and 5-pyrrolyl CH), and 11.3 (s, 1, NH).

Anal. Calcd for $C_{12}H_9ON_3$: C, 68.24; H, 4.30; N, 19.89. Found: C, 68.04; H, 4.29; N, 20.02.

B. By Thermal Decomposition of 8.—Melted **8** (0.50 g) was kept at 145–155° (internal temperature) until evolution of EtOH had practically ceased (2–3 min). Upon cooling, there was obtained 0.35 g (85%) of crude **11**, mp 158–168°.

Hydrolysis of 11 to Pyrrole-1,2-dicarboximide (13).—A mixture of 0.50 g of **11** and 5 ml of dilute hydrochloric acid was heated on the steam bath for 0.5 hr. Cooling of the product followed by filtration yielded 0.30 g of **13**, mp 206–210°. After recrystallization from ethanol, the melting point of the product became 209–211° (lit.[4] mp 209–211°).

1-Phenylaminopyrrolo[1,2-*c*]imidazol-3-one (12). A. From 11.—Recrystallization of crude **11** from methanol or ethanol gave **12** in the form of light yellow crystals: mp 167.5–168.5°; ir 3290, 3170, 1720, 1640, 1580, 1520, 1400, 1340, 1280, 1230, 1175, 1085, 1070, 1040, 910, 870, 855, 795, 760, 745, 710, 680, 580, and 510 cm^{-1}; nmr, same as for **11**.

Anal. Calcd for $C_{12}H_9ON_3$: C, 68.24; H, 4.30; N, 19.89. Found C, 68.36; H, 4.50; N, 20.11.

B. From 14.—A solution of 1.0 g of **14** and 5 ml of aniline in 50 ml of absolute ethanol was stirred magnetically, at room temperature, for 48 hr. At the end of this period, filtration yielded 0.50 g (36%) of **12**, mp 163–165°. Longer reaction times and/or increased concentration of aniline led to higher yields of less pure product.

Hydrolysis of 12 to 13.—As described for the hydrolysis of **11**, from 0.50 g of **12** and 5 ml of dilute hydrochloric acid, there was obtained 0.20 g of **13**, mp 209–212°.

2-Thiopyrrole-1,2-dicarboximide (14). A. From 1.—A mixture of 5.0 g of **1** and 15 ml of quinoline was heated in a 25-ml erlenmeyer flask until the temperature of the escaping vapor reached 170–180°. The resulting tarry material was cooled, then mixed with cold, dilute hydrochloric acid, and extracted with ether. After it had been washed with water, treated with charcoal, and dried ($MgSO_4$), the ether solution was evaporated to dryness to yield 3.3 g (87%) of **14**, mp 135–138°. Recrystallization from aqueous ethanol gave the pure compound in the form of orange-red crystals: mp 140–141.5°; ir 3200, 1760, 1550, 1400, 1300, 1200, 1150, 1060, 1010, 890, 750, 700, 690, 660, 620, and 475 cm^{-1}; nmr δ 6.6 (m, 1, CH), 7.0 (m, 1, CH), 7.4 (m, 1, CH), and 12.3 (broad s, 1, NH)

Anal. Calcd for $C_6H_4ON_2S$: C, 47.35; H, 2.65; N, 18.41. Found: C, 47.46; H, 2.60; N, 18.29.

B. From 13.—A mixture of 0.50 g of **13**, 2.0 g of phosphorus pentasulfide, and 25 ml of dioxane was refluxed for 1 hr. After it had been cooled, the reaction mixture was diluted with 200 ml of ether and filtered. The resulting ether solution was washed with water, treated with decolorizing charcoal, dried ($MgSO_4$), and evaporated to dryness. Recrystallization of the residue from carbon tetrachloride gave 0.30 g (50%) of **14**, mp 138–139.5°.

Oxidation of 14 to 13.—To an ice-cold solution of 0.30 g of **14** and one crushed pellet of sodium hydroxide in 10 ml of absolute ethanol was added 5 ml of hydrogen peroxide (30%) and the resulting mixture was kept in an ice–water bath for 2 hr. After dilution with water to 50 ml and acidification with dilute hydrochloric acid, the solution was saturated with sodium chloride and extracted with ether. The extract was washed with saturated brine, treated with charcoal, dried ($MgSO_4$), and evaporated to dryness to yield 0.10 g of **13**, mp 208–211°.

2-Thiopyrrole-1,2-dicarboximide *S*-Oxide (15).—To an ice-cold mixture of 1.0 g of **14**, 1.0 g of sodium acetate, and 10 ml of acetic acid was added 5 ml of hydrogen peroxide (30%), in five portions. Upon standing at room temperature, the orange-red solid went into solution and a new, yellow precipitate was formed. Dilution with water followed by filtration yielded 0.9 g (82%) of **15**, mp 150–150.5° dec. An analytical sample was obtained by recrystallization from ethanol as yellow crystals: mp 150.5–151° dec; ir 3280, 3130, 1770, 1550, 1400, 1300, 1240, 1200, 1175, 1050, 1020, 955, 900, 820, 780, 740, 710, 690, 630, 580, and 480 cm^{-1}; nmr δ 6.7–7.0, 7.4 (m, 2, CH), 7.8 (m, 1, CH), and 12.9 (broad s, 1, NH).

Anal. Calcd for $C_6H_4O_2N_2S$: C, 42.85; H, 2.40; N, 16.66. Found: C, 42.91; H, 2.61; N, 16.86.

Pyrrole-1,2-dithiodicarboximide (16). A. From 14.—The mixture obtained when 1.0 g of **14**, 4.0 g of phosphorus pentasulfide, and 50 ml of xylene had been refluxed for 25 hr was cooled, diluted with 400 ml of ether, and filtered. Following treatment with decolorizing charcoal and anhydrous magnesium sulfate, the ether solution was evaporated to dryness, and the resulting residue was recrystallized from carbon tetrachloride to yield 0.60 g (55%) of pure **16** as dark purple crystals: mp 183–184°; ir 3150 (broad), 1550, 1410, 1320, 1240, 1205, 1130, 1040, 1000, 895, 820, 735, 650, 520, and 440 cm^{-1}; nmr δ 6.6 (t, 1, J = 3 Hz, CH), 7.1 (d, 1, J = 3 Hz, CH), 7.5 (d, 1, J = 3 Hz, CH), and 13.7 (s, 1, NH).

Anal. Calcd for $C_4H_4N_2S_2$: C, 42.83; H, 2.40; N, 16.66. Found: C, 42.79; H, 2.66; N, 16.72.

B. From 13.—To a mixture of 1.0 g of **13**, 4.0 g of phosphorus pentasulfide, and 30 ml of xylene, which had been refluxed for 24 hr, was added another 4.0 g of phosphorus pentasulfide and the refluxing was continued for a further 41 hr. Following the same procedure as in the previous preparation, there was obtained 0.70 g (64%) of **16**, mp 180–184°.

Oxidation of 16 to 13.—A mixture of 0.30 g of **16**, 0.30 g of sodium acetate, 3 ml of acetic acid, and 3 ml of hydrogen peroxide (30%) was allowed to stand at room temperature for 24 hr. At the end of this period, a further 3 ml of hydrogen peroxide was introduced into the reaction mixture, which was then allowed to stand for an additional 24 hr. Dilution with water followed by extraction with ether yielded a solution, which was washed with water and aqueous sodium bicarbonate, dried ($MgSO_4$), and evaporated to dryness. Trituration of the residue with petroleum ether (bp 30–60°) yielded 0.050 g of **13**, mp 210–212°.

***N*-Carbamoylpyrrole-2-thiocarboxamide (17).**—Brief (4–5 min) standing of a solution of 1.0 g of **14** in 2 ml of concentrated aqueous ammonia resulted in the formation of a precipitate which was collected by filtration. The yield was 0.80 g (73%) of **17**, mp 169–171°. The pure compound was obtained in the form of yellow crystals by recrystallization from water: mp 171–172°; ir 3390, 3370, 3250, 1730, 1580, 1540, 1330, 1280, 1130,

1060, 1035, 960, 885, 850, 840, 745, 580, 565, 540, and 450 cm^{-1}; nmr δ 6.3 (m, 1, CH), 7.3 (m, 1, CH), 7.4 (m, 1, CH), 7.8 and 9.1 (broad singlets, 2, $-NH_2$), 10.8 (s, 1, imide NH), and 11.7 (s, 1, pyrrole NH).

Anal. Calcd for $C_6H_7ON_3S$: C, 42.59; H, 4.17; N, 24.83. Found C, 42.75; H, 4.21; N, 24.62.

Oxidation of 17 to *N*-Carbamoylpyrrole-2-carboxamide (18).—Hydrogen peroxide (30%, 5 ml) was added in one portion to an ice-cold solution of 0.20 g of **17** and two pellets of NaOH in a mixture of 5 ml of ethanol and 1 ml of water. Following standing of 1–2 min in an ice–water bath, the mixture was acidified with dilute hydrochloric acid and filtered. There was obtained 0.12 g of **18**, mp 239–240° (lit.[4] mp 240–241°).

1-Morpholinopyrrolo[1,2-*c*]imidazol-3-one (19). A. From 9.—A mixture of 2.0 g of **9** and 3 ml of quinoline was boiled in a 25-ml erlenmeyer flask until the temperature of the escaping vapor reached 150–160°, and then it was cooled and filtered. There resulted 1.5 g (94%) of **19**, mp 180–182°. An analytical sample, colorless crystals obtained by recrystallization from carbon tetrachloride, melted at 184–185°: ir 1730, 1600, 1530, 1410, 1350, 1290, 1270, 1230, 1195, 1165, 1115, 920, 880, 770, 740, 725, 685, 620, 590, and 535 cm^{-1}; nmr δ 3.9 (s, 8, morpholine CH), 6.6 (t, 1, J = 3 Hz, pyrrolyl CH), 7.0 (d, 1, J = 3 Hz, pyrrolyl CH), and 7.7 (d, 1, J = 3 Hz, pyrrolyl CH).

Anal. Calcd for $C_{10}H_{11}O_2N_3$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.57; H, 5.43; N, 20.53.

B. From 14.—A solution of 1.0 g of **14** and 0.60 g of morpholine in 30 ml of absolute ethanol was allowed to stand at room temperature for 2 hr. Filtration yielded 0.50 g of **19**, mp 184–185°, and an overnight stay of the filtrate afforded a further 0.10 g of material having the same melting point (total yield 46%).

Hydrolysis of 19 to 13.—A mixture of 0.30 g of **19** and 3 ml of dilute hydrochloric acid was heated on the steam bath for 30 min. Following a cooling treatment, filtration yielded 0.15 g of **13**, mp 208–210°.

2-(2-Pyrrolyl)quinazolin-4(1*H* or 3*H*)-one (21). A. From 8.—A mixture of 2.0 g of **8** and 5 ml of quinoline was placed in a 25-ml erlenmeyer flask and boiled until the temperature of the escaping vapor reached 160–170°. The resulting dark brown liquid was cooled, then mixed with CCl_4 and filtered. There was obtained 1.3 g (81%) of **21**, mp 274–276°. Recrystallization from ethanol yielded the pure compound as colorless needles: mp 277–278°; ir 3420, 1680, 1600, 1540, 1500, 1420, 1320, 1270, 1240, 1165, 1105, 1075, 1050, 1020, 980, 910, 890, 870, 770, 740, 685, 650, 630, 590, 550, 530, and 500 cm^{-1}; nmr δ 6.4 (m, 1, pyrrolyl CH), 7.2 (m, 1, pyrrolyl CH), 7.3–8.3 (m, 5, pyrrolyl and phenyl CH), 11.8 (s, 1, NH), and 12.3 (s, 1, NH).

Anal. Calcd for $C_{12}H_9ON_3$: C, 68.24; H, 4.30; N, 19.89. Found: C, 68.14; H, 4.34; N, 19.88.

B. From 12.—A mixture of 0.30 g of **12** and 3 ml of quinoline was heated to the boiling point, then cooled and diluted with CCl_4. Filtration yielded 0.10 g of **21**, mp 275–277°.

1-Ethoxycarbonylimino-2-phenylpyrrolo[1,2-*c*]imidazol-3-one (22).—Addition of 3 ml of triethylamine to an ice-cold mixture of 2.0 g of **1** and 3.6 g of phenyl isocyanate caused a vigorous reaction to occur with evolution of a gas. After an overnight stay in the refrigerator, the product was mixed with 50 ml of chloroform, and the resulting mixture was filtered to yield 1.0 g of a colorless solid, mp 240–242°, identified as *N*,*N*′-diphenylurea (infrared spectrum, mixture melting point). Evaporation of the filtrate to dryness, followed by trituration of the residue with ethanol and filtration, afforded 1.5 g of **22**, mp 155–162°. The pure compound was obtained in the form of colorless crystals by recrystallization from ethanol: mp 163–164°; ir 1780, 1700, 1650, 1610, 1490, 1280, 1260, 1240, 1165, 1145, 1120, 1010, 830, 795, 750, 700, 690, 640, 620, 610, 580, and 500 cm^{-1}; nmr δ 1.3 (t, 3, J = 7 Hz, $-CH_3$), 4.4 (q, 2, J = 7 Hz, $-OCH_2-$), 6.9 (t, 1, J = 3 Hz, pyrrolyl CH), 7.2 (d, 1, J = 3 Hz, pyrrolyl CH), 7.8 (s, 5, phenyl CH), and 8.0 (d, 1, J = 3 Hz, pyrrolyl CH).

Anal. Calcd for $C_{15}H_{13}O_3N_3$: C, 63.58; H, 4.63; N, 14.84. Found: C, 63.66; H, 4.64; N, 14.72.

The gas evolved in this reaction was identified as carbonyl sulfide in the following manner. It was conducted into a solution of 2 ml of piperidine in 20 ml of dry ether and the precipitate formed (mp 111–112° dec) was recrystallized from dry acetone to yield a colorless, crystalline solid, mp 113–114°. The identity of this as piperidinium 1-piperidinecarbothiolate (lit.[19] mp 117°) was established by comparison with an authentic sample prepared from COS and piperidine in ether.

Hydrolysis of 22. A. To *N*-Phenylpyrrole-1,2-dicarboximide (23).—A mixture of 0.50 g of **22** and 5 ml of concentrated hydrochloric acid was boiled for 1–2 min. Cooling of the product, followed by filtration, yielded 0.30 g of **23**, mp 208–220°, raised to 224–226° by recrystallization from ethanol (lit.[3] mp 226–227°).

B. To 1-Phenyliminopyrrolo[1,2-*c*]imidazol-3(2*H*)-one (11).—Boiling of a mixture of 1.0 g of **22** and 10 ml of 10% aqueous sodium hydroxide for 1–2 min yielded a precipitate, which was collected by filtration, suspended in a small amount of water, and acidified with dilute hydrochloric acid. A new filtration afforded 0.50 g of **11**, mp 165–167°.

***N*-Ethoxycarbonylpyrrole-1-thiocarboxamide (24).**—Pyrrolylpotassium was prepared in a nitrogen atmosphere by the gentle refluxing of a stirred mixture of 40.2 g (0.60 mol) of pyrrole, 100 ml of tetrahydrofuran, and 19.5 g (0.50 g-atom) of potassium, until all of the metal had reacted. Following dilution with 150 ml of solvent and chilling of the slurry in an ice–salt bath, there was introduced a solution of 59.0 g (0.45 mol) of ethoxycarbonyl isothiocyanate in 100 ml of tetrahydrofuran, dropwise, at such a rate that the reaction temperature was kept below 10° (addition time 1.5 hr). The reaction mixture was stirred for a further 0.5 hr, then it was mixed with 2 lb of absolute ether and filtered. The potassium salt thus obtained was dissolved in water, and the resulting solution was washed with ether, chilled, and acidified with acetic acid. Filtration yielded 39.8 g (45%) of crude **24**, mp 77–80°, and recrystallization from petroleum ether (bp 60–90°) afforded the pure compound as yellow needles: mp 80–81°; ir 3210, 1730, 1500, 1320, 1220, 1125, 1095, 1070, 1040, 1015, 970, 880, 795, 755, 735, 685, 630, 600, and 570 cm^{-1}; nmr ($CDCl_3$) δ 1.3 (t, 3, J = 7 Hz, $-CH_3$), 4.3 (q, 2, J = 7 Hz, $-OCH_2-$), 6.3 (t, 2, J = 2 Hz, pyrrolyl CH), 7.4 (t, 2, J = 2 Hz, pyrrolyl CH), and 8.7 (s, 1, NH).

Anal. Calcd for $C_8H_{10}O_2N_2S$: C, 48.47; H, 5.09; N, 14.13. Found: C, 48.70; H, 5.07; N, 14.12.

Oxidation of 24 to 25.—The mixture resulting from the addition of two crushed pellets of NaOH and 1 ml of hydrogen peroxide (30%) to an ice-cold solution of 0.20 g of **24** in 2 ml of ethanol was kept in an ice–water bath for 15 min. A further 1 ml of hydrogen peroxide was then added, and the reaction mixture was allowed to stand at room temperature for an additional 15 min. At the end of this period, acidification yielded 0.050 g of **25**, mp 114–115°. Recrystallization from aqueous ethanol raised the melting point to 120–122° (lit.[4] mp 121.5–123°).

Pyrrole-1-thiocarboxamide (26).—A solution of 0.50 g of **24** in 10 ml of 10% aqueous sodium hydroxide was brought quickly to the boiling point and then heated on the steam bath, under reduced pressure (water aspirator), for 5 min. Following addition of 5 ml of water the heating was continued under suction for a further 5 min. The resulting solution was made ice-cold and weakly acidic to yield 0.25 g (78%) of **26**, mp 157–160°. An analytical sample was obtained as colorless crystals by recrystallization from water: mp 159–160°; ir 3320, 3275, 3150, 1625, 1280, 1115, 1075, 950, 830, 745, 735, 710, 645, 590, 575, and 535 cm^{-1}; nmr δ 6.3 (t, 2, J = 2 Hz, pyrrolyl CH), 7.7 (t, 2, J = 2 Hz, pyrrolyl CH), and 9.1–9.4 (broad, overlapping d, 2, $-NH_2$).

Anal. Calcd for $C_5H_6N_2S$: C, 47.60; H, 4.79; N, 22.20. Found: C, 47.55; H, 4.94; N, 22.32.

Oxidation of 26 to Pyrrole-1-carboxamide (27).—To an ice-cold solution of 0.30 g of **26** in 3 ml of 10% aqueous sodium hydroxide was added 1 ml of hydrogen peroxide (30%) and the resulting mixture was allowed to stand in an ice–water bath for 2–3 min. Filtration yielded 0.15 g of **27**, mp 162–164° (lit.[20] mp 165–166°).

***N*-Phenylcarbamoylpyrrole-1-thiocarboxamide (28).**—A mixture of 0.50 g of **24** and 2 ml of aniline was brought quickly to the boiling point, then cooled and diluted with ethanol. Filtration yielded 0.20 g (32%) of **28**, mp 208–210°. The pure compound was obtained as colorless crystals by recrystallization from 1-butanol: mp 209–210°; ir 3240, 3160, 1685, 1600, 1560, 1300, 1230, 1120, 1050, 1020, 970, 900, 850, 750, 730, 690, 570, 530, and 510 cm^{-1}; nmr δ 6.4 (t, 2, J = 2 Hz, pyrrolyl CH), 7.1–7.7(m, 7, pyrrolyl and phenyl CH), 10.4 (s, 1, NH), and 9.6–11.6 (very diffuse signal, 1, NH).

Anal. Calcd for $C_{12}H_{11}ON_3S$: C, 58.76; H, 4.52; N, 17.13. Found: C, 58.90; H, 4.60; N, 17.20.

(19) J. Parrod, *C. R. Acad. Sci.*, **234**, 1062 (1952).

(20) D. A. Shirley, B. H. Gross, and P. A. Roussel, *J. Org. Chem.*, **20**, 225 (1955).

Oxidation of 28 to *N*-Phenylcarbamoylpyrrole-1-carboxamide (29).—Upon addition of 2 ml of hydrogen peroxide (30%) to an ice-cold mixture of 0.20 g of **28**, two crushed pellets of NaOH, and 2 ml of ethanol, a vigorous reaction took place with formation of a white precipitate. Dilution with water yielded 0.10 g of **29**, mp 221–222°, raised to 229–230° by recrystallization from ethanol (lit.[4] mp 229–230°).

***N*-Ethoxycarbonyl-*N'*-phenylpyrrole-1-carboxamidine (30).**—After a mixture of 2.0 g of **24** and 5 ml of aniline had stood at room temperature for 4 days, the resulting solution was placed on a watch glass and allowed to evaporate to dryness in a current of air. The residue thus obtained was recrystallized from aqueous ethanol to yield 2.2 g (85%) of **30**, colorless crystals, mp 112–114°. Further recrystallization from aqueous ethanol gave the pure compound: mp 114–115°; ir 3330, 1725, 1650, 1590, 1530, 1500, 1340, 1230, 1090, 1070, 1020, 960, 915, 830, 770, 745, 695, 660, 620. 590, 580, and 540 cm^{-1}; nmr δ 1.0 (t, 3, J = 7 Hz, $-CH_3$), 3.9 (q, 2, J = 7 Hz, $-OCH_2-$), 6.3 (t, 2, J = 2 Hz, pyrrolyl CH), 7.0–7.4 (m, 7, pyrrolyl and phenyl CH), and 10.1 (s, 1, NH).

Anal. Calcd for $C_{14}H_{15}O_2N_3$; C, 65.35; H, 5.88; N, 16.33. Found: C, 65.39; H, 5.82; N, 16.41.

Hydrolysis of 30 to 25.—Heating on the steam bath of a mixture of 0.50 g of **30** and 5 ml of dilute hydrochloric acid for 1–2 min resulted in the formation of a heavy oil, which yielded upon cooling 0.30 g of **25**, mp 119–121°, raised to 121–123° by recrystallization from ethanol.

***N'*-Ethoxycarbonylpyrrole-1-carboxamidine (31).**—A mixture of 1.0 g of **24** and 10 ml of absolute ethanol saturated with ammonia at 0° was placed in a pressure bottle and heated on the steam bath for 0.5 hr. The resulting solution was cooled and diluted with water to yield 0.80 g (88%) of **31** as a colorless solid: mp 124–126°, raised to 125–126° by recrystallization from ethanol; ir 3375, 3325, 1670, 1620, 1510, 1320, 1280, 1260, 1210, 1100, 1120, 970, 940, 890, 810, 740, and 690 cm^{-1}; nmr δ 1.3 (t, 3, J = 7 Hz, $-CH_3$), 4.2 (q, 2, J = 7 Hz, $-OCH_2-$), 6.4 (t, 2, J = 2 Hz, pyrrolyl CH), 7.7 (t, 2, J = 2 Hz, pyrrolyl CH), and 9.1 (s, 2, $-NH_2$).

Anal. Calcd for $C_8H_{11}O_2N_3$: C, 53.03; H, 6.12; N, 23.19. Found: C, 53.06; H, 6.14; N, 23.30.

Hydrolysis of 31 to 25.—When a mixture of 0.50 g of **31** and 5 ml of dilute hydrochloric acid had been heated on the steam bath for 20 min, a considerable amount of tar was formed. Chilling of the solution caused precipitation of 0.10 g of **25**, mp 120–121°. After recrystallization from ethanol, the melting point became 121–123°.

***N'*-Ethoxycarbonyl-*N*,*N*-oxybisethylenepyrrole-1-carboxamidine (32).**—A solution of 2.0 g of **24**, 5 ml of morpholine, and 10 ml of absolute ethanol was boiled for 3 min, then chilled and diluted with water to yield 0.60 g (24%) of **32**, mp 109–111°. Recrystallization from carbon tetrachloride afforded the pure compound in the form of colorless crystals: mp 110–111°; ir 1680, 1610, 1310, 1290, 1260, 1250, 1210, 1170, 1120, 1095, 1045, 950, 905, 875, 845, 800, 750, 715, 635, 600, and 520 cm^{-1}; nmr δ 1.0 (t, 3, J = 7 Hz, $-CH_3$), 3.4 (m, 4, morpholine $-CH_2-NCH_2-$), 3.7 (m, 4, morpholine $-CH_2OCH_2-$), 3.9 (q, 2, J = 7 Hz, $-OCH_2-$), 6.3 (t, 2, J = 2 Hz, pyrrolyl CH), and 6.9 (t, 2, J = 2 Hz, pyrrolyl CH).

Anal. Calcd for $C_{12}H_{17}O_3N_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.18; H, 6.72; N, 16.77.

Hydrolysis of 32 to 25.—Heating on the steam bath for a few moments of a mixture of 0.40 g of **32** and 5 ml of dilute hydrochloric acid, followed by cooling and filtration, yielded 0.20 g of **25**, mp 120–122°.

2-(1-Pyrrolyl)quinazolin-4(1*H* or 3*H*)-one (33).—When melted **30** (0.40 g) had been kept at 140–150° (internal temperature) for a few minutes (until complete solidification), there resulted 0.30 g (90%) of **33**, mp 266–267°. Recrystallization from ethanol yielded the pure compound in the form of colorless needles: mp 267–268°; ir 1675, 1615, 1570, 1540, 1360, 1340, 1250, 1070, 970, 910, 770, 735, 710, 630, 590, 555, and 505 cm^{-1}; nmr δ 6.4 (t, 2, J = 2 Hz, pyrrolyl CH), 7.8 (t, 2, J = 2 Hz, pyrrolyl CH), 7.3–8.3 (m, 4, benzene ring CH), and 11.7–13.3 (weak, very broad signal, NH).

Anal. Calcd for $C_{12}H_9ON_3$: C, 68.24; H, 4.30; N, 19.89. Found: C, 68.08; H, 4.50; N, 19.65.

1-Thiopyrrole-1,2-dicarboximide (34).—A mixture of 5.0 g of **24** and 5 ml of quinoline was heated in a 25-ml erlenmeyer flask until the temperature of the escaping vapor reached 150–160°. The resulting tarry material was treated as described earlier for **14** to yield 2.2 g (58%) of crude **34**, mp 179–185°. The pure compound was obtained as yellow crystals by recrystallization from toluene: mp 197–198.5°; ir 3150, 1750, 1550, 1300, 1260, 1140, 1055, 1000, 900, 725, 700, 690, 665, 600, 570, and 495 cm^{-1}; nmr δ 6.6 (t, 1, J = 3 Hz, CH), 6.9 (d, 1, J = 3 Hz, CH), 7.6 (d, 1, J = 3 Hz, CH), and 12.5 (broad s, 1, NH).

Anal. Calcd for $C_6H_4ON_2S$: C, 47.36; H, 2.65; N, 18.41. Found: C, 47.56; H, 2.68; N, 18.29.

Oxidation of 34 to 13.—A mixture of 0.50 g of **34**, 0.50 g of sodium acetate, 5 ml of acetic acid, and 3 ml of hydrogen peroxide (30%) was stirred magnetically at room temperature for 24 hr. Following addition of another 2 ml of hydrogen peroxide, stirring was continued for a further 18 hr. At the end of this period, dilution with water yielded 0.20 g of **13**, mp 210–212°.

Registry No.—**1**, 37488-43-0; **3**, 37488-44-1; **4**, 37488-45-2; **6**, 37488-46-3; **8**, 37488-47-4; **9**, 37488-48-5; **10**, 37488-49-6; **11**, 37488-50-9; **12**, 37488-51-0; **13**, 13939-91-8; **14**, 37488-53-2; **15**, 37488-54-3; **16**, 37488-55-4; **17**, 37488-56-5; **19**, 37488-57-6; **21**, 37488-58-7; **22**, 37488-59-8; **24**, 37488-60-1; **26**, 37488-61-2; **28**, 37488-62-3; **30**, 37488-63-4; **31**, 37488-64-5; **32**, 37488-65-6; **33**, 37488-66-7; **34**, 37500-25-7; pyrrole, 109-97-7; ethoxycarbonyl isothiocyanate, 16182-04-0; pyrrole potassium salt, 16199-06-7.

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Reactions of Azides with Isocyanates. Cycloadditions and Cycloreversions

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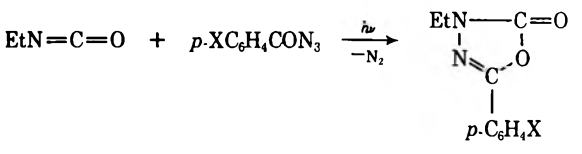
Reactions of alkyl azides with aryl isocyanates, acyl isocyanates, carboalkoxy isocyanates, and sulfonyl isocyanates, as well as reactions of aryl azides with sulfonyl isocyanates, provide a convenient method for the synthesis of 1,4-disubstituted Δ^2-tetrazolin-5-ones (**5**, **6**, and **9**). 1-Alkyl-4-sulfonyl-Δ^2-tetrazolin-5-ones (**9a–e**) undergo cycloreversion upon thermolysis. The forward and reverse reactions are accelerated by the introduction of electron-withdrawing groups on the isocyanate moiety. The kinetics of the cycloreversion reaction of selected examples were studied; energies of activation and heats of reaction were determined.

Only a few reactions of azides with isocyanates have been reported. The lack of interest in this topic probably originates from the recognition that alkyl and aryl isocyanates can be prepared from acyl azides by the well-known Curtius rearrangement,[1] and, hence, do not react with their precursors. Photochemically, however, aroyl azides yield aroylnitrenes,[2] which were shown by Lwowski[3] to react with ethyl isocyanate to give 2-aryl-4-ethyl-1,3,4-oxadiazolin-5-ones (**1**). Thermolysis and photolysis of azidoformates in the presence of alkyl isocyanates also led to oxadiazolinones, but the major products in this case were 1-carboalkoxy-2,4-dialkylurazoles (**2**). The intermediacy of 1-carboalkoxy-4-alkyl-Δ^2-tetrazolin-5-ones (**3**) in this reaction might be postulated but is questionable.



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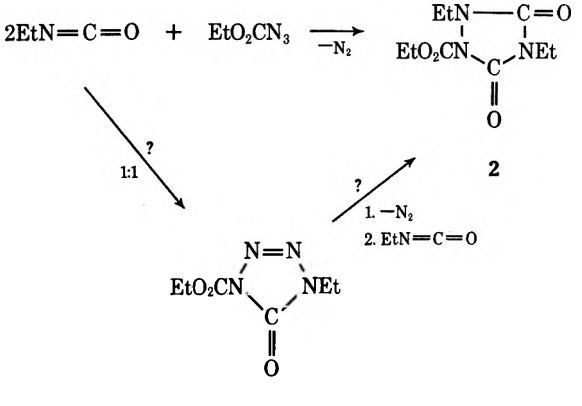

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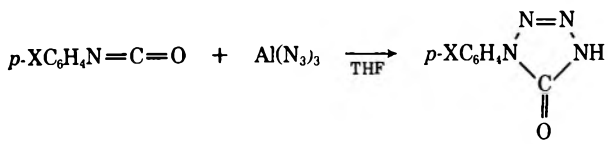
3

A suitable synthetic route to monosubstituted Δ^2-tetrazolin-5-ones (**4**) is available and involves the reaction of aluminum azide with aryl isocyanates in tetrahydrofuran.[4] Sodium azide failed to react with isocyanates, while hydrazoic acid reacted in a different manner to give carbamoyl azides.[5]

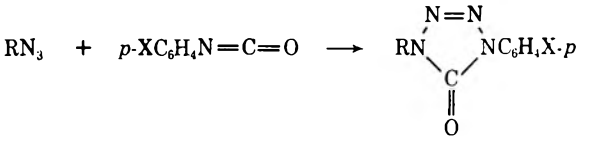


4

1,4-Disubstituted Δ^2-tetrazolin-5-ones, though synthesized on several occasions,[6] were until now not accessible by a general and direct method. We now wish to report that several 1,4-disubstituted Δ^2-tetrazolin-5-ones are readily prepared by 1,3-dipolar cycloaddition of alkyl azides, and to a lesser extent aryl azides, with suitable isocyanates. We also found that electronegatively substituted adducts undergo cycloreversion on thermolysis. The results are described in the present paper.

Additions to Aryl Isocyanates.—Butyl isocyanate was found to be unreactive toward all azides used, *i.e.*, butyl azide, phenyl azide, *p*-nitrophenyl azide, *p*-methoxyphenyl azide, and tosyl azide. No change in the ir spectra was observed when the reagents were mixed and allowed to stand for several months at 60°.

Although aryl isocyanates also did not react with aryl azides and tosyl azide, slow addition was observed with equimolar amounts of butyl azide and cyclohexyl azide. The reactions were monitored by ir (2200 and 2100 cm^{-1}) and the corresponding cycloadducts (**5**) were isolated in high yields (see Table I).



5

TABLE I

SYNTHESIS OF 1-ALKYL-4-ARYL-Δ^2-TETRAZOLIN-5-ONES (**5**)

Compd	R	X	Solvent, temp in °C, time	Yield, %	Mp, °C
5a	*n*-C_4H_9	H	130, 23 days	80	Liquid, bp 132 (0.7 mm)
5b	*n*-C_4H_9	NO_2	C_6H_6,[a] reflux, 40 hr	72	86.5–87
5c	*c*-C_6H_{11}	NO_2	55, 10 days	86	192–195

[a] Carried out in 1 *M* solution.

(1) P. A. S. Smith, *Org. React.*, **3**, 337 (1946).

(2) L. Horner and A. Christmann, *Chem. Ber.*, **96**, 388 (1963); L. Horner, G. Bauer, and J. Dörges, *ibid.*, **98**, 2631 (1965).

(3) W. Lwowski, *Trans. N. Y. Acad. Sci.*, **33**, 259 (1971).

(4) J. P. Horwitz, B. E. Fisher, and A. J. Tomasewski, *J. Amer. Chem. Soc.*, **81**, 3076 (1959).

(5) E. Lieber, R. L. Minnis, and C. N. R. Rao, *Chem. Rev.*, **65**, 377 (1965).

(6) (a) K. Hattori, E. Lieber, and J. P. Horwitz, *J. Amer. Chem. Soc.*, **78**, 411 (1956); (b) D. F. Perceival and R. M. Herbst, *J. Org. Chem.*, **22**, 925 (1957); (c) J. K. Elwood and J. W. Gates, *ibid.*, **32**, 2956 (1967); (d) W. S. Wadsworth, *ibid.*, **34**, 2994 (1969); (e) R. Raap and J. Howard, *Can. J. Chem.*, **47**, 813 (1969).

Characterization of the products followed from spectral and microanalysis. In particular, the ir spectra exhibited the expected[4,6] strong C=O absorptions at 1725–1735 cm^{-1} (absence of electron delocalization).

Chemically, compounds of type **5** were thermally stable and inert toward acids as previously reported.[6] Thus, heating a sample of **5a** at 250° for several hours did not induce decomposition. It must be pointed out that a concerted thermal supra–supra elimination of nitrogen from **5** is symmetry forbidden.[7]

Additions to Acyl and Carboalkoxy Isocyanates.—Efforts to obtain cycloadducts from the reactions of aryl azides with benzoyl isocyanate, chloroacetyl isocyanate, and trichloroacetyl isocyanate (few months at 60°) were unsuccessful. On the contrary, when isocyanates were treated with alkyl azides in the absence of solvent, 1-alkyl-4-acyl (or carboalkoxy) Δ^2-tetrazolin-5-ones (**6**) were obtained in good yields. Table II lists

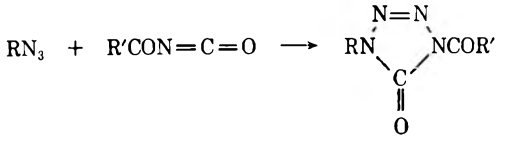


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TABLE II
SYNTHESIS OF 1-ALKYL-4-ACYL (OR CARBOALKOXY) Δ^2-TETRAZOLIN-5-ONES (6)

Compd	R	R′	Temp, °C	Time, days	Yield, %	Mp, °C
6a	n-C_4H_9	C_6H_5	25	30	0	
			100	7	>80	Oil
6b		p-$NO_2C_6H_4$	55	13	65	79–81.5
6c		$ClCH_2$	25	2	0	
			55	6	>80	*a*
6d		Cl_3C	25	6	>80	Oil
6e		OC_2H_5	55	30	>80	Oil
6f		OC_6H_5	55	30	>80	Oil
6g	i-C_3H_7	$ClCH_2$	55	8	70	104–107
6h		Cl_3C	25	10	>80	*a*
6i		OC_6H_5	55	25	82	120–124.5
6j	c-C_5H_9	C_6H_5	100	11	73	56–58
6k	c-C_6H_{11}	C_6H_5	100	7	82	96–99
6l		$ClCH_2$	55	8	75	113–125
6m		Cl_3C	25	6	>80	*a*
6n		OC_6H_5	55	25	87	111–113

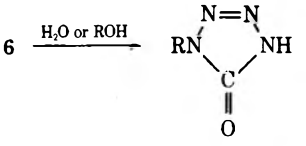
[a] Hygroscopic solids which hydrolyze in contact with atmosphere.

the results and also illustrates the rate enhancement by the introduction of electron-withdrawing substituents on the isocyanate.

The structures **6a–n** were ascertained by spectral analyses. Worth mentioning are the typical ir absorptions at 1770–1810 and at 1720–1730 cm^{-1} corresponding respectively to the side chain C=O[8] and ring C=O stretching vibrations.

To test thermal stability, one selected example (**6n**) was heated in nitrobenzene at 150° for 3 days and recovered in almost quantitative yield. The ir spectrum of the crude product, however, showed the presence of a small amount of azide (2100 cm^{-1}), resulting from cycloreversion.

The new compounds of type **6** all exhibited the unusual properties attributed to azolides.[8] For instance, they underwent facile hydrolysis and alcoholysis at room temperature to yield 1-alkyl-Δ^2-tetrazolin-5-ones (**7**). In some cases, hydrolysis even occurred with



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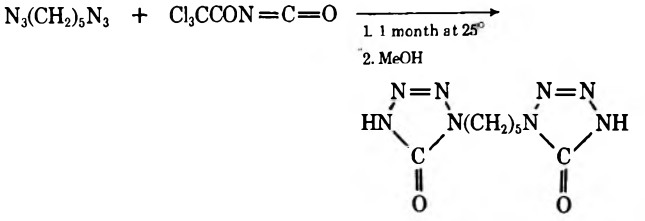
atmospheric moisture, preventing the isolation of the adducts in the pure state (see Table II). We made use of this property to prepare bistetrazolinone **8** by



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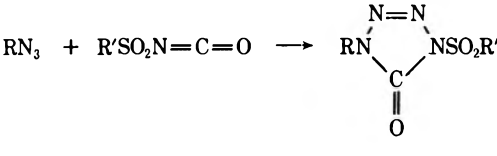
reaction of 1,5-diazidopentane with trichloroacetyl isocyanate and subsequent methanolysis of the crude mixture. Compound **8** was isolated in 65% overall yield. The existence of **7** and **8** in the keto form rather than in the tautomeric hydroxytetrazole form has been established previously.[4,6a,9]

Additions to Sulfonyl Isocyanates.—Sulfonyl isocyanates were found to react readily with alkyl and aryl azides to give 1-alkyl (or aryl) 4-sulfonyl-Δ^2-tetrazolin-5-ones (**9**) in good yields (see Table III). Bistetrazolinones were also prepared by this method from diisocyanates or diazides. Thus, **9j** was obtained from m-phenylenedisulfonyl isocyanate and n-butyl azide (55°, 3 days), and **9k** resulted from the interaction of p-tolylsulfonyl isocyanate and 1,5-diazidopentane (55°, 6 days).



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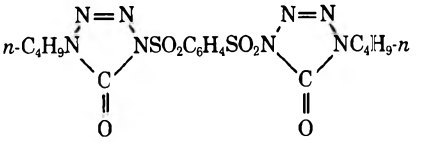
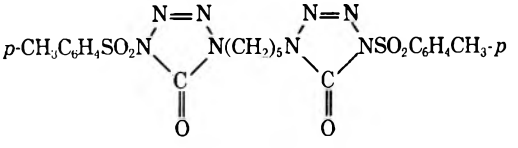


9j (40%, mp 119–120°)



9k (62%, mp 144–145°)

(7) R. B. Woodward and R. Hoffman, *Angew. Chem.*, **81**, 797 (1969); *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969). Photochemically induced elimination of nitrogen from 1,4-dimethyl-Δ^2-tetrazolin-5-one has been reported; see ref 6d.

(8) H. A. Staab, *Angew. Chem.*, **74**, 407 (1962); *Angew. Chem., Int. Ed. Engl.*, **1**, 351 (1962).

(9) J. C. Kauer and W. A. Sheppard, *J. Org. Chem.*, **32**, 3580 (1967).

TABLE III

SYNTHESIS OF 1-ALKYL (OR ARYL) 4-SULFONYL-Δ^2-TETRAZOLIN-5-ONES (9)

Compd	R	R'	Solvent	Temp, °C	Time, days	Yield, %	Mp, °C
9a	n-C_4H_9	p-$CH_3C_6H_4$		55	6	70	51–52.5
			Toluene[a]	25	60	79	
9b		C_6H_5		55	5	82	42.5–43.5
			CCl_4[b]	25	30	85	
9c		p-ClC_6H_4	Toluene[a]	25	30	84	76–77.5
9d		p-$NO_2C_6H_4$	Toluene[a]	25	17	75	124–125
9e		m-$NO_2C_6H_4$	Toluene[a]	25	22	75	90–91
9f		Cl	C_6H_6	25	Instantaneous	±95	[c]
9g	C_6H_5	p-ClC_6H_4		55	90	±60	177.5–178
9h	p-$CH_3C_6H_4$	p-ClC_6H_4		87	7	35	195.5–196.5
9i	p-$CH_3OC_6H_4$	p-ClC_6H_4		55	30	70	183.5–184

[a] Carried out in 0.6 M solution. [b] Carried out in 1.5 M solution. [c] Colorless, hygroscopic liquid, bp 60–70° (2 mm), ir 1765 cm^{-1}.

TABLE IV

KINETICS OF CYCLOREVERSION OF 1-n-BUTYL-4-SULFONYL-Δ^2-TETRAZOLIN-5-ONES IN CHLOROBENZENE (0.05 MOL $l.^{-1}$)

		10^4k_1, min^{-1}		$\Delta E^{\ddagger}$, kcal mol^{-1}		$\Delta S^{\ddagger}$ at 114.8°, eu	
Compd	Temp, °C	C=O method	N_3 method	C=O	N_3	C=O	N_3
9a	100.8	1.1	1.4	33.6	29.3	2.9	−0.3
	114.8	6.6	5.9				
	124.8	18.0	15.7				
9b	100.8	1.6	2.0	33.2	31.6	2.5	6.7
	114.8	9.0	10.1				
	124.8	26.4	29.0				
9c	100.8	4.0	4.1	32.7	30.2	3.1	4.5
	114.8	23.0	20.3				
	124.8	63.1	47.4				
9d	92.0	7.7		30.4		2.3	
	100.8	22.3	16.1				
	114.8	91.0	87.5				
9e	92.0	8.4		30.0		−0.9	
	100.8	26.9	23.3				
	114.8	103.0	98.6				

Compounds **9a–k** exhibited strong ir (KBr) absorptions near 1750 cm^{-1}. As expected,[8] they were more resistant than **6** toward nucleophilic attack by water and alcohol. For instance, ethanolysis of **9c** only occurred after being held more than 2 days at reflux temperature. An exception to this general behavior was provided by compound **9f**, which decomposed in contact with the atmosphere to give an unidentified viscous material.

Cycloreversions of 1-Alkyl-4-sulfonyl-Δ^2-tetrazolin-5-ones.—Although retro Diels–Alder reactions are well known,[10] only a few cycloreversions of 1,3-dipole adducts have been reported.[11] No examples are known in the azide field.[12] We have now found that 1-alkyl-4-sulfonyl-Δ^2-tetrazolin-5-ones (**9**) undergo thermal decomposition at about 100° into starting materials. The reactions gave equilibrium compositions, for which the rates of cycloreversion and cycloaddition were equal. Kinetic measurements were carried out with typical examples (**9a–e**) in chlorobenzene solution using ir techniques. The reaction rates were determined both by recording the decrease of the tetrazolinone C=O absorption (1750 cm^{-1}) and the progressive formation of the azide absorption (2100 cm^{-1}). Good agreement was obtained between the two methods. The initial first-order rate constants (k_1) and activation parameters are given in Table IV.

A linear Hammett correlation was observed with a ρ value of +1.4 at 114.8°. Thus, the rate of cycloreversion increased with increasing electronegativity of the isocyanate moiety, as was also observed for the forward reaction. The activation entropies of the cycloreversions are low compared with values reported for ring opening of substituted 5-aminotetrazoles,[13] and, hence, are not consistent with an open-chain betaine intermediate. The influence of solvent polarity on the rate of cycloreversion also points to the same conclusion. Thus, the decomposition rate constants for **9b** in chlorobenzene and nitrobenzene at 125° were 26.4 × 10^{-4} and 70 × 10^{-4} min^{-1}, respectively. The observed increase is too low to account for a betaine intermediate.[14]

All the results thus far obtained on the cycloaddition and cycloreversion reactions are compatible with a

(10) H. Kwart and K. King, *Chem. Rev.*, **68**, 415 (1968).

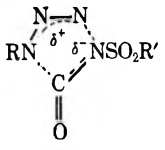
(11) A. Mustafa, *J. Chem. Soc.*, 234 (1949); G. K. Buckley, *ibid.*, 1850 (1954); R. Grashey and K. Adelsberger, *Angew. Chem.*, **74**, 292 (1962); *Angew. Chem., Int. Ed. Engl.*, **1**, 267 (1962); R. Grashey, H. Leitermann, R. Schmidt, and K. Adelsberger, *Angew. Chem.*, **74**, 491 (1962); *Angew. Chem., Int. Ed. Engl.*, **1**, 406 (1962); R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **101**, 2568 (1968); **102**, 736 (1969).

(12) R. Huisgen [*Angew. Chem., Int. Ed. Engl.*, **2**, 570 (1963)] reported briefly the formation of methyl azide and benzonitrile upon thermolysis of 2-methyl-5-phenyltetrazole. The reaction, however, was not reversible.

(13) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Amer. Chem Soc.*, **77**, 2264 (1955).

(14) R. Huisgen, *Angew. Chem.*, **75**, 741 (1963); *Angew. Chem., Int. Ed. Engl.*, **2**, 633 (1963); *J. Org. Chem.*, **33**, 2291 (1968).

concerted mechanism, involving a charge imbalance in the transition state as shown in **10**.



10

Since the systems give equilibrium mixtures, the equilibrium constants at different temperatures were determined and the heats of reaction were calculated (see Table V). The cycloreversions were endothermic

TABLE V
EFFECT OF TEMPERATURE ON EQUILIBRIUM CONSTANTS

K_{eq} = [azide][isocyanate]/[adduct]

Compd	Temp, °C	K_{eq}, mol l.$^{-1}$ C=O method	K_{eq}, mol l.$^{-1}$ N_3 method	Heat of reaction, kcal mol^{-1}
9a	101.0	3.6	4.4	18.1
	107.7	6.2	5.9	
	114.7	7.8	7.4	
	124.5	15.9	15.7	
9c	101.3	4.1	4.4	15.9
	107.7	7.0	7.1	
	114.7	9.3	8.9	
	124.2	15.3	15.8	
9e	101.0	4.6	5.1	10.8
	107.5	7.0	6.0	
	115.5	9.4	8.6	
	119.7	9.6	10.1	

for 10–18 kcal mol^{-1}. From the activation energies of the cycloreversion and the heats of reaction, a rough estimation of the activation energies of the cycloaddition process can be made. The values thus obtained (13–19 kcal mol^{-1}) are in good agreement with those published for reactions of azides with dipolarophiles.[15]

Finally a *concluding remark* concerning the reaction leading to compound **2** is in order. At least thermally, compound **3** cannot be an intermediate for two reasons. First, alkyl isocyanates do not react at all with azides. Second, compounds of type **3** do not eliminate nitrogen on thermolysis but, instead, were shown to cycloreverse slowly. The mechanism of the reaction remains obscure.

Experimental Section

Aryl isocyanates,[16] acyl isocyanates,[17] and sulfonyl isocyanates[18] were prepared as reported.

General Procedure for the Synthesis of 1,4-Disubstituted Δ^2-Tetrazolin-5-ones (5, 6, and 9).—Equimolar amounts of azide and isocyanate were allowed to react in the absence of solvent, unless otherwise stated (see Tables I–III). In the case of **6b** an excess of azide was used. After complete reaction (monitored by ir), the adducts were isolated by crystallization from ether (solids) or by distillation under reduced pressure (liquids). The solids were recrystallized from ether, except **9k**, which was recrystallized from acetone. The products were characterized by ir (KBr or neat), nmr, and microanalysis. The C, H, N, and O analyses of the water-stable adducts were within 0.3%.

Acid Treatment of Tetrazolinones 5a and 5b.—Compound **5a** (1 g) was heated in HCl solution (20 ml, 10 *N*) at 60° for 24 hr. The mixture was then neutralized with NaOH and extracted with ether to regenerate **5a** in quantitative yield.

Compound **5b** (2.5 g) was heated in concentrated H_2SO_4 solution (15 ml) for 24 hr. The mixture was poured into ice and **5b** was recovered in nearly quantitative yield.

Hydrolysis and Methanolysis of 6.—Compounds of type **6** hydrolyzed or methanolyzed instantaneously in contact with water or methanol. The ir absorption bands at 1770–1810 cm^{-1} disappeared in favor of bands in the region 1680–1750 cm^{-1}. The following products were isolated in the pure state: **7** (R = c-C_6H_{11}), 75%, mp 122–123° (toluene); **7** (R = c-C_5H_9), 79% mp 134–135°; **8**, 65%, mp 164–166° (MeOH).

Thermolysis of 9c.—Compound **9c** was heated at 130° in a distillation flask. Butyl azide was distilled off and characterized by comparison with an authentic sample. The residue was shown to contain *p*-chlorobenzenesulfonyl isocyanate, ir 2200 cm^{-1}.

Kinetics.—Pure tetrazolinone was accurately weighed and dissolved in dry solvent. The solution was maintained at constant temperature, and the reaction was followed spectrometrically (Perkin-Elmer ir 521 instrument) using the intensity of the tetrazolinone C=O and azide N_3 absorption bands. The concentrations were determined from the observed absorptions using calibration curves. Measurements were made within the first 20% conversion. The first-order rate constants were determined from the slopes of log (C=O or N_3) *vs* time. The energies of activation were determined from the Arrhenius plots of log k_1 *vs.* $1/T$. The entropies of activation were calculated from the rate constants at 114.8° by use of the Eyring equation: $\Delta S^{\ddagger} = 4.576 \log k_1 (\text{sec}^{-1}) - 49.14 - 4.576 \log T + \Delta E^{\ddagger}/T$.

Determination of Equilibrium Constants.—The constants K_{eq} were determined under strictly anhydrous conditions, using high-vacuum techniques. Sealed samples of tetrazolinone in chlorobenzene were allowed to equilibrate at the appropriate temperature. Product concentrations were then determined by ir. Heats of reaction were calculated from the curves of log K_{eq} *vs.* $1/T$. (Decomposition of the azide under the equilibrium conditions occurred to a small extent. Thus, when butyl azide was heated in chlorobenzene at 115° for 5 days, 10% decomposition was observed.)

Registry No.—**5a**, 37495-05-9; **5b**, 37495-06-0; **5c**, 37495-07-1; **6a**, 37495-08-2; **6b**, 37528-57-7; **6c**, 37495-09-3; **6d**, 37495-10-6; **6e**, 37495-11-7; **6f**, 37495-12-8; **6g**, 37495-13-9; **6h**, 37495-14-0; **6i**, 37495-15-1; **6j**, 37495-16-2; **6k**, 37495-17-3; **6l**, 37495-18-4; **6m**, 37495-19-5; **6n**, 37528-58-8; **7** (R = c-C_6H_{11}), 37495-20-8; **7** (R = c-C_5H_9), 37495-21-9; **8**, 37495-22-0; **9a**, 37495-23-1; **9b**, 37495-24-2; **9c**, 37495-25-3; **9d**, 37666-05-0; **9e**, 37528-59-9; **9f**, 37495-26-4; **9g**, 37642-67-4; **9h**, 37495-27-5; **9i**, 37495-28-6; **9j**, 37495-29-7; **9k**, 37495-30-0; RN_3 (R = *n*-C_4H_9), 7332-00-5; RN_3 (R = c-C_6H_{11}), 19573-22-9; RN_3 (R = *i*-C_3H_7), 691-57-6; RN_3 (R = c-C_5H_9), 33670-50-7; RN_3 (R = C_6H_5), 622-37-7; RN_3 (R = *p*-$CH_3C_6H_4$), 2101-86-2; RN_3 (R = *p*-$CH_3OC_6H_4$), 2101-87-3; *p*-XC_6H_4NCO (X = H), 103-71-9; *p*-XC_6H_4NCO (X = NO_2), 100-28-7; R'CONCO (R' = C_6H_5), 4461-33-0; R'CONCO (R' = *p*-$NO_2C_6H_4$), 4461-37-4; R'CONCO (R' = $ClCH_2$), 4461-30-7; R'CONCO (R' = Cl_3C), 3019-71-4; R'CONCO (R' = OC_2H_5), 19617-43-7; R'CONCO (R' = OC_6H_5), 5843-43-6; $R'SO_2NCO$ (R' = *p*-ClC_6H_4), 5769-15-3; $R'SO_2NCO$ (R' = *p*-$CH_3C_6H_4$), 4083-64-1; $R'SO_2NCO$ (R' = C_6H_5), 2845-62-7; $R'SO_2NCO$ (R' = *p*-$NO_2C_6H_4$), 5769-16-4; $R'SO_2NCO$ (R' = *m*-NO_2-C_6H_4), 7018-79-3; $R'SO_2NCO$ (R' = Cl), 1189-71-5; 1,5-diazidopentane, 17607-21-5; *m*-phenylenedisulfonyl isocyanate, 3611-91-4.

Acknowledgment.—The authors are indebted to the IWONL (J. M. V.) and to the NFWO (G. L'a.) for fellowships. Financial support from the Ministry of National Education (FKFO) is gratefully acknowledged.

(15) G. L'abbé, *Chem. Rev.*, **69**, 345 (1969).
(16) R. L. Shriner, W. H. Horne, and R. F. B. Cox, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1946, p 453.
(17) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **28**, 1805 (1963); A. J. Speziale, L. R. Smith, and J. E. Fedder, *ibid.*, **30**, 4306 (1965).
(18) H. Ulrich, B. Tucker, and A. A. R. Sayigh, *ibid.*, **31**, 2658 (1966).

Studies on Reactions of Isoprenoids. XVIII.[1] Reactions of Chlorosulfonyl Isocyanate with Bicyclic Monoterpene Olefins

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The reactions of chlorosulfonyl isocyanate (CSI) with α-pinene (**1**), β-pinene (**18**), camphene (**26**), and Δ^3-carene (**38**) were carried out in ether or methylene chloride. The corresponding CSI adducts **2** from **1** rearranged to 4-azabrendan-5-one derivative **3** which was further converted into γ-lactam **6** and pyrrolidine **7** and *N*-formyl lactam **4**. The structure of **6** was proved by an alternative synthesis from 6,7,7-trimethyltricyclo[3.2.1.$0^{3,6}$]octan-4-one (**11a**) *via* its oxime (**11b**). The initial adduct **2** was converted into β-lactam **5**, azetidine **8**, and β-amino acid **9**. An initial β-pinene adduct **19** was converted into the corresponding spiroazetidinone **20** and azetidine **21**. Thermal rearrangement of **19** afforded 4-chlorosulfonyl-6,6-dimethyl-4-azatricyclo[5.2.1.$0^{1,5}$]-decan-3-one (**22**) accompanied with H-migration product **24**. Thermally unstable camphene adduct **27** was converted into spiro-2-azetidinone **33** and azetidine **34**. The reaction of CSI with **38** gave the corresponding adduct **39** which was thermally stable and was converted into β-lactam **41** and azetidine **42**. Application of the Eu(dpm)$_3$ nmr shift reagent to lactam functions was shown to be useful for structural elucidation of **5**, **6**, and **41**.

Since the discovery of the exceptionally reactive chlorosulfonyl isocyanate (CSI) by Graf in 1956,[2] its facile (2 + 2) cycloaddition reactions to various olefins have provided a versatile method for introducing an azetidinone (β-lactam) function into these substrates.[3-5] However, the number of syntheses of ring-fused azetidines utilizing cycloadditions of CSI to appropriate substrates seems to be quite limited.[6] Furthermore, the reactions of CSI with bicyclic terpene olefins have not been well documented except for the reaction with camphene.[7-9] This paper deals with the results of the cycloaddition reactions of CSI with α-pinene (**1**), β-pinene (**18**), camphene (**26**), and Δ^3-carene (**38**) as the bicyclic monoterpene olefins. The corresponding adducts and their rearrangement products were converted into 2,8,8-trimethyl-3-azatricyclo[5.1.1.$0^{2,5}$]nonane (**8**), 7,8,8-trimethyl-4-azatricyclo[4.2.1.$0^{3,7}$]nonane (**7**), azetidine-4-spiro-2′-(6′,6′-dimethyl)bicyclo[3.1.1]heptane (**21**), azetidine-4-spiro-2′-(3′,3′-dimethyl)bicyclo-[2.2.1]heptane (**34**), and 3,9,9-trimethyl-4-azatricyclo-[6.1.0.$0^{3,6}$]nonane (**42**).

Results and Discussion

Reaction with α-Pinene (1).—The reaction of CSI with **1** in ether or methylene chloride under refluxing for 18–22 hr afforded a 1:1 adduct **3** in 40% yield after purification on a silica gel column. The structure of **3** was determined as 4-chlorosulfonyl-7,8,8-trimethyl-4-azatricyclo[4.2.1.$0^{3,7}$]nonan-5-one by spectral data and by comparison of its hydrolysis product **6** with a specimen prepared from 6,7,7-trimethyltricyclo[3.2.1.$0^{3,6}$]octan-4-one (**11a**). Appearance of the nmr ($CDCl_3$) signals at τ 5.80 (d, 1, J = 8.3 Hz, NCH), 8.85 (s, 3, CH_3), 9.03 [s, 6,C(CH_3)$_2$], and 7.47–8.56 (m, 6, methine and methylene protons) suggested structure **3** or 4-chlorosulfonyl-2,8,8-trimethyl-4-azatricyclo[5.1.1.$0^{2,5}$]nonan-3-one (a regioisomer of **2**) (Scheme I). However, a considerably lower carbonyl stretching at 1768 cm^{-1} in the ir spectrum favored the former possibility of **3**.[10] The more conclusive evidence for the assigned structure was obtained by alkaline hydrolysis[11] of the adduct to the corresponding lactam **6** and by an alternative synthesis of **6** from 1-diazo-3-(2,2,3-trimethylcyclopent-3-enyl)-propan-2-one (**10**) *via* **11a** and **11b** (Scheme I).[12] Compound **6** had a mass spectral M^+ ion peak at *m/e* 179 and ir (KBr) absorptions at 3190, 3080, and 1690 cm^{-1} attributable to a γ-lactam. Reduction of **6** with lithium aluminum hydride afforded the corresponding amine **7**, which had a mass spectral M^+ ion peak at *m/e* 165, and a characteristic three-proton multiplet due to $-CHNHCH_2-$ at τ 6.1–6.95 in the nmr spectrum. On heating at 75–80° in dimethylformamide (DMF), **3** afforded only an *N*-formyl derivative **4** but no nitrile derivative; treatment of **6** with sulfuryl chloride in DMF gave also **4**. These facts also supported the assigned structure **3**.[13]

On the other hand, the reaction of CSI with **1** at −73° in ether for 3 hr afforded a very unstable 1:1 adduct **2** in 65% yield which was isolated as colorless crystals after recrystallization from ether–*n*-hexane. The structure of **2** was determined as 3-chlorosulfonyl-2,8,8-trimethyl-3-azatricyclo[5.1.1.$0^{2,5}$]nonan-4-one on the basis of analytical and spectral data, and of rearrangement to **3** as well as hydrolysis to a β-lactam **5**. In the ir spectrum, **2** exhibited a characteristic carbonyl absorption due to a 1-chlorosulfonyl-2-azetidinone moiety at 1805

(1) Part XVII of this series: T. Sasaki, S. Eguchi, M. Sugimoto, and F. Hibi, *J. Org. Chem.*, **37**, 2317 (1972).

(2) R. Graf, *Chem. Ber.*, **89**, 1071 (1956).

(3) For recent reviews, see (a) R. Graf, *Angew. Chem.*, **80**, 179 (1968); *Angew. Chem. Int. Ed. Engl.*, **7**, 172 (1968); (b) E. J. Moriconi, *Mech. React. Sulfur Compounds*, **3**, 131 (1968); (c) H. Bestian, "Cycloaddition Reactions," Butterworths, London, 1971, p 611.

(4) For the reactions with conjugated dienes, see (a) E. J. Moriconi and W. C. Meyer, *J. Org. Chem.*, **36**, 2841 (1971); (b) P. Goebel and K. Clauss, *Justus Liebigs Ann. Chem.*, **722**, 122 (1969).

(5) For 1,4, 1,5, and 1,6 cycloadditions of CSI as well as those with strained σ bonds, see L. A. Paquette, G. R. Allen, Jr., and M. J. Broadhurst, *J. Amer. Chem. Soc.*, **93**, 4503 (1971), and references cited therein.

(6) For example, see E. J. Moriconi and P. H. Mazzocchi, *J. Org. Chem.*, **31**, 1372 (1966), and references therein.

(7) (a) R. Graf and H. Biener, *Angew. Chem.*, **75**, 857 (1963); *Angew. Chem., Int. Ed. Engl.*, **2**, 546 (1963); (b) K. Clauss, *Justus Liebigs Ann. Chem.*, **722**, 10 (1969).

(8) For the reactions with bridged bi- and tricyclic olefins, see (a) E. J. Moriconi and W. C. Crawford, *J. Org. Chem.*, **33**, 370 (1968); (b) E. J. Moriconi and C. C. Jalandoni, *ibid.*, **35**, 2073 (1970).

(9) The reaction with α-pinene has been studied very recently: Professor E. J. Moriconi, private communication; G. T. Furst, M. A. Wachsman, J. Pieroni, J. G. White, and E. J. Moriconi, *Tetrahedron Lett.*, in press.

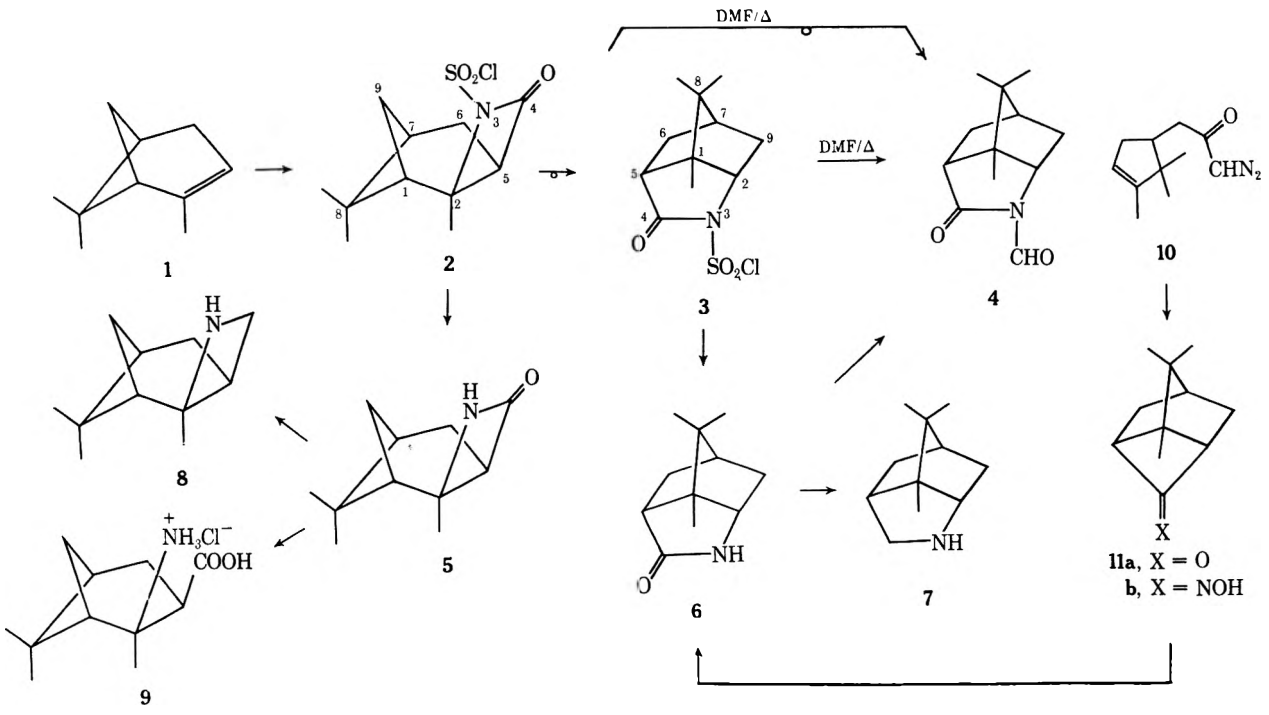
(10) The latter possibility is disfavored in view of the general trend in the cycloaddition orientation of CSI; *cf.* E. J. Moriconi and J. F. Kelly, *J. Org. Chem.*, **33**, 3036 (1968).

(11) *Cf.* T. Durst and M. J. O'Sullivan, *ibid.*, **35**, 2043 (1970).

(12) For the preparation of **10** and **11a**, see P. Yates and A. G. Fallis, *Tetrahedron Lett.*, 2493 (1968).

(13) For the formation of α,β-unsaturated nitrile from 4,4-dialkyl-1-chlorosulfonyl-2-azetidinone, see E. J. Moriconi and C. C. Jalandoni, *J. Org. Chem.*, **35**, 3796 (1970).

SCHEME I



cm^{-1}, which, however, disappeared gradually in the infrared light and, instead, a new absorption at 1773 cm^{-1} assignable to a *N*-chlorosulfonyl-γ-lactam moiety appeared; the former absorption disappeared almost completely after 45 min. The similar change was observed also in the nmr ($CDCl_3$, 25°) spectrum of **2** but more slowly: the nmr signals of **2** at τ 6.79 (d of d, 1, J = 9.5 and 2.5 Hz, H_5), 8.19 (s, 3, C_2CH_3), 8.42 (d, 1, J = 5.5 Hz, H_{9s}), 8.64 (s, 3, $C_{8x}CH_3$), 9.09 (s, 3, $C_{8n}CH_3$), and 7.3–8.1 (m, 5, other protons) changed to those similar to nmr spectrum of **3** described above; the half-life of **2** was calculated as *ca.* 90 hr at 25° from the signal change. The rearrangement of **2** to **3** occurred effectively on a silica gel column also. The structural assignment of **2** was also supported by its hydrolysis which gave the corresponding β-lactam **5**. Ir absorptions at 3190 and 1710 cm^{-1} and nmr signals at τ 7.16 (d of d, 1, J = 9.8 and 2.5 Hz, H_5), 8.52 (s, 3, C_2CH_3), 8.66 (s, 3, $C_{8x}CH_3$) and 9.08 (s, 3, $C_{8n}CH_3$) were compatible with the assigned structure **5**. Lithium aluminum hydride reduction of **5** gave the corresponding azetidine **8** which had nmr signals at τ 6.14 (t, 1, J = 9.5 Hz) and 6.96 (d of d, 1, J = 9.5 and 6.0 Hz) due to $-CHCH_2NH-$ supporting the assignment. Hydrolysis of **5** with hydrochloric acid afforded a β-amino acid **9** isolated as its hydrochloride;[14] the nmr (D_2O) spectrum disclosed signals at τ 6.52 (t, 1, J = 9.0 Hz) and 8.33 (s, 3) assignable to H_3 and C_2CH_3, respectively.

These results indicate clearly that the CSI addition to **1** proceeds regiospecifically to give **2** in accordance with the well-known Markovnikov orientation of CSI addition to olefinic substrates.[3,15] The initial adduct **2** rearranges to **3** thermally or on contact with silicic acid *via* the Wagner–Meerwein rearrangement of a dipolar intermediate **12** as illustrated in Scheme II.[16] No isomerization of **2** to **17** *via* path b was observed, though rearrangements of cyclopropanolamines and cyclobutanones have been reported.[17–19]

Reaction with β-Pinene (18) and Camphene (26).— The addition of CSI to **18** at −73° in ether afforded a 1:1 adduct **19** which precipitated as colorless crystals and had ir (neat) absorption at 1809 cm^{-1}, but **19** was extremely unstable and decomposed to a brownish oil in a few minutes at room temperature. However, reductive hydrolysis of **19** at −5° afforded a thermally stable product **20** which was characterized as 2-azetidinone-4-spiro-2′-(6′,6′-dimethyl)bicyclo[3.1.1]heptane; **20** had a mass spectral ion peak at m/e 179 (M^+) and ir (KBr) absorptions at 3230 (NH) and 1758 and 1705 (β-lactam C=O) cm^{-1}; in the nmr spectrum, appearance of the signals at τ 3.40 (mound, 1, NH), 7.25 (AB q, 2, J = 14 Hz, $J/\Delta\tau$ = 0.899, β-lactam CH_2), 8.71 (d, *ca.* 1, J = 9.5 Hz, partly hidden by $C_{6'x}CH_3$ signal, $H_{7'x}$), 8.74 (s, 3, $C_{6'x}CH_3$), 9.14 (s, 3, $C_{6'n}CH_3$), and 7.4–8.4 (m, 7, other protons), supported the assigned structure (see also europium shift parameter discussed below).[20] Lithium aluminum hydride reduction of **20** afforded the corresponding spiroazetidine **21** which had a mass spectral M^+ ion peak at m/e 165 and characteristic nmr signals at τ 6.39 (unsym t, 2, J = 8.5 Hz, $-CH_2NH$), 7.19

(14) Compound **6** was very stable against acidic hydrolysis.

(15) A less hindered exo addition of CSI to **1** was reasonably assumed, which was also compatible with the nmr study of **5** in the presence of Eu(dpm)$_3$ as discussed below; *cf.*, for addition of dichlorocarbene, J. Hatem and B. Waegell, *Tetrahedron Lett.*, 2069 (1971); for epoxidation of **1**, D. Swern, *Org. React.*, **7**, 378 (1953).

(16) This type of rearrangement is well known, *e.g.*, the rearrangement of **1** hydrochloride to bornyl chloride: P. de Mayo in "The Chemistry of Natural Products," Vol. 2, K. W. Bentley, Ed., Interscience, New York, N. Y., 1959, p 98.

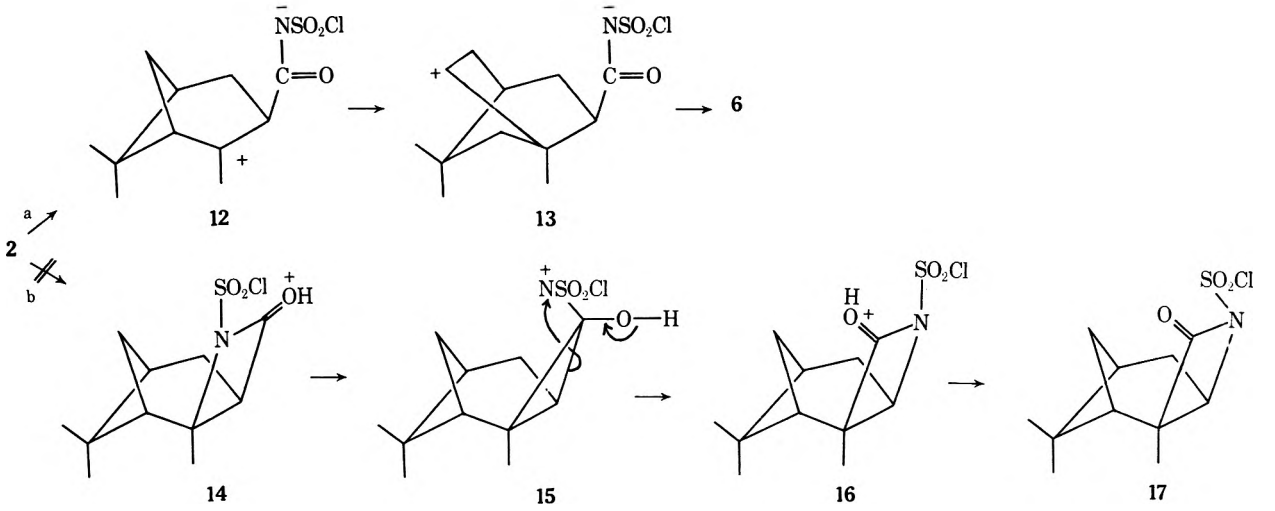
(17) For β-lactam synthesis from cyclopropanolamines, see H. H. Wasserman, H. W. Adickes, and O. E. de Ochoa, *J. Amer. Chem. Soc.*, **93**, 5586 (1971).

(18) For cyclobutanone rearrangement, see W. F. Erman, R. S. Treptow, P. Bakuzis, and E. Wenkert, *ibid.*, **93**, 657 (1971).

(19) During the course of the present study, we believed strongly that **2** had rearranged to **17**; however Professor E. J. Moriconi kindly suggested to us that our rearrangement product might be **3** identical with the compound isolated by him, whose structure was established by X-ray crystallography.[9] This was confirmed when the nmr spectra of **3** and of the compound isolated by Moriconi were shown to be superimposable (private communication from Professor E. J. Moriconi).

(20) For geminal coupling constants of 2-azetidinones, see K. D. Barrow and T. M. Spottiswood, *Tetrahedron Lett.*, 3325 (1965).

SCHEME II



(broad s, 1, NH), 8.75 (s, 4, $C_{6'x}CH_3$ and H_{7s}), 9.19 (s, 3, $C_{6'n}CH_3$), and 7.45–8.55 (m, 9, other protons).

Thermal rearrangement of **19** afforded a complex mixture of products in contrast to clear rearrangement of **2** to **3**. Purification on a silica gel column afforded two crystalline products **22** and **25** in 12.6 and 6.5% yields, respectively. Compound **22** had mass spectral ion peaks at *m/e* 277 (M^+) and 279 (M + 2) is *ca.* 3 : 1 ratio and an ir absorption at 1780 cm^{-1}, suggesting the presence of 1-chlorosulfonyl-2-pyrrolidone moiety in **22**. In the nmr spectrum, **22** exhibited signals at τ 6.57 (s, 1, H_5), 7.42 (s, 2, $-CH_2CON-$), 8.78 and 8.89 [each s, each 3, $C_6(CH_3)_2$], and 7.5–8.8 (m, 7, other protons); a comparison of the spectrum with that of the known compound **28** from camphene[7,21] permitted the assignment of **22** as 4-chlorosulfonyl-6,6-dimethyl-4-azatricyclo[5.2.1.$0^{1,5}$]decan-3-one. Treatment of **22** with sodium sulfite gave the corresponding lactam **23** which had a characteristic one-proton singlet due to C_5H at τ 6.87 (Scheme III). The minor product **25** had a mass spectral molecular ion peak at *m/e* 179 and ir absorptions at 3340, 3170, 1650 (sh), and 1625 (primary amide and C=C) cm^{-1}. In the nmr spectrum, appearance of signals at τ 3.5–5.0 (very broad singlet superimposed with singlet at τ 4.38, 3, $CONH_2$ and C=CH), 6.9–8.5 (m, *ca.* 8, ring protons), and 8.70, 8.81, 8.92, and 9.04 [each s, 6, the ratio of the former two to the latter two is *ca.* 2:3, $C(CH_3)_2$] allowed **25** to be assigned as a mixture of geometrical isomers derived from H migration of a dipolar intermediate **35**, followed by hydrolysis (Scheme IV).[22]

The formation of **22** is of interest in view of the migratory aptitude of the participating bonds in the intermediate **35** in Scheme IV; a-bond migration can give rise to **22**, b-bond migration, **28**. The fact that no trace of **28** was produced from **19** indicates a selective a-bond migration contrary to the well-known fact that the migratory aptitude of tertiary is higher than that of secondary carbon.[23,24]

The readily accessible camphene adduct **28** was heated in DMF to give *N*-formyl derivative **31** which was reduced to *N*-methylpyrrolidine derivative **32**. Direct reduction of **28** with $LiAlH_4$ gave **30** characterized as its picrate. On the other hand, low-temperature reductive hydrolysis of the thermally unstable initial adduct (**27**)[25] of CSI to **26** afforded the corresponding β-lactam **33** which was converted into a spiroazetidine **34**. The structural assignment of **33** and **34** were evidenced by analytical and spectral data.

Reaction with Δ^3-Carene (38).—Addition of CSI to **38** proceeded smoothly in ether by refluxing for 23 hr and a 1:1 adduct **39** was obtained in 72% yield, while the same reaction in methylene chloride gave only a 29% yield of **39**. However, no 1:2 adduct was produced under both conditions, though **38** can be regarded as a bifunctional substrate against CSI.[26]

The structure of **39** was determined as 4-chlorosulfonyl-3,9,9-trimethyl-4-azatricyclo[6.1.0.$0^{3,6}$]nonan-5-one by spectral data and its conversion into **41** and **42** (Scheme V). Compound **39** exhibited strong ir absorptions at 1809 (C=O), 1404, and 1153 (SO_2) cm^{-1} and characteristic nmr signals at τ 6.93 (d of d, 1, $J_{6,7x}$ = 4.5 Hz, $J_{6,7n}$ = 1.5 Hz, C_6H), 7.25–8.15 (broad m, 2, $C_{2x}H$ and $C_{7x}H$), 8.29 (s, 3, C_3CH_3), 8.91 and 9.00 [s, each 3, $C_9(CH_3)_2$], and 8.65–9.40 (m, 4, other ring protons). Comparison of the chemical shift values due to C_6H and C_3CH_3 with reported examples[10] supported the assigned orientation which is in good accord with the general trend of CSI cycloaddition.[3] Addition of CSI to **38** from the less hindered exo side was assumed by analogy with the carbene addition to **38** and epoxidation of **38**[27,28] (see also discussion on application of a shift reagent). Although two conformations (**39** or **43a**) are possible for the CSI adduct to **38**, the observed coupling constants 4.5 and 1.5 Hz of C_6H are very close to the calculated values 4.5 and 0.9 Hz from the dihedral angles for H_6–H_{7x} and H_6–H_{7n} of **39** but not to 4.8 and 7.5 Hz of **43a**,[29] and, hence, **39** is concluded to

(21) The spectrum was very similar but C_5H of **28** appeared as a double doublet at τ 6.05 (J = 8.0 and 5.0 Hz).

(22) A similar H migration is well known for the camphene adduct **27**; *cf.* ref 7.

(23) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968, pp 3–60.

(24) T. Sasaki, S. Eguchi, and T. Ishii, *J. Org. Chem.*, **35**, 2257 (1970).

(25) The formation of **27** has been proved by K. Clauss but its conversion into **33** and **34** is not recorded; see ref 7b.

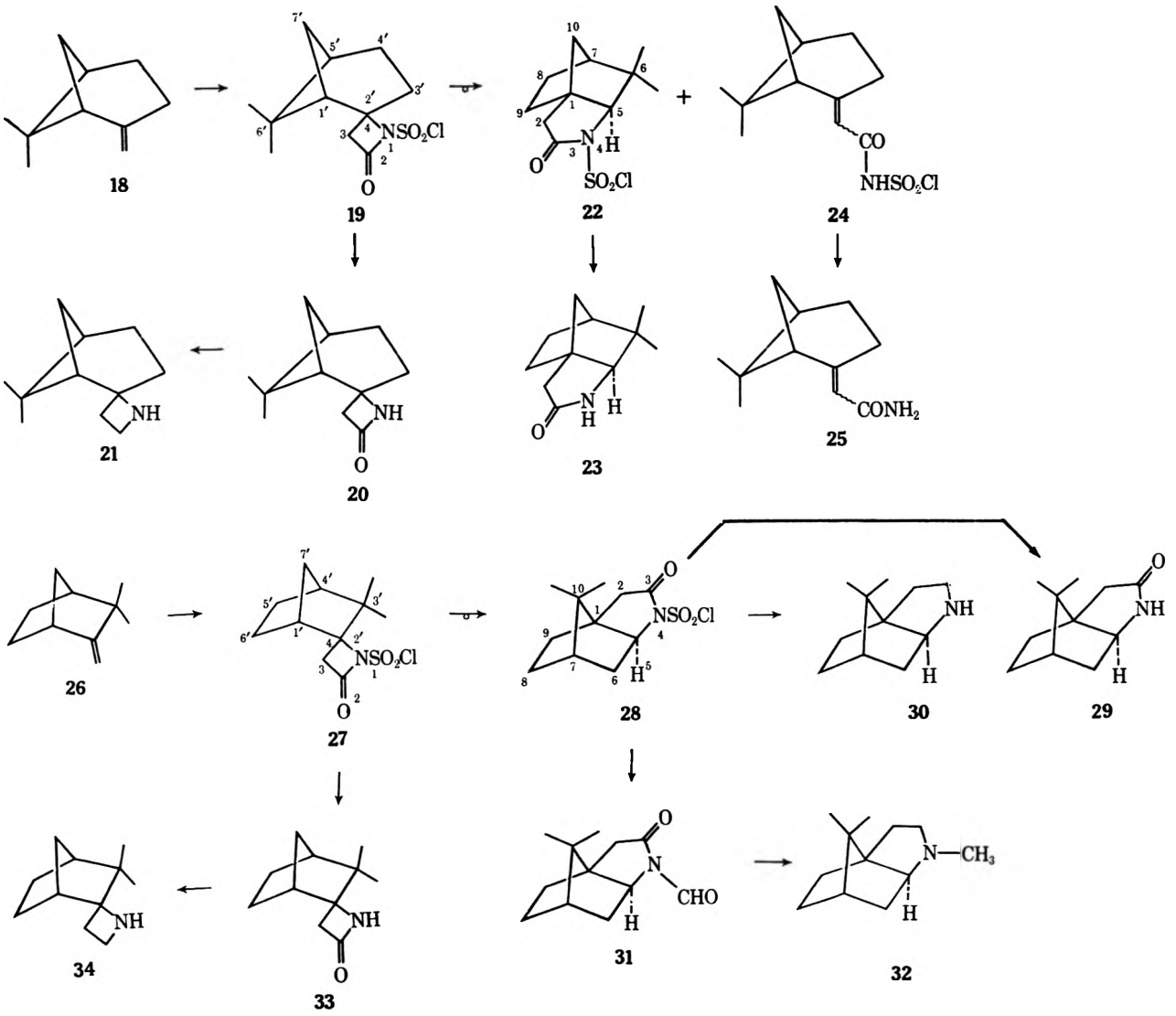
(26) For the reaction of CSI with cyclopropane derivatives, see E. J. Moriconi, J. F. Kelly, and R. A. Salomone, *J. Org. Chem.*, **33**, 3448 (1968).

(27) For carbene addition, see H. Frishleder, J. Graefe, H. Van Phiet, and M. Muehlstaedt, *Tetrahedron*, **25**, 2081 (1969), and references therein.

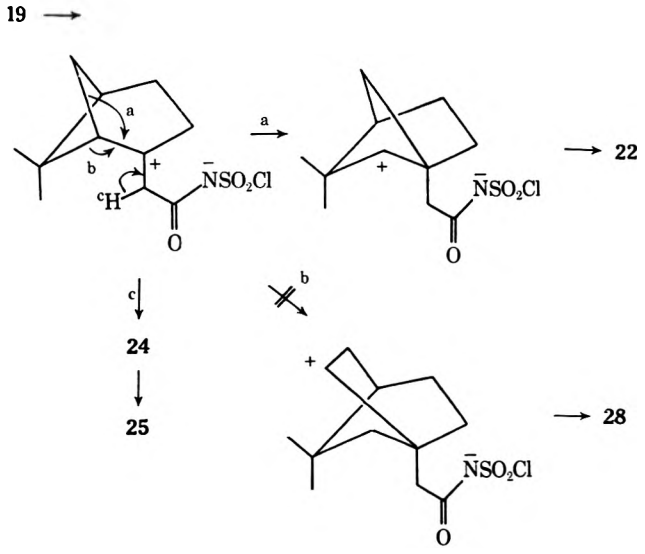
(28) B. A. Arbuzov, A. N. Vereshchagin, S. G. Vul'fson, and Z. G. Isaeva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1966 (1968); *Chem. Abstr.*, **70**, 11813p (1969).

(29) The values were calculated by utilizing a modified Karplus equation: K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961).

SCHEME III



SCHEME IV

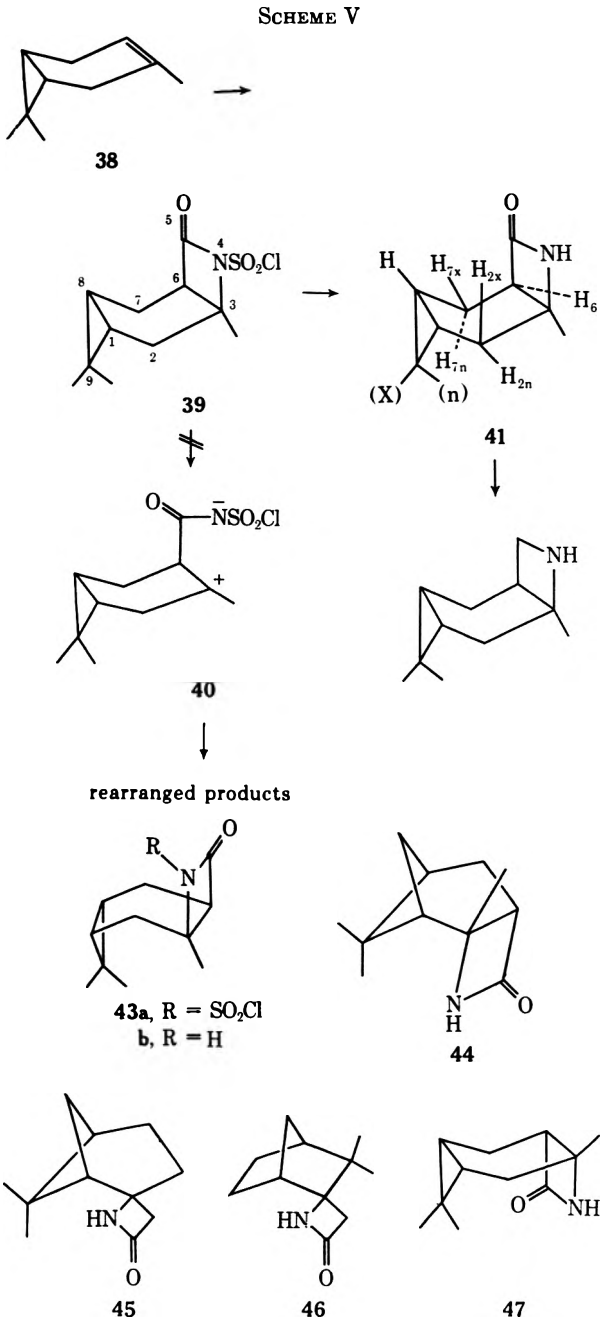


be the preferred conformer compared with **43a**, in which a severe steric repulsion between $C_{9n}CH_3$ and C_3CH_3 and C_6H may exist.

Treatment of **39** with sodium sulfite gave β-lactam **41** in 65% yield, which had ir absorptions at 3240, 1763, and 1717 (β-lactam) cm^{-1} and a mass spectral M^+ ion peak at *m/e* 179. The nmr data were compatible with the assigned structure. Lithium aluminum hydride reduction of **41** afforded the corresponding azetidine **42**, mp 128–130°, which did not afford a crystalline picrate. In order to confirm that **39** is the initial adduct of CSI to **38**, the crude adduct was reduced with sodium sulfite directly without purification on a silica gel column. However, only the same β-lactam **41** was obtained. This fact indicates that the cycloaddition of CSI to **38** is regiospecific, and the adduct **39** is stable on contact with silicic acid. Treatment of **39** with silicic acid and/or BF_3 etherate in benzene under more drastic conditions of refluxing for 18 hr and/or room temperature for 1 day resulted only in polymerization or decomposition.

Application of Tris(dipivalomethanato)europium Shift Reagent to β-Lactam and γ-Lactam Functions.—Although successful applications of nmr shift reagents have been reported for a variety of functional groups, no report concerning β- and γ-lactam functions appears to

SCHEME V



exist.[30-33] We have applied the Eu(dpm)$_3$ shift reagent to β-lactams **5**, **20**, **33**, **41**, and γ-lactam **6** in order to obtain further supports for the assigned structures.

In Figure 1, the original spectrum of **5** and that in the presence of the shift reagent are shown. The complex multiplets due to ring protons are better resolved in the latter spectrum. Each signal was assigned as shown with the aid of spin–spin decoupling experiments.[34]

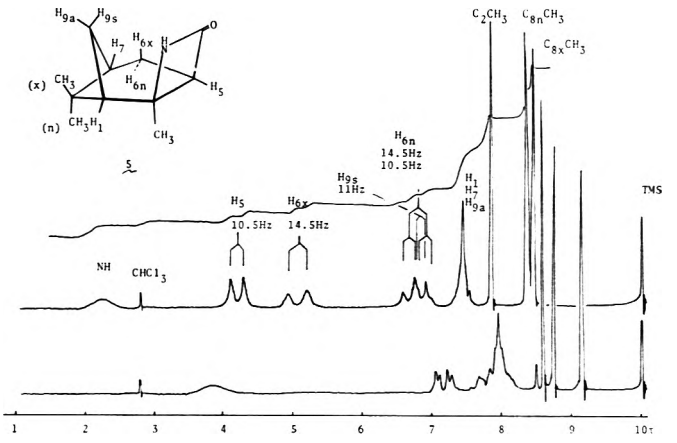


Figure 1.—Nmr spectra of **5** in $CDCl_3$ at 60 MHz; Eu(dpm)$_3$/**5** = 0 and 0.339.

The chemical shift of each proton varied linearly with the molar ratio of Eu(dpm)$_3$ to **5** and the so-called europium shift parameter S value[35] was obtained as summarized in Table I. As is well known, the S value should be greatest for hydrogens which are closest to the complexed europium. Since the estimation of the exact position of the europium atom in the complex is difficult, we measured the distance r between the centers of hydrogen and of oxygen of the cyclobutenol structure corresponding to the β-lactam using a Fieser molecular model. This is, of course, a very rough estimation of the separation; nevertheless the obtained S–r^{-2} correlation seems to be useful for distinguishing the assigned structure **5** from its endo isomer **44**, *i.e.*, 8n-CH_3 in **44** is very close to the β-lactam carbonyl but the observed S value of 2.18 is apparently in the range expected from the r value for **5**. Thus, the assumption of an exo addition of CSI to **1** is verified.

Similarly, the nmr spectra of **6**, **20**, **33**, and **41** were analyzed with the aid of the Eu(dpm)$_3$ shift reagent, and the obtained S values are summarized in Table I. The larger S value (15.9) for H_6 in **6** than that (4.47) for H_3 indicates clearly the preferred complex formation near the carbonyl side rather than the amide nitrogen; the similar results are also obtained for 4-azahomoadamantan-5-one and 4-aza-1,1-bishomoadamantan-5-one.[33] Therefore, application of the S–r relationships to distinguishing the assigned structures **20** and **33** (spiroazetidinone) from the endo addition isomers **45** and **46** seems not to be effective.[36] However, the S–r^{-2} relationship for **41** is excellent and comparison of the r values for structures **43b** and **47** revealed that $C_{9n}CH_3$ value (1.38) is best correlated only with the assigned structure **41**.

There are still some problems concerning the position of complex formation and the effect of the distance on the S values as well as the problem of the anisotropy of lactam function. However, above examples might provide further successful application of the shift reagent to lactam function.

(30) For europium shift reagent, see, for example, J. K. M. Sanders, S. W. Hanson, and D. H. Williams, *J. Amer. Chem. Soc.*, **94**, 5325 (1972), and references cited therein.

(31) For an application to azetidin-3-ol, see T. Okutani, A. Morimoto, T. Kaneko, and K. Masuda, *Tetrahedron Lett.*, 1115 (1971).

(32) For studies related to amide functions, see (a) T. H. Siddall, III, *Chem. Commun.*, 452 (1971); (b) C. Beauté, Z. W. Wolkowski, and N. Thoai, *ibid.*, 700 (1971).

(33) For an example of application to 4-azahomoadamantan-5-one and 4-aza-1,1-bishomoadamantan-5-one, see T. Sasaki, S. Eguchi, and M. Mizutani, *Chem. Lett.*, 991 (1972).

(34) For nmr study of α-pinene, see R. B. Bates and V. P. Thalacker, *J. Org. Chem.*, **33**, 1730 (1968).

(35) *Cf.* A. F. Cockerill and D. M. Rackham, *Tetrahedron Lett.*, 5149 (1970).

(36) For these compounds, application of Eu(dpm)$_3$ on the corresponding spiroazetidines may be useful. For examples of the preferred exo addition to **18** and **26**, *cf.* (a) hydroboration of **18**, G. Zweifel and H. C. Brown, *J. Amer. Chem. Soc.*, **86**, 393 (1964); (b) epoxidation of **26**, P. Hirsjarvi, P. Eenila, J. Peltonen, L. Pirila, and A. Paallysaho, *Suom. Kemistilehti B*, **36**, 126 (1963).

TABLE I

EUROPIUM SHIFT PARAMETERS FOR 5, 6, 20, 33, AND 41[a,b]

5	S (r Å)	6	S[c] (r, Å)	20	S[c] (r, Å)	33	S[c] (r, Å)	41	S[c] (r, Å)
H_1	1.77	H_3	4.47	H_3[d]	9.67	H_3[d]	6.50	C_3CH_3	2.74
	(5.4)		(4.5)		(3.2)		(3.1)	(4.2)	(4.2)
C_2CH_3	2.30	H_6	15.9	$C_{6n}CH_3$	1.97	H_1	3.15	H_6	11.3
	(4.4)		(2.8)		(4.7)		(4.5)		(3.0)
H_5	9.71	C_7CH_3	3.70	$C_{6x}CH_3$	0.890	$C_{3n}CH_3$	1.77	H_{7x}	9.53
	(3.0)		(3.9)		(6.6)		(4.2)		(3.2)
H_{6x}	7.76	$C_{8a}CH_3$	2.80	H_{7s}	1.25	$C_{3x}CH_3$	1.28	H_{7n}	2.82
	(3.0)		(5.0)		(5.7)		(4.3)		(4.4)
H_{6n}	4.35	$C_{8b}CH_3$	1.75			H_4	0.593	$C_{9n}CH_3$	1.38
	(4.0)		(6.0)				(6.8)		(5.6)
H_7	1.77	H_{9n}	8.70					$C_{9x}CH_3$	0.763
	(5.2)		(3.2)						(6.0)
$C_{8x}CH_3$	1.00								
	(6.8)								
$C_{8n}CH_3$	2.18								
	(4.2)								
H_{9s}	5.00								
	(3.4)								
H_{9a}	1.77								
	(5.2)								

[a] The values were obtained from the nmr data at 60 MHz in $CDCl_3$ (25°) up to the ratio of Eu(dpm)$_3$ to the substrate: 0.339–0.506. [b] The distance r was approximated by measuring the internuclear distance between the hydrogen and the oxygen of the iminol molecule corresponding to the lactams in Å using a Fieser model. [c] Other protons could not be analyzable because of the overlapping of the signals. [d] From the chemical shift of a center of an AB quartet type signal.

Experimental Section[37]

Reaction of CSI with α-Pinene (1).—To a cooled (−73°) solution of 2.72 g (20.0 mmol) of freshly distilled **1**, bp 61–64° (44 mm), in 30 ml of anhydrous ether was added dropwise a solution of 2.83 g (20.0 mmol) of CSI in 30 ml of anhydrous ether with stirring under nitrogen. After the addition was completed, stirring was continued for further 3 hr and, to the mixture, *n*-hexane was added until colorless precipitates began to separate. After removal of the solvent by using a siphon, the precipitates were recrystallized from ether–*n*-hexane at −73° to afford **3-chlorosulfonyl-2,8,8-trimethyl-3-azatricyclo[5.1.1.0^{2,5}]nonan-4-one (2)** as colorless crystals (3.60 g, 64.8%): mp 62–65°; ir (KBr) 1805, 1395, and 1170 cm^{-1}; mass spectrum *m/e* (rel intensity) 279 (40, M + 2), 278 (20, M + 1), 277 (100, M$^+$), 242 (25), 180 (30), 179 (27), 135 (35), 134 (40), 119 (70), and 108 (90).

Anal. Calcd for $C_{11}H_{16}NO_3SCl$: C, 47.57; H, 5.81; N, 5.04. Found: C, 47.80; H, 5.64; N, 4.92.

When the reaction mixture of **1** and CSI at −73° was allowed to warm up to room temperature and then refluxed for 18–19 hr, a brownish oily product was obtained after removal of the solvent. Purification on a silica gel column eluting with benzene and/or ether–*n*-hexane afforded **4-chlorosulfonyl-7,8,8-trimethyl-4-azatricyclo[4.2.1.0^{3,7}]nonan-5-one (3)** as colorless crystals (2.20 g, 40%). An analytical sample was recrystallized from *n*-hexane: mp 85–87°; ir (KBr) 1768, 1406, and 1167 cm^{-1}; mass spectrum *m/e* 280 (6.5, M + 3), 279 (37, M + 2), 278 (14, M + 1), 277 (90, M$^+$), 242 (41), 109 (81), 108 (100), and 93 (75).

Anal. Calcd for $C_{11}H_{16}NO_3SCl$: C, 47.57; H, 5.81, N, 5.04. Found: C, 47.30; H, 5.92; N, 4.90.

Compound **2** changed to a brownish oil on standing at room temperature and purification on a silica gel column afforded also **3** in 30–60% yields.

Reaction of 2 and 3 with DMF.—A solution of 1.10 g (3.96 mmol) of **3** in 3 g (*ca.* 40 mmol) of DMF was stirred at 75–80° for 21 hr. The resulting dark brown mixture was poured onto 30 ml of cold water and extracted with *n*-hexane (5 × 20 ml) and benzene (5 × 20 ml) successively. The combined extracts were dried (Na_2SO_4) and evaporated. Work-up and recrystallization from *n*-hexane–benzene afforded **4-formyl-7,8,8-trimethyl-4-azatricyclo[4.2.1.0^{3,7}]nonan-5-one (4)** as crystals: mp 133–134°; ir (KBr) 1737 (C=O) and 1678 (CHO) cm^{-1}; nmr ($CDCl_3$) τ 0.99 (s, 1, CHO), 5.93 (br d, 1, *J* = 8.3 Hz, C_5H), 7.41–8.73 (m, 6, other ring protons), 8.94 (s, 3, C_7CH_3), and 9.02 (s, 6, 2 C_8CH_3); mass spectrum *m/e* 207 (1.8, M$^+$), 179 (19, M − CO), 178 (98, M − CHO), 163 (46), 137 (46), 136 (33, M − CONCHO), 135 (67), 181 (53), 109 (92), 108 (89), 107 (100), 96 (98), 95 (63), 93 (58), 92 (95), 90 (59), and 54 (88).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.23; H, 8.12; N, 6.62.

The same reaction of **2** gave a similar result.

2,8,8-Trimethyl-3-azatricyclo[5.1.1.0^{2,5}]nonan-4-one (5).—The reaction mixture from each 20.0 mmol of **1** and CSI in ether was added slowly to an ice-cooled mixture of about two parts of 20% aqueous sodium sulfite and one part of ether. The aqueous phase was kept between pH 8 and 9 by addition of 10% aqueous KOH solution. After stirring was continued for 15 hr under ice-cooling and then, for 15 hr at room temperature, work-up as usual gave 2.19 g (61%) of **5** as colorless crystals from *n*-hexane: mp 110.5–112°; uv end (EtOH) 202, 220, and 250 nm (ε 3800, 576, and 230); mass spectrum *m/e* 180 (1.8, M + 1),[38] 179 (8.7, M$^+$), 178 (3.6, M − 1), 164 (17, M − CH_3), 136 (47, M − NHCO), 121 (36), 110 (36), 99 (43), 93 (100), 92 (91), 91 (45), 70 (45), and 44 (78).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.98; H, 9.68; N, 8.00.

7,8,8-Trimethyl-4-azatricyclo[4.2.1.0^{3,7}]nonan-5-one (6).—Reduction of 500 mg (1.80 mmol) of **3** with 20% sodium sulfite solution and work-up as above afforded 251 mg (78%) of **6** as colorless crystals from *n*-hexane: mp 218–220° (sealed tube); uv end (EtOH) 204, 220, and 250 nm (ε 2090, 466, and 53.0); nmr ($CDCl_3$) τ 3.75 (mound, 1, NH), 6.66 (br, d, 1, *J* = 8.5 Hz, C_3H), 7.65–8.8 (m, 6, other ring protons), 8.90 (s, 3, C_7CH_3), and 9.06 (s, 6, 2 C_8CH_3); mass spectrum *m/e* 179 (2.8, M$^+$), 178 (25, M − 1), 177 (100, M − 2), 176 (98), 162 (34), 138 (25), 136 (23), 109 (83), 94 (63), and 42 (31).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.43; H, 9.35; N, 7.62.

Reaction of 6 with Sulfuryl Chloride.—A mixture of 65 mg (0.36 mmol) of **6**, 135 mg (1.0 mmol) of sulfuryl chloride, and 1 ml of DMF was heated at 60° for 1 hr, and the cooled mixture was extracted with *n*-hexane (5 × 20 ml) after dilution with

(37) Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. Melting points were determined on a Yanagimoto hot-stage type melting point apparatus and are uncorrected. Ir spectra were obtained on a JASCO IRA-1 grating infrared spectrophotometer and uv spectra on a JASCO ORD/UV-5 spectrometer. Nmr spectra were taken with a JEOL-C-60HL spectrometer using TMS as the internal standard, and mass spectra with a JEOL-01SG spectrometer at 75 eV.

(38) *Cf.* Q. N. Porter and J. Baldas, "Mass Spectrometry of Heterocyclic Compounds," A. Weissberger and E. C. Taylor, Ed., Wiley-Interscience, New York, N. Y., 1970, p 303.

water. Combined extracts were dried (Na_2SO_4) and evaporated to afford 28 mg (27%) of **4**, the ir spectrum of which was superimposable on that of specimen obtained from **3**.

7,8,8-Trimethyl-4-azatricyclo[4.2.1.0^{2,7}]nonane (7).—A mixture of 180 mg (1.01 mmol) of **6** and 370 mg of $LiAlH_4$ in 10 ml of dry THF was refluxed for 40 hr. Work-up in the usual way gave 100 mg (60%) of **7** as colorless crystals from petroleum ether (bp <40°): mp 106–109° (sealed tube); ir (KBr) 3340, 2950, 1489, and 1367 cm^{-1}; nmr ($CDCl_3$) τ 8.71 (s, 1, NH), 6.10–6.95 (m, 3, $-CH_2NHCH-$), 7.35–8.96 (m, 6, other ring protons), 9.02 (s, 3, C_7CH_3), and 9.12 (s, 6, 2 C_9CH_3). The picrate of **7**: mp 208–211° dec; mass spectrum *m/e* 166 (2.5, M + 1), 165 (14, M$^+$), 164 (2.5, M − 1), 150 (36 M − CH_3), 136 (3.1, M − $NHCH_2$), 124 (41), 122 (26), 108 (69), 95 (99), 94 (92), 93 (62), 82 (77), 57 (82), 56 (98), 55 (52), and 44 (100).

Anal. Calcd for $C_{17}H_{22}N_4O_7$: C, 51.77; H, 5.62; N, 14.21. Found: C, 51.62; H, 5.49; N, 14.48.

2,8,8-Trimethyl-3-azatricyclo[5.1.1.0^{2,5}]nonane (8).—A mixture of 358 mg (2.00 mmol) of **5** and 700 mg of $LiAlH_4$ in 10 ml of dry THF was refluxed for 24 hr. Work-up as usual afforded 200 mg (62%) of **8** as an oil: n^{22}D 1.4988; ir (neat) 3360, 2920, 1535 and 1418 cm^{-1}; nmr ($CDCl_3$) τ 6.14 (t, 1, *J* = 9.5 Hz, C_4H), 6.96 (d of d, 1, *J* = 9.5 and 6.0 Hz, C_4H), 7.32 (br s, 1, NH, disappeared on shaking with D_2O), 7.30–8.57 (m, 7, other ring protons), 8.62 (s, 3, C_2CH_3), 8.74 (s, 3, $C_{3x}CH_3$), and 9.21 (s, 3, $C_{3n}CH_3$). The picrate of **8**: mp 143–145° dec; nmr (DMSO-d_6, 100 MHz) τ 1.48 (s, 2, aromatic protons), 5.92 (t, 1, *J* = 11 Hz, C_4H), 6.47 (d of d, 1, *J* = 11 and 7.0 Hz, C_4H), 6.76 (br s, NH), 6.96–8.40 (m, 7, other ring protons), 8.46 (s, C_2CH_3), 8.75 (s, 3, $C_{3x}CH_3$), and 9.25 (s, 3, $C_{3n}CH_3$); mass spectrum *m/e* 166 (2.0, M + 1), 165 (5.1, M$^+$), 164 (1.5, M − 1), 150 (6.1, M − CH_3), 136 (4.4, M − $NHCH_2$), 93 (20), and 44 (100).

Anal. Calcd for $C_{17}H_{22}N_4O_7$: C, 51.77; H, 5.62; N, 14.21. Found: C, 51.76; H, 5.66; N, 14.22.

2-*exo*-Amino-2,6,6-trimethylbicyclo[3.1.1]heptane-3-*exo*-carboxylic Acid Hydrochloride (9).—A mixture of 2.0 ml of 18% hydrochloric acid, 2.0 ml of ethanol, and 200 mg (1.12 mmol) of **5** was stirred for 4.5 hr at 0–5°. Removal of the solvent in a desiccator over concentrated sulfuric acid under reduced pressure afforded solid residue which was washed with ether and recrystallized from EtOH–Et_2O to give 100 mg (38%) of **9** as fine crystals: mp 204–205° dec (sealed tube); ir (KBr) 3600–2400 and 1695 cm^{-1}; nmr (D_2O) τ 6.52 (t, 1, *J* = 9.0 Hz, C_3H), 7.05–8.15 (m, 6, other ring protons), 8.33 (s, 3, C_2CH_3), 8.70 and 8.90 (s, each 3, 2 C_6CH_3); mass spectrum *m/e* 179 (1.1, M$^+$), 164 (5.2, M − CH_3), 136 (5.4), 121 (11), 93 (96), 70 (100), and 44 (87).

Anal. Calcd for $C_{11}H_{20}NO_2Cl$: C, 56.33; H, 8.62; N, 5.99. Found: C, 56.45; H, 8.61; N, 6.08.

6,7,7-Trimethyltricyclo[3.2.1.0^{3,6}]octan-4-one Oxime (11b).—To a stirred mixture of 690 mg (10.0 mmol) of hydroxylamine hydrochloride, 1 ml of water, 164 mg (1.00 mmol) of 6,7,7-trimethyl[3.2.1.0^{3,6}]octan-4-one (**11a**),[12] and 5 ml of methanol was added dropwise 5 ml of 10% KOH aqueous solution. After stirring was continued for 1 day at room temperature, the mixture was concentrated under reduced pressure to afford colorless precipitates which were filtered and recrystallized from *n*-hexane to give **11b** as colorless crystals (100 mg, 56%): mp 129.5–130°; ir (KBr) 3240 (doublet), 1700, and 935 cm^{-1}; nmr (CCl_4) τ 0.85 (s, 1, NOH), 6.85–8.70 (m, 7, ring protons), 8.89 (s, 3, C_6CH_3), and 9.09 (s, 6, 2 C_7CH_3); mass spectrum *m/e* 179 (20, M$^+$), 161 (30, M − H_2O), 108 (100), and 93 (95).

Anal. Calcd for $C_{11}H_{17}ON$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.85; H, 9.58; N, 7.91.

Beckmann Rearrangement of 11b.—A mixture of 0.260 g (1.45 mmol) of **11b**, 1 ml of polyphosphate ester, and 2 ml of chloroform was heated at 50–55° for 2 hr. The cooled mixture was diluted with water (5 ml) and stirred at room temperature for 12 hr. Basified (10% aqueous KOH) mixture was extracted with methylene chloride (5 × 10 ml), and the combined extracts were dried (Na_2SO_4) and evaporated to give an oily product (330 mg) which revealed three major peaks in 1.0:5.4:8.5 ratio on glpc analysis (10% silicone SE-30 on Chromosorb W at 150°). Purification on preparative tlc (silica gel, 5% CH_2Cl_2–*n*-hexane) afforded 81 mg (31%) of **6** as the Beckmann rearrangement product identified by the superimposable ir spectrum on that of **6** from CSI adduct **3** and by glpc retention times. Unreacted **11b** was recovered as the hydrolysis product **11a** (100 mg, 42% recovery). A Beckmann-fission product was also obtained as an oil (50 mg, 21.4%):[39] ir (neat) 2230 (C≡N), 1650, and 885 (C=CH_2) cm^{-1}; nmr ($CDCl_3$) τ 5.11 and 5.35 (s, each 1, C=CH_2), 7.00 (s, 1, allylic bridgehead methine), 7.38–8.55 (m, 6, other ring protons), and 8.94 (s, 6, 2 CH_3), which was assigned tentatively as 5-*exo*-cyano-2,2-dimethyl-3-methylenenorbornane.

Anal. Calcd for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69. Found: C, 81.98; H, 9.54; N, 8.47.

Reaction of CSI with β-Pinene (18).—To a stirred solution of 1.42 g (10.0 mmol) of CSI in 10 ml of anhydrous ether was added slowly a solution of 1.36 g (10.0 mmol) of freshly distilled **18**, bp 62.5–63° (25 mm), in 10 ml of ether at −73° under nitrogen. After the addition was completed, the stirring was continued for 3 hr. Precipitated crystals could not be isolated because their decomposition occurred rapidly at room temperature (ir, neat, 1809 cm^{-1}). The mixture was allowed to warm up to room temperature and stood for 1 day. Removal of the solvent afforded a dark brownish oil which was purified on a silica gel column eluting with *n*-hexane–ether–methanol to give 350 mg (12.6%) of **4-chlorosulfonyl-6,6-dimethyl-4-azatricyclo[5.2.1.0^{1,5}]decan-3-one (22)** as crystals after recrystallization from *n*-hexane: mp 113–115°; ir (KBr) 1780, 1400, and 1175 cm^{-1}; mass spectrum *m/e* 279 (15, M + 2), 277 (40, M$^+$), 242 (42), 236 (50), 234 (65), 197 (55), 195 (70), 179 (70), 178 (100), 149 (40), 136 (45), and 136 (65).

Anal. Calcd for $C_{11}H_{16}NO_3SCl$: C, 47.56; H, 5.81; N, 5.04. Found: C, 47.55; H, 5.61; N, 5.24.

Further elution with Et_2O–MeOH gave an oily product which was purified on preparative tlc (silica gel, 10% MeOH–C_6H_6) to afford 116 mg (6.5%) of **7,7-dimethyl-2-carbamoylmethylenenorpinane (25)** as crystals after recrystallization from *n*-hexane–CH_2Cl_2: mp 157–160°; mass spectrum *m/e* 180 (60, M + 1), 179 (100, M$^+$), 178 (60), 177 (80), 164 (40), 162 (50), 136 (60), 135 (50), and 91 (90).

Anal. Calcd for $C_{11}H_{17}ON$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.86; H, 9.29; N, 7.90.

2-Azetidinone-4-spiro-2′-(6′,6′-dimethyl)bicyclo[3.1.1]heptane (20).—A reaction mixture of CSI (4.25 g, 30.0 mmol) with **18** (4.08 g, 30.0 mmol) in 30 ml of ether for 4 hr at −73° was stirred with 20 ml of 20% aqueous sodium sulfite at pH 8–9.5 (10% aqueous KOH) and at −5 to 0° for 1 day. After stirring was continued for further 10 hr at room temperature, the organic layer was separated and the aqueous layer was extracted with ether (5 × 20 ml). The combined organic layer and extracts were dried (Na_2SO_4) and evaporated to afford 2.55 g of solid product. Three recrystallization from *n*-hexane afforded 1.67 g (31.3%) of **20**: mp 114–116°; mass spectrum *m/e* 180 (20, M + 1), 179 (96, M$^+$), 163 (54), 160 (27), 149 (98), 136 (95), 124 (84), 108 (98), 96 (100), and 93 (78).

Anal. Calcd for $C_{11}H_{17}ON$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.58; H, 9.26; N, 7.52.

6,6-Dimethyl-4-azatricyclo[5.2.1.0^{1,5}]decan-3-one (23).—Treatment of 20 mg (0.0702 mg) of **22** with 20% sodium sulfite aqueous solution (3 ml) and ether (5 ml) at room temperature for 7 hr and work-up as above afforded 10 mg (79.6%) of **23** as colorless plates: mp 163–165° (*n*-hexane); ir (KBr) 3380, 3280, 1710, and 1675 cm^{-1}; nmr ($CDCl_3$) τ 3.67–4.67 (mound, 1, disappeared on deuteration, NH), 6.87 (s, 1, C_5H), 7.74 (AB q, 2, *J* = 15 Hz, $J/\Delta\tau$ = 0.789, 2 C_2H), 7.86–9.07 (m, 7, other ring protons), 8.93 and 9.08 (each s, 6, 2 C_6CH_3); mass spectrum *m/e* 180 (5.8, M + 1), 179 (22, M$^+$), 150 (24), 136 (20, M − NHCO), 122 (27), 109 (91), 108 (95), 96 (100), 93 (56), 44 (64), and 41 (82).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.84; H, 9.32; N, 7.72.

Direct reduction of crude rearranged product of **19** with 20% sodium sulfite, followed by purification on a silica gel column eluting with $CHCl_3$–MeOH afforded **23** in 1.7% yield.

Azetidine-4-spiro-2′-(6′,6′-dimethyl)bicyclo[3.1.1]heptane (21).—A mixture of **20** (716 mg, 4.00 mmol) and lithium aluminum hydride (1.19 g, 31.3 mmol) in dry tetrahydrofuran (20 ml) was refluxed for 22 hr. Work-up as usual after decomposition of excess $LiAlH_4$ by adding water afforded **21** as an oil (0.61 g, 92%): n^{20}D 1.5030; ir (neat) 3032, 1462, 1385, 1367, and 1125 cm^{-1}; mass spectrum *m/e* 166 (13, M + 1) 165 (70, M$^+$), 150 (17), 136 (58), 121 (51), 108 (56), 105 (71), 98 (78), 93 (100), 91 (73), 79 (66), 77 (56), 69 (50), and 41 (86).

(39) For the Beckmann and Schmidt fissions, *cf.* T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, **36**, 2457 (1971), and references therein.

Anal. Calcd for $C_{11}H_{19}N$: C, 79.94; H, 11.59; N, 8.48. Found: C, 80.08; H, 11.48; N, 8.44.

Reaction of CSI with Camphene (26). A.—The reaction of **26** (2.75 g, 20.0 mmol) in ether (40 ml) with CSI (2.84 g, 20.0 mmol) at −3 to 0° for 1.5 hr afforded crude adduct as crystals after removal of the solvent, which were purified by extraction with hot methanol in order to remove *N*-chlorosulfonyl-α,β-unsaturated carboxylic acid amide as the side product,[7] to afford 4.03 g (77%) of **4-chlorosulfonyl-10,10-dimethyl-4-azatricyclo[5.2.1.0^{1,5}]decan-3-one (28)**, mp 125–126° (lit.[7] mp 126°). Reduction of **28** with sodium sulfite gave 97% yield of **10,10-dimethyl-4-azatricyclo[5.2.1.0^{1,5}]decan-3-one (29)** as colorless crystals from *n*-hexane–benzene: mp 173–175° (lit.[7] mp 190°); nmr ($CDCl_3$) τ 3.20–4.13 (mound, 1, NH), 6.52 (d of d, 1, $J_{5n,6n}$ = 8.0 and $J_{5n,6x}$ = 4.5 Hz, C_5H), 7.83 (AB q, 2, J = 18 Hz, $J/\Delta\tau$ = 0.900, 2 C_2H), 7.97–8.87 (m, 7, other ring protons), 8.99 and 9.08 (s, 6, 2 $C_{10}CH_3$).

B.—A reaction mixture of **26** (3.18 g, 23.4 mmol) and CSI (3.32 g, 23.4 mmol) in ether (40 ml) at −73° for 3 hr was stirred at −5 to 0° for 20 hr after addition of 20% sodium sulfite (20 ml) and 10% aqueous potassium hydroxide (*ca.* 10 ml). Work-up as above gave 2.50 g of crude product which was recrystallized from *n*-hexane after two sublimations, bp (60–120° (5 mm), to give **2-azetidinone-4-spiro-2′-(3′,3′-dimethyl)bicyclo[3.3.1]heptane (33)** as colorless crystals (1.48 g, 35%): mp 206–208°; ir (KBr) 3210, 1750 (sh), and 1710 cm^{-1}; nmr ($CDCl_3$) τ 3.09 (mound, 1, NH), 7.26 (AB q, 2, J = 16 Hz, $J/\Delta\tau$ = 0.889, 2 C_3H), 7.85 (unsymmetrical s, 1, C_1H), 8.0–9.0 (m, 7, other ring protons), and 9.02 (s, 6, 2 $C_2{}'CH_3$); mass spectrum *m/e* 180 (13, M + 1), 179 (60, M^+), 163 (14), 151 (30), 149 (20), 136 (100), 121 (30), 109 (28), 96 (54), 93 (27), and 73 (28).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.51; H, 9.78; N, 7.80.

Azetidine-4-spiro-2-(3′,3′-dimethyl)bicyclo[3.3.1]heptane (34).—A mixture of **33** (120 mg, 0.670 mmol) and $LiAlH_4$ (300 mg, 7.89 mmol) in tetrahydrofuran (10 ml) was refluxed for 20 hr, and work-up as usual gave **34** as an oil (100 mg, 90%): $n^{20}D$ 1.5054; ir (neat) 3260, 1464, 1385, 1365, 1341, and 1112 cm^{-1}; nmr ($CDCl_3$) τ 6.1–7.1 (m, 2, $-CH_2NH-$), 7.40 (s, 1, NH), 7.3–8.9 (m, 9, other ring protons), 9.05 and 9.15 (each s, 6, 2 $C_3{}'CH_3$); mass spectrum *m/e* 166 (20, M + 1), 165 (85, M^+), 150 (25), 137 (60), 136 (55), 122 (75), 121 (85), 96 (95), 93 (100), 82 (85), 69 (70), 67 (35), and 41 (95).

Anal. Calcd for $C_{11}H_{19}N$: C, 79.94; H, 11.59; N, 8.48. Found: C, 80.11; H, 11.44; N, 8.45.

10,10-Dimethyl-4-azatricyclo[5.2.1.0^{1,5}]decane (30).—A mixture of **28** (278 mg, 1.00 mmol) and $LiAlH_4$ (500 mg, 13.1 mmol) in dry tetrahydrofuran was refluxed for 26 hr. Work-up afforded **30** as colorless solid (75 mg, 45%) which was characterized as picrate: mp 248–250° dec (CH_2Cl_2–Et_2O); ir (KBr) 2940 and 1363 cm^{-1}; nmr ($CDCl_3$) τ 1.08 (s, 2, aromatic protons), 5.85–7.05 (m, 3, 2 C_3H and C_5H), 7.55–8.85 (m, 9, other ring protons), and 9.03 (s, 6, 2 $C_{10}CH_3$); mass spectrum *m/e* 166 (7.7, M + 1), 165 (25, M^+), 130 (37), 103 (54), 91 (62), and 44 (100).

Anal. Calcd for $C_{17}H_{22}N_4O_7$: C, 51.77; H, 5.62; N, 14.21. Found: C, 51.61; H, 5.60; N, 14.17.

4-Formyl-10,10-dimethyl-4-azatricyclo[5.2.1.0^{1,5}]decan-3-one (31).—Heating of a mixture of **28** (554 mg, 2.00 mmol) and DMF (730 mg, *ca.* 10 mmol) at 75–80° for 39 hr and conventional work-up afforded **31** as colorless crystals from *n*-hexane (250 mg, 60%): mp 87.5–88°; ir (KBr) 1737 and 1672 cm^{-1}; nmr ($CDCl_3$) τ 0.99 (s, 1, CHO), 6.34 (d of d, 1, J = 7.5 and 5.2 Hz, C_5H), 7.59 (s, 2, $-CH_2CO-$), 7.68–9.00 (m, 7, other ring protons), 9.07 and 9.09 (s, 6, 2 $C_{10}CH_3$); mass spectrum *m/e* 207 (3.4, M^+), 179 (11, M − CO), 133 (98), 123 (95), 120 (73), 108 (71), 95 (100), and 93 (56).

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.39; H, 8.03; N, 6.65.

4,10,10-Trimethyl-4-azatricyclo[5.2.1.0^{1,5}]decane (32).—Reduction of **31** (100 mg, 0.483 mmol) with $LiAlH_4$ as above afforded **32** as solid (57 mg, 66%) which was characterized as picrate: mp 211–213° dec ($CHCl_3$–EtOH); ir (KBr) 2960, 1483, and 1365 cm^{-1}; nmr ($CDCl_3$) τ 5.65 (m, 1, C_5H), 6.50–7.30 (m, 2, 2 C_3H), 7.11 (br s, 3, NCH_3), 7.4–8.9 (m, 9, other ring protons), 8.99 and 9.09 (s, 6, 2 $C_{10}CH_3$); mass spectrum *m/e* 180 (5.6, M + 1), 179 (25, M^+), 164 (26, M − CH_3), 138 (19), 124 (98), 96 (17), and 44 (100).

Anal. Calcd for $C_{18}H_{24}N_4O_7$: C, 52.93; H, 5.92; N, 13.72. Found: C, 52.89; H, 5.91; N, 13.49.

Reaction of CSI with Δ^3-Carene (38).—The reaction was carried out similarly as described above by using freshly distilled **38**, bp 73.5–75° (32 mm) (2.72 g, 20.0 mmol) and CSI (2.84 g, 20.0 mmol) in ether at 0–25° for 9 hr. Purification of crude adduct on a silica gel column eluting with benzene afforded **4-chlorosulfonyl-3,9,9-trimethyl-4-azatricyclo[6.1.0.0^{3,6}]-nonan-5-one (39)** as a colorless oil (4.02 g, 72%): $n^{20}D$ 1.5172; ir (neat) 1807, 1403, and 1165 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}NO_3SCl$: C, 47.57; H, 5.81; N, 5.04. Found: C, 47.26; H, 5.65; N, 5.06.

3,9,9-Trimethyl-4-azatricyclo[6.1.0.0^{3,6}]nonan-5-one (41).—Reduction of **39** (4.02 g, 18.1 mmol) with sodium sulfite followed by conventional work-up gave **41** as colorless crystals (1.70 g, 65%) from *n*-hexane: mp 111–114°; uv end (EtOH) 203, 220, and 250 nm (ε 2210, 302, and 63.2); nmr ($CDCl_3$) τ 3.83–4.23 (mound, 1, NH), 7.33 (unsym d, 1, J = 4.5 Hz, H_6), 7.58–8.20 (br m, 2, H_{2x} and H_{7n}), 8.64 (s, 3, C_3CH_3), 8.70–9.50 (m, 4, other ring protons); mass spectrum *m/e* 180 (2.9, M + 1), 179 (5.7, M^+), 164 (6.7, M − CH_3), 136 (57, M − NHCO), 121 (42), 93 (100), and 44 (98).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.55; H, 9.46; N, 7.75.

3,9,9-Trimethyl-4-azatricyclo[6.1.0.0^{3,6}]nonane (42).—Reduction of **41** (180 mg, 1.01 mmol) with $LiAlH_4$ as above afforded **42** as fine needles after sublimation (50 mg, 30%): mp 128–130° (sealed tube); ir (KBr) 3450, 2935, 1550, and 1405 cm^{-1}; nmr ($CDCl_3$) τ 6.58 and 7.72 (unsym br t, each 1, J = 7.5 Hz, $-CH_2-NH-$), 7.11 (br s, 1, disappeared on addition of D_2O, NH), 7.9–9.5 (br m, 7, other ring protons), 8.74 (s, 3, C_3CH_3), 8.90 (s, 3, $C_{9x}CH_3$), and 9.05 (s, 3, $C_{9n}CH_3$); on addition of CF_3COOH, τ 2.96 (NH), 6.08 and 7.35 ($-CH_2NH-$), and 7.5–9.5 (other protons); mass spectrum *m/e* 165 (3.1, M^+), 164 (6.8, M − 1), 150 (17, M − CH_3), 136 (7.7, M − $NHCH_2$), 122 (17), 121 (14), 97 (39), 93 (49), 82 (100), 69 (85), 54 (55), 44 (70), 42 (80), and 41 (76).

High-resolution mass spectrum had a M^+ at *m/e* 165.154; calcd (for $C_{11}H_{19}N$) 165.152.

Registry No.—**1**, 80-56-8; **2**, 37500-21-3; **3**, 37488-41-8; **4**, 37488-42-9; **5**, 35182-62-8; **6**, 37488-26-9; **7**, 37448-27-0; **7** picrate, 37488-25-8; **8** picrate, 35182-67-3; **9**, 35182-66-2; **11a**, 19406-38-3; **11b**, 37488-29-2; **18**, 127-91-3; **20**, 37528-64-6; **21**, 37528-65-7; **22**, 37500-23-5; **23**, 35182-68-4; **25**, 37528-71-5; **26**, 79-92-5; **28**, 37500-22-4; **30** picrate, 35211-89-3; **31**, 35182-69-5; **32** picrate, 35182-70-8; **33**, 37528-61-3; **34**, 37488-24-7; **38**, 13466-78-9; **39**, 35182-72-0; **41**, 35187-17-8; **42**, 35182-73-1; chlorosulfonyl isocyanate, 1189-71-5; 5-*exo*-cyano-2,2-dimethyl-3-methylenenorbornane, 37528-62-4.

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Sulfenylation of Hindered Phenols with Aryl Disulfides

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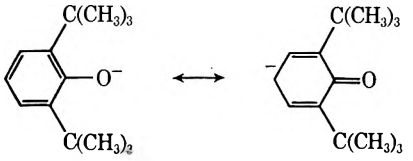
A series of 4-arylthio-2,6-di-*tert*-butylphenols have been prepared in good yields by the reaction of 2,6-di-*tert*-butylphenol with aryl disulfides in basic media. As a base sodium ethoxide was effective. Some other 4-arylthio-2,6-dialkylphenols were also prepared, and their yields were greatly influenced by the bulkiness of the ortho substituents of the starting phenols. The effects of steric hindrance on the reaction and the reaction path are discussed.

Hindered phenols, which have bulky groups such as *tert*-butyl at both ortho positions, show considerably different reactivities from other phenolic compounds.[1] Some of them are known to give stable radicals on oxidation,[2] while 2,6-di-*tert*-butylphenol is readily oxidized to give a diphenoquinone derivative.[3] The electrophilic reaction of the hindered phenol with compounds bearing a sulfur–chlorine bond such as sulfur chlorides and sulfenyl chlorides, which are commonly used for the direct sulfuration to aromatic nuclei,[4] is usually accompanied by a homolytic reaction, although it has been found to proceed smoothly in such a polar solvent as acetonitrile, giving the corresponding arylthiolated phenols in good yields.[5] Furthermore, 2,6-di-*tert*-butylphenol (**1**) is known to exist as an ambident anion between phenolate anion I and carbanion II in basic media.[6] The carbanion II reacts with various



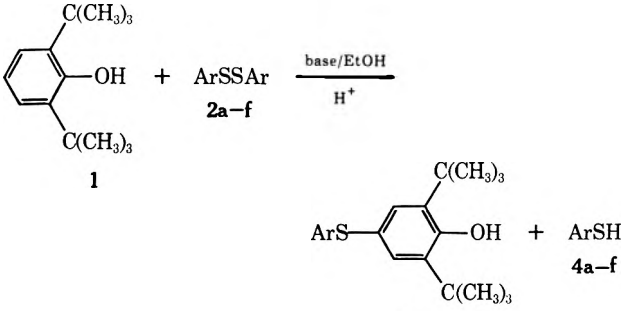
I II

electrophiles: substitution with alkyl halides[6] and acyl halides,[7] condensation with carbonyl compounds,[7] and Michael-type addition to acrylonitrile.[6] In addition, it has been used in alkylation reaction with trialkylboranes as an effective base.[8]

Meanwhile, cleavage reactions of sulfur–sulfur bonds have attracted much attention for much synthetic and biochemical interest. The ionic scission of the sulfur–sulfur bonds by such nucleophilic reagents as phosphine and thiolate, cyano, hydroxy, and thiocyano anions is well documented and involves an SN2 mechanism.[9] The reactivity of the nucleophiles toward divalent sulfur is designated by the term thiophilicity, and a carbanion has more thiophilic character than an alkoxide or phenolate anion.[9] Thus, the disulfide may be one of the useful sulfenylating agents and the cleavage reaction may provide a convenient method for the formation of sulfides. The examples recently disclosed are reactions with Grignard reagents[10] and amines[11] to give alkyl sulfide and sulfenamide, respectively, in good yields. A facile reaction of the carbanion, readily prepared from hindered phenols in basic media, with elemental sulfur has also been reported.[12]

In the present paper, we describe a sulfenylation reaction of hindered phenols with aryl disulfides which provides a convenient means of preparing arylthiolated phenols. The only compound of this class reported so far is 4-phenylthio-2,6-di-*tert*-butylphenol (**3c**), which was obtained by a tedious route.[13]

When an ethanol solution of 2,6-di-*tert*-butylphenol (**1**), aryl disulfide (**2**), and a base was refluxed for 20



1 **2a–f** **3a–f** **4a–f**

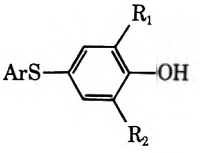
a, Ar = 4-$CH_3OC_6H_4$
b, Ar = 4-$CH_3C_6H_4$
c, Ar = C_6H_5
d, Ar = 4-ClC_6H_4
e, Ar = 4-BrC_6H_4
f, Ar = 4-OH-3,5-$(t\text{-}C_4H_9)_2C_6H_2$

hr, 4-arylthio-2,6-di-*tert*-butylphenol (**3**) was obtained after neutralization with hydrochloric acid, along with the corresponding thiophenol (**4**). Results of the reaction with various aryl disulfides are summarized in Table I. The optimal molar ratio for **1**, **2**, and base was found to be 2:1:4. As a base, potassium hydroxide or sodium ethoxide led to a successful result, while no reaction took place with triethylamine. When potassium hydroxide was used as a base, yields of asymmetric sulfides (**3a–e**) were moderate, although the corresponding thiophenols (**4a–e**) were obtained in good yields at the same time. In these cases, nucleophilic scission of disulfides by hydroxide anion[14] occurred simultaneously. A control experiment with-

(1) G. H. Stillson, D. W. Sawyer, and C. K. Hunt, *J. Amer. Chem. Soc.*, **67**, 303 (1945).
(2) E. R. Altwicker, *Chem. Rev.*, **67**, 475 (1967).
(3) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1439 (1957).
(4) E. Müller, Ed., "Methoden der Organischen Chemie," Vol. IX, Georg Thieme Verlag, Stuttgart, 1955, p 136.
(5) T. Fujisawa, M. Yamamoto, and G. Tsuchihashi, *Synthesis*, 624 (1972).
(6) N. Kornblum and R. Seltzer, *J. Amer. Chem. Soc.*, **83**, 3668 (1961).
(7) T. H. Coffield, A. H. Filbey, G. G. Ecke, and A. J. Kolka, *ibid.*, **79**, 5019 (1957).
(8) H. C. Brown, H. Nambu, and M. M. Rogic, *ibid.*, **91**, 6852 (1969).
(9) (a) A. J. Parker, *Acta Chem. Scand.*, **16**, 855 (1962); (b) A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).
(10) A. W. P. Jarvie and D. Skelton, *J. Organometal. Chem.*, **30**, 145 (1971).
(11) M. D. Bentley, I. B. Douglass, J. A. Lacadie, and D. C. Weaver, *Chem. Commun.*, 1625 (1971).
(12) T. Fujisawa, K. Hata, and T. Kojima, *Synthesis*, in press.
(13) E. Müller, H. B. Stegmann, and K. Scheffler, *Justus Liebigs Ann. Chem.*, **645**, 79 (1961).
(14) J. P. Danehy and K. N. Parameswaran, *J. Org. Chem.*, **33**, 568 (1968).

TABLE I[a]

SULFENYLATION OF 2,6-DIALKYLPHENOL WITH ARYL DISULFIDE



Compd	R_1	R_2	Ar	Mp, °C	Yield, %[b] With potassium hydroxide	Yield, %[b] With sodium ethoxide
3a	*t*-C_4H_9	*t*-C_4H_9	4-$CH_3OC_6H_4$	141–142°	61	88
3b	*t*-C_4H_9	*t*-C_4H_9	4-$CH_3C_6H_4$	96–98	44	108
3c	*t*-C_4H_9	*t*-C_4H_9	C_6H_5	101–102[c]	36	113
3d	*t*-C_4H_9	*t*-C_4H_9	4-ClC_6H_4	89–90	59	88
3e	*t*-C_4H_9	*t*-C_4H_9	4-BrC_6H_4	100–101	36	98
3f	*t*-C_4H_9	*t*-C_4H_9	4-OH-3,5-(*t*-C_4H_9)$_2C_6H_2$	137–138[d]	84[e]	80[e]
9a	CH_3	*t*-C_4H_9	4-$CH_3OC_6H_4$	104–105		28
9c	CH_3	*t*-C_4H_9	C_6H_5	Oil		24
9e	CH_3	*t*-C_4H_9	4-BrC_6H_4	Oil		46
10a	$CH(CH_3)_2$	$CH(CH_3)_2$	4-$CH_3OC_6H_4$	Oil		26
10c	$CH(CH_3)_2$	$CH(CH_3)_2$	C_6H_5	Oil		18
10e	$CH(CH_3)_2$	$CH(CH_3)_2$	4-BrC_6H_4	Oil		31

[a] Satisfactory analytical data (±0.3% for C, H, and S) were reported for all new compounds listed in the table.[24] [b] Based on the phenols. Determined by glpc. [c] Lit.[14] mp 99–101°. [d] Lit.[14] mp 135–136°. [e] Determined by nmr.

out **1** showed the formation of **4** and the corresponding sulfinic acid **5**. In the case of **2f** the high yield of **3f**

$$\underset{\mathbf{2}}{ArSSAr} \xrightarrow[H^+]{OH^-/EtOH} \underset{\mathbf{4}}{ArSH} + \underset{\mathbf{5}}{ArSO_2H}$$

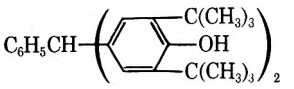
is due to the simultaneous desulfuration reaction of the disulfide with alcoholic potassium hydroxide.[13] On the other hand, sodium ethoxide, which has less thiophilic character, was found to be a better base for the reaction and the yields of **3** were greatly increased. The yields exceeding the stoichiometric amount are due to the partial oxidation of the anion of the resulting **4** to the starting disulfide during the reaction course. This is verified by a control experiment on the reaction of **1** with *p*-thiocresol in place of **2b**, where **3b** was obtained in a yield of 5%.

$$ArS^- \xrightarrow{[O]} \underset{\mathbf{2}}{ArSSAr}$$

The reaction proceeds substantially even at lower temperature (50°) in a more diluted solution (see kinetic runs). In the case of aryl disulfides having electron-withdrawing groups (**2d–e**), the reaction was accomplished quantitatively within 1 hr. Even in the case of tolyl disulfide (**2b**), *ca.* 80% **3b** was formed within 3 hr. *p*-Nitrophenyl disulfide, however, gave not the expected sulfide, but thiobis(2,6-di-*tert*-butylphenol) (**3f**), which may be formed by further reaction of the primary product with **1**.

On the other hand, *n*-butyl disulfide did not react with **1** under the same conditions and the starting materials were recovered intact. When benzyl disulfide was used as a substrate, the reaction proceeded in quite a different way. Bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)phenylmethane (**6**), which has been reported to be prepared from benzaldehyde and **1**,[7] was obtained in 65% yield. The product may result from benzaldehyde intermediately formed by alkaline decomposition of benzyl disulfide.[14]

$$C_6H_5CH_2SSCH_2C_6H_5 \xrightarrow{OH^-} C_6H_5CHO \xrightarrow{II}$$



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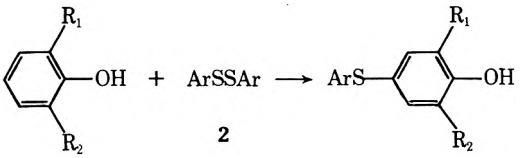
The effect of substituents of phenols plays an important role in the reaction. The sulfenylation using various 2,6-dialkylphenols as nucleophiles was studied and the yields of the products, 4-arylthio-2,6-dialkylphenols, are also shown in Table I. Compared with the data on 2,6-di-*tert*-butylphenol, 2-methyl-6-*tert*-



7, R_1 = *t*-C_4H_9; R_2 = CH_3 **9**, R_1 = *t*-C_4H_9; R_2 = CH_3

8, $R_1 = R_2$ = $CH(CH_3)_2$ **10**, $R_1 = R_2$ = $CH(CH_3)_2$

butylphenol (**7**), and 2,6-diisopropylphenol (**8**) gave the corresponding sulfides (**9** and **10**) in low yields, while 2,6-dimethylphenol and unsubstituted phenol did not react with disulfides. The order of yields of the products was inversely related to the specific conductivities of the phenols,[15] which are reported to be in close correlation with steric hindrance. Accordingly, this order indicates that the reaction was affected by the bulkiness of the substituents of the phenols.

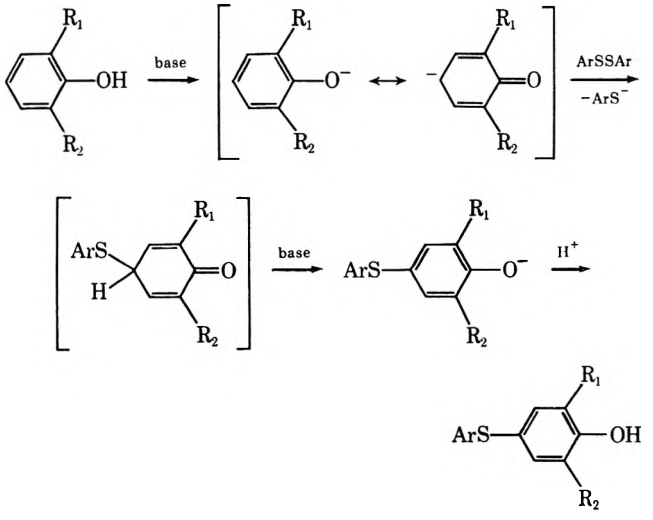
These results indicate a low reactivity of phenolate anions toward disulfides. The electron density of the aromatic ring, especially at the para position, of 2,6-disubstituted phenols increases according to the bulkiness of the substituent in the order dimethyl ≪ diisopropyl ≤ *tert*-butylmethyl < di-*tert*-butyl. Accordingly, their reactivities vary in the above order. This effect is best explained by "steric hindrance to solva-

(15) R. Perrin and N. Brondel, *C. R. Acad. Sci.*, **260**, 2809 (1965).

tion";[16] solvation of I is prevented by the bulky *tert*-butyl groups. This concept has also been seen in properties[17] and oxidation reactions[18] of hindered phenols. 2,6-Dimethylphenol showed no reactivity in this system, while it gave thiobis(2,6-dimethylphenol) by the sulfenylation with elemental sulfur as reported previously.[12] The difference of its reactivities toward aryl disulfide and toward sulfur may be due to the susceptibility of the S–S bond to nucleophilic attack, which is related to the bond energies: 64 kcal/mol for phenyl disulfide[19] and 33 kcal/mol for the eight-membered sulfur molecule.[20]

To corroborate the reaction pathway, the reaction rates were measured in ethanol at 50.0° using **1** and various para-substituted diphenyl disulfides. The rate of the scission of the sulfur–sulfur bond of the disulfides by hydroxide anion was also measured under the same conditions. As shown in Figure 1, linear relationships for both reactions were observed between the logarithms of the second-order rate constant and the Hammett para-substituent constant σ_p, and the gradient of the plots gave a value for the reaction constant ρ of +3.1 for both reactions. The rate of the bond scission of a disulfide by hydroxide anion was observed to be almost the same as that by the carbanion II. This is in substantial accord with the experimental data in Table I, which show a reduction of the yields of **3** in the use of potassium hydroxide as a base. In this case a half of the disulfide was consumed simultaneously by the attack of hydroxide anions. On the other hand, the use of sodium ethoxide as a base gave exclusively the product **3**, since the rate of disulfide scission by the ethoxide anion is negligibly slow.

Reactions of both the carbanion and the hydroxide anion proceed faster in the cases of aryl disulfides with electron-withdrawing groups rather than those with electron-releasing ones. This shows that the smaller the pK_a value of thiol, *i.e.*, the more stable the leaving thiolate anion, the faster is the reaction.[14] Therefore, the reaction of disulfides with the carbanion of hindered phenols involves a bimolecular nucleophilic mechanism as follows.



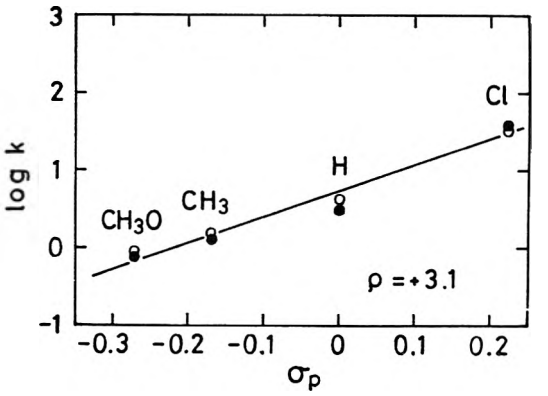


Figure 1.—Correlation of the rate constant with Hammett substituent constant σ_p: Reaction was conducted in ethanol at 50.0°: ●, reaction of **1** with **2**; ○, reaction of **2** with KOH.

In conclusion, aryl disulfides react only at carbon in the ambident anion of hindered phenols, giving 4-arylthiophenols.

Experimental Section

All melting points are uncorrected. Proton nmr spectra were measured with a Varian HA-100 spectrometer. Glpc analyses were conducted using a Hitachi K-53 chromatograph with a 1-m SE-30 column (3% on Chromosorb W). Aryl disulfides and benzyl disulfide were prepared by the oxidation of the corresponding thiophenols in dimethyl sulfoxide.[21] Bis(*p*-bromophenyl) disulfide[22] and bis(*p*-nitrophenyl) disulfide[23] were prepared by known procedures as referenced. Phenol and 2,6-dialkylated phenols were obtained commercially.

General Procedure for Preparation of 4-Arylthio-2,6-di-*tert*-butylphenol (3).—2,6-Di-*tert*-butylphenol (1) (10 mmol) and aryl disulfide **2** (5 mmol) were dissolved in ethanol (25 ml) containing a base (20 mmol). The solution was heated under reflux for 20 hr, and then was poured into 2 *N* hydrochloric acid. The products were extracted with benzene (20 ml). The benzene extract was washed with 1 *N* NaOH solution, dried ($MgSO_4$), concentrated, and subjected to distillation to remove **1**. The resulting sulfide **3** was recrystallized from ethanol–water. The yields and the melting points are shown in Table I. Nmr spectra consistent with the structure were obtained for all compounds.[24]

Reaction of Aryl Disulfides with Potassium Hydroxide.—An ethanol solution of **2b–d** (5 mmol) and potassium hydroxide (20 mmol) was heated under reflux for 20 hr. After neutralization with hydrochloric acid, the products were extracted with benzene, and the extract was submitted to glpc analysis. The yields of **4** based on **2** were as follows: **4b**, 68%; **4c**, 84%; **4d**, 48%. After evaporation of benzene from the extract, crystalline sulfinic acid was filtered. The yields were as follows: **5b**, 28%; **5c**, 15%; **5d**, 18%.

Reaction of 1 with *p*-Thiocresol.—In place of **2b**, *p*-thiocresol (**4b**) (10 mmol) was used in the presence of sodium ethoxide, other conditions being the same as the general procedure. 4-*p*-Tolylthio-2,6-di-*tert*-butylphenol (**3b**) was obtained in a yield of 5%.

Reaction of 1 with Bis(*p*-nitrophenyl) Disulfide.—The reaction was carried out in the same manner as the general procedure described above, using bis(*p*-nitrophenyl) disulfide (1.55 g, 5 mmol) in the presence of potassium hydroxide. The product obtained from the reaction mixture was thiobis(2,6-di-*tert*-butylphenol) (**3f**), 0.50 g (23%), mp 135–138°.

Reaction of 1 with Benzyl Disulfide.—As a disulfide, benzyl disulfide (1.25 g, 5 mmol) was used in the presence of sodium

(16) P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Amer. Chem. Soc.*, **76**, 2349 (1954).
(17) L. A. Cohen, *J. Org. Chem.*, **22**, 1333 (1957).
(18) H. R. Gersmann and A. F. Bickel, *J. Chem. Soc.*, 2356 (1962).
(19) H. Mackle and R. G. Mayrick, *Trans. Faraday Soc.*, **58**, 238 (1962).
(20) A. V. Tobolsky and A. Eisenberg, *J. Amer. Chem. Soc.*, **81**, 780 (1959).
(21) C. N. Yiannios and J. V. Karabionos, *J. Org. Chem.*, **28**, 3246 (1963).
(22) E. Bourgeois and A. Abraham, *Recl. Trav. Chim. Pays-Bas*, **30**, 407 (1911).
(23) T. Zincke and S. Lenhardt, *Justus Liebigs Ann. Chem.*, **400**, 2 (1913).
(24) Additional tables of analytical and nmr spectral data will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to code number JOC-73-687. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

ethoxide, other conditions being the same as the general procedure. After evaporation of the solvent from the benzene extract, bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)phenylmethane (**6**) was obtained as white crystals, yield 1.63 g (65%), mp 161–162° (lit.[3] mp 161–163°).

When potassium hydroxide was used as a base, 1.49 g (60%) of **6** was obtained.

Reaction of 2,6-Dialkylphenols 7 and 8 with Aryl Disulfide.—The reaction was conducted in the same manner as the general procedure using 2,6-di-*tert*-butylphenol. The base used in the reaction was sodium ethoxide. The separation and purification was achieved by column chromatography on silica gel and preparative glpc. The yields of the products, 4-arylthio-2,6-dialkylphenols (**9** and **10**), are summarized in Table I.[24]

Procedure of Kinetic Runs. A. Reaction of 1 with 2.—In a typical experiment, an ethanol solution (25 ml) of **1** (1.25 mmol) and **2** (0.50 mmol) in a stoppered ampoule was flushed with argon and placed in a constant-temperature bath at 50.0°. An ethanolic sodium ethoxide solution (0.50 *N*, 25 ml) at the same temperature was added to the above solution. A 1-ml aliquot of the resulting solution was pipetted out at definite intervals and poured into a mixture of benzene (2 ml) and 1 *N* hydrochloric acid (5 ml). The amount of **3** in the benzene layer was determined by glpc. The initial rate was determined graphically from the yield of **3** *vs.* time. This rate was confirmed to be the same as that of the consumption of **2** within experimental error (5%).

B. Reaction of 2 with Potassium Hydroxide.—An ethanol solution (25 ml) of **2** (0.50 mmol) and an ethanolic potassium hydroxide solution (0.50 *N*, 25 ml) were treated in the same manner as described above. In this reaction, the rate was determined from the consumption of **2**: $-d[2]/dt = k[2][KOH]$.

Registry No.—**1**, 128-39-2; **2a**, 5335-87-5; **2b**, 103-19-5; **2c**, 882-33-7; **2d**, 1142-19-4; **2e**, 5335-84-2; **2f**, 6386-58-9; **3a**, 32551-11-4; **3b**, 32551-15-8; **3c**, 32551-12-5; **3d**, 32551-13-6; **3e**, 32551-14-7; **3f**, 4673-51-2; **7**, 2219-82-1; **8**, 2078-54-8; **9a**, 37610-74-5; **9c**, 37610-75-6; **9e**, 37610-76-7; **10a**, 37610-77-8; **10c**, 37610-78-9; **10e**, 37610-79-0; bis(*p*-nitrophenyl) disulfide, 100-32-3.

Acknowledgment.—We are grateful to the Kawakami Memorial Foundation for partial support of this research.

Chemistry of the Sulfur–Nitrogen Bond. IV.[1,2] The Effects of Nuclear Substitution, Solvent, Temperature, and Time on the Rearrangement of Arenesulfenanilides to *o*- and *p*-Aminodiphenyl Sulfides

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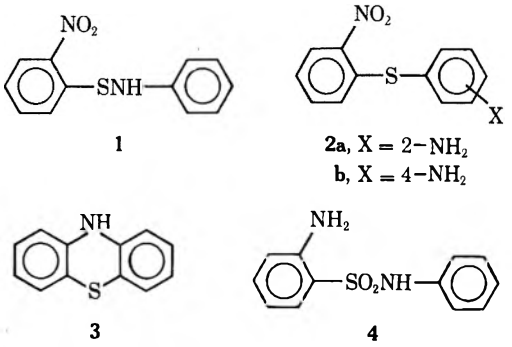
The scope and limitations of the thermal rearrangement of arenesulfenanilides to 2- and 4-aminodiphenyl sulfides has been investigated. Arenesulfenanilides undergo two thermal reactions: disproportionation to give aryl disulfides and azobenzenes and rearrangement to 2- and 4-aminodiphenyl sulfides. Electron-withdrawing groups favor rearrangement as does the addition of aniline hydrochloride. Electron-donating groups accelerate the rate of rearrangement. The effects of nuclear substitution, solvent, temperature, and time on the composition of the reaction products are discussed.

Compounds containing the sulfur–nitrogen bond are of considerable importance both from a practical as well as a theoretical standpoint. An understanding of the chemistry of sulfenamides is important in elucidating the various types of interaction possible between adjacent sulfur and nitrogen. At least three types of interactions may be considered: lone-pair interactions resulting from the presence of lone pairs of electrons on sulfur and nitrogen; bond polarization resulting from the difference in electronegativity between sulfur and nitrogen; and the donation of electrons from nitrogen to sulfur (p–d π bonding).

There is considerable evidence in support of some sort of electron donation from nitrogen to sulfur in the ground state of arenesulfenanilides which affects both torsional barriers[4] and displacement reactions at the S–N bond.[5] However, the extent to which this effect, as well as the other effects, determine reactions of sulfenamides is less well understood.

Recently, we reported an unusual thermal reaction for 2-nitrobenzene sulfenanilide (**1**).[6] When heated in aniline at 200°, **1** gave 2- and 4-aminodiphenyl sulfides (**2a–b**), phenothiazine (**3**), and 2-aminobenzenesulfonanilide (**4**). It was inferred at that time that arenesulfenanilides undergo two types of reactions: rearrangement to 2- and 4-aminodiphenyl sulfides and disproportionation to give amino and sulfenyl radicals.[6]



Subsequently it was shown that the 2-nitrobenzenesulfenyl radical resulting from the disproportionation reaction underwent an intramolecular oxidation–reduc-

(1) Part III: F. A. Davis and R. P. Johnston II, *J. Org. Chem.*, **37**, 859 (1972).

(2) Presented in part at the 7th MARM, Philadelphia, Pa., Feb 1972.

(3) National Science Foundation Undergraduate Research Participant, 1971.

(4) M. Raban and F. B. Jones, Jr., *J. Amer. Chem. Soc.*, **93**, 2692 (1971).

(5) F. A. Davis, S. Divald, and A. H. Confer, *Chem. Commun.*, 678 (1971).

(6) F. A. David, R. B. Wetzel, T. J. Devon, and J. F. Stackhouse, *J. Org. Chem.*, **36**, 799 (1971).

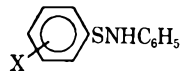
tion to give **4**.[7] Phenothiazine (**3**) resulted from a thermal Smiles rearrangement of **2a**.[8] It was also established that aminodiphenyl sulfides **2a, b** were not formed in the disproportionation reaction.[1]

An understanding of the arenesulfenanilide rearrangement mechanism is important in determining the contributions of the various types of interaction between sulfur and nitrogen to the chemistry of sulfenamides. Furthermore, this rearrangement is a member of an important class of N-substituted aminoaromatic rearrangements which include the benzidine, quinamine, and nitramine rearrangements, among others.[9]

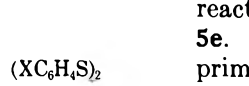
An understanding of this rearrangement must first be based upon a knowledge of the scope and limitations of the rearrangement. In this paper we have explored the effect of nuclear substitution, solvent, temperature, and time on the rearrangement.

Results

Effect of Nuclear Substitution.—To determine the scope of the arenesulfenanilide rearrangement, sulfenanilides **5a–f** were heated at 195° in purified commercial aniline for 15.5 hr. The composition of the reaction products was determined by glc analysis by comparison with authentic samples. Four types of products were identified: azobenzene (**6**), aryl disulfides (**7**), 2-aminodiphenyl sulfides (**8**), and 4-aminodiphenyl sulfides (**9**). These results are summarized in Table I.



5a, X = 4-CH_3
b, X = H
c, X = 4-Cl
d, X = 4-Br
e, X = 3-NO_2
f, X = 4-NO_2



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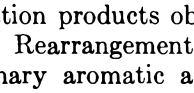

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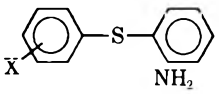

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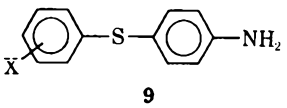

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The results summarized in Table I indicate that the rearrangement of arenesulfenanilides to 2- and 4-aminodiphneyl sulfides is quite general. Electron-donating groups favor dispropoportionation (disulfide and azobenzene formation), whereas electron-withdrawing groups favor rearrangement. With the exception of **5e**, the ortho/para ratios for **5a–f** are nearly identical, suggesting a similar mechanism. The method of synthesis of the sulfenanilide also appears to have an effect on the composition of the reaction products. Sulfenanilide **5c** (entry 3, Table I), prepared from the corresponding sulfenyl chloride, gave a higher yield of rearrangement than did **5c** prepared *via* the silver nitrate method.[10] We will come back to this in a later section.

Azobenzene (**6**) isolated in the thermal rearrangement of sulfenanilides **5a–c**, is formed by thermal disproportionation of hydrazobenzene.[11] The hydrazobenzene is formed by dimerization of two amino radicals resulting from homolytic cleavage of the S–N

$$ArNH\cdot \longrightarrow ArNH\text{–}NHAr \longrightarrow ArNH_2 + ArN{=}NAr$$

bond.[7] Under the reaction conditions hydrazobenzene in aniline gave a nearly quantitative yield of azobenzene.[12]

TABLE I

REARRANGEMENT OF SULFENANILIDES **5a–f** AT 195° IN ANILINE[a] FOR 15.5 HR (PER CENT YIELD)

Entry	Sulfenanilide[b]	Azobenzene (6)	Disulfide (7)	Aminodiphenyl sulfide ortho (8)	Aminodiphenyl sulfide para (9)	Total rearrangement	Ortho/para
1	**5a**	20	69	5	10	15	0.5
2	**5b**	34	43	9[c]	17[d]	26	0.53
3	**5c**		28	24	46	70	0.5
4	**5c**[e]	13	48	14	28	43	0.5
5	**5d**		29	21	39	60	0.54
6	**5e**			27[f]	69[f]	96	0.4
7	**5f**			33[g]	67[g]	100	0.49

[a] Purified commercial aniline; mole ratio of sulfenanilide to aniline, 1:15. [b] Prepared from the corresponding sulfenyl chloride unless otherwise noted. [c] Reference 19. [d] Reference 20. [e] Prepared *via* the silver nitrate method; ref 10. [f] Reference 6. [g] Reference 21.

Solvents Effects.—The solvent used in the arenesulfenanilide rearrangement is critical in determining the composition of the reaction products. Table II summarizes the effects of various solvents on the reaction products obtained from sulfenanilides **5c** and **5e**. Rearrangement is favored only in secondary[7] and primary aromatic amine solvents. In anisole, *N,N*-diethylaniline, dimethylacetamide, or in the absence of solvent disproportionation was favored giving disulfide.

The type of aniline used as the solvent is also important. Commercial aniline (aniline I) favors rearrangement. Aniline prepared by hydrogenation of nitrobenzene (aniline II) favors disproportionation (entries 1, 12, and 3, 13, Table II). Both anilines were purified by distillation from potassium hydroxide. Commercial aniline is prepared by metal–hydrochloric acid reduction of nitrobenzene. A trace impurity that may not have been removed in the purification steps is aniline hydrochloride. This impurity would not be present in aniline prepared by hydrogenation of nitrobenzene.

Addition of a small amount of aniline hydrochloride to aniline II resulted in 99 and 100% yields of rearrangement for sulfenanilides **5c** and **5e**, respectively (entries 2 and 14, Table II). Addition of aniline hydrochloride to **5c** in anisole, or in the absence of solvent, was also observed to increase the percentage of rearrangement (entries 6 and 11, Table II). These results support the above interpretation as well as inferring that the arenesulfenanilide rearrangement is acid catalyzed.

The lower yield of rearrangement obtained from **5c** prepared *via* the silver nitrate method compared with the higher yield of rearrangement obtained from **5c** prepared from the sulfenyl chloride (compare entries 3 and 4, Table I) is readily explained in terms of acid

(7) F. A. Davis and R. P. Johnston, II, *J. Org. Chem.*, **37**, 854 (1972).
(8) F. A. Davis and R. B. Wetzel, *Tetrahedron Lett.*, 4483 (1969).
(9) (a) H. J. Shine, "Aromatic Rearrangements," Vol. 6, Elsevier, New York, N. Y., 1967, Chapter 3; (b) M. J. S. Dewar in "Molecular Rearrangement," P. De Mayo, Ed., Interscience, New York, N. Y., 1963, Chapter 5.
(10) M. D. Bentley, I. B. Douglass, J. A. Lacadie, D. C. Weaver, F. A. Davis, and S. J. Eitelman, *Chem. Commun.*, 1625 (1971).
(11) P. Walker and W. A. Water, *J. Chem. Soc.*, 1632 (1962); L. G. Korolik and V. O. Lukaghevich, *Dokl. Chem.*, 649 (1961).
(12) It is interesting to note that benzidine was not detected. The thermal benzidine rearrangement is known to give, among other products, benzidine and azobenzene. See ref 9a, p 171.

TABLE II

EFFECTS OF SOLVENT ON THE REARRANGEMENT OF ARENESULFENANILIDES AT 195° FOR 15.5 HR (PER CENT YIELD)

Entry	Sulfenanilide[a]	Solvent[b]	Disulfide (7)	Aminodiphenyl sulfides ortho (8)	Aminodiphenyl sulfides para (9)	Total rearrangement
1	5c	Aniline I[c]	28	24	46	70
2	5c	Aniline I + $C_6H_5NH_3Cl$[d]		44	48	92
3	5c	Aniline III[e]	44			0
4	5c	Aniline II + $C_6H_5NH_3Cl$[d]		45	51	96
5	5c	Anisole	91	6	2	8
6	5c	Anisole + $C_6H_5NH_3Cl$[d]	45	19	6	25
7	5c	*N,N*-Diethylaniline	31			0
8	5c	Phenol	57	Trace		
9	5c	Dimethylacetamide	55	1	4	5
10	5c	None	62	2	4	6
11	5c	$C_6H_5NH_3Cl$[f]		27	25	52
12	5e	Aniline I[c]		27	69	96
13	5e	Aniline II[e]	42	7	12	19
14	5e	Aniline II + $C_6H_5NH_3Cl$[d]		34	65	99

[a] Prepared from the corresponding sulfenyl chloride. [b] Mole ratio of sulfenanilide to solvent, 1:15. [c] Purified commercial aniline. [d] Mole ratio of aniline hydrochloride to sulfenanilide, 1:11. [e] Purified aniline prepared by hydrogenation of nitrobenzene. [f] Mole ratio of sulfenanilide to aniline hydrochloride, 4.4:1.

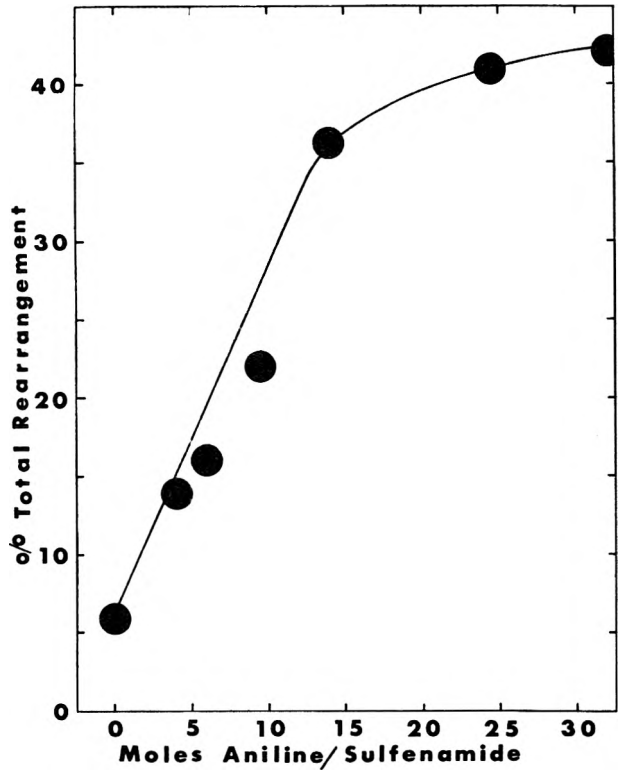


Figure 1.—Per cent total rearrangement *vs.* the mole ratio of aniline to sulfenanilide **5c**.

catalysis by aniline hydrochloride. A by-product in the synthesis of sulfenanilides from the sulfenyl chloride is aniline hydrochloride. Aniline hydronitrate is the corresponding by-product in the preparation of sulfenanilides *via* the silver nitrate method.[10] The latter impurity is apparently more easily removed than the aniline hydrochloride in the purification of the 4-chlorobenzenesulfenanilide (**5c**).

The concentration of the aniline solvent is also important in determining the composition of the reaction products. Figure 1 shows a plot of the per cent yield of total rearrangement *vs.* the mole ratio of aniline to sulfenanilide **5c**. At low concentrations of aniline little rearrangement is observed. As the concentration of aniline increases, the per cent rearrangement increases to a maximum of 42%. Figure 1 may also be interpreted in terms of acid catalysis by the impurity aniline hydrochloride. As the concentration of aniline increases the aniline hydrochloride impurity also increases and rearrangement is favored. It may have been anticipated that rearrangement should have increased as the concentration of aniline increased, since the concentration of the impurities should also be increasing. It may be that at these higher concentrations the sulfenanilide has to compete with aniline for the acid.

Effects of Temperature and Time.—The effects of temperature and time on the composition of the reaction products were determined for sulfenanilides **5b, 5c** and **5f**. These sulfenanilides were heated in aniline and aniline containing aniline hydrochloride at appropriate temperatures and time intervals. The products were analyzed by glc. In the absence of complete rearrangement only the yield of the *p*-aminodiphenyl sulfides could be determined.[13] To minimize problems resulting from trace impurities, experiments were performed with the same batch of sulfenanilide and solvent. These results are summarized in Table III.

In the absence of aniline hydrochloride (entries 1–4, Table III) a lower temperature slows the rate of reaction. A reaction time of 96 hr (monitoring the disappearance of the NH proton in the nmr) was required for complete reaction of sulfenamide **5c** at 110°. However, at 190 or 150° the reaction was complete after 16 hr. When the reaction was allowed to go to completion the lower temperature favored rearrangement (entries 2 and 4, Table III). Addition of aniline hydrochloride (entries 5–23, Table III), in all cases, accelerated the rate of rearrangement and favored it over disproportionation. Sulfenanilide **5b** in the absence of added aniline hydrochloride give only 10% rearrangement after 2 hr, whereas, with added aniline hydrochloride, rearrangement was complete after 0.5 hr (compare entries 1 and 5, Table III).

(13) The 2-aminodiphenyl sulfides and the sulfenanilide could not be satisfactorily separated by glc. Sulfenanilides **5e** and **5f** may rearrange on the glc column to the corresponding 2-aminodiphenyl sulfides. No evidence was obtained for rearrangement of any of the sulfenanilides to the 4-aminodiphenyl sulfides in the glc. It is possible that the mechanism for rearrangement to the 2- and 4-aminodiphenyl sulfides may be different, and there is some evidence which suggests this. See following paper.[14]

(14) F. A. Davis, C. J. Horner, E. R. Fretz, and J. F. Stackhouse, *J. Org. Chem.*, **38**, 695 (1973).

TABLE III

THE EFFECT OF TEMPERATURE AND TIME ON THE REARRANGEMENT OF ARENESULFENANILIDES IN ANILINE[a] (PER CENT YIELD)

Entry	Sulfenanilide[b]	Time, hr	Temp, °C	Disulfide (7)	Aminodiphenyl sulfide o- (8)	Aminodiphenyl sulfide p- (9)	Total rearrangement
1	5b	2	190	c		10	10
2	5c	16	190	28	14	46	70
3	5c	16	150	10	31	53	84
4	5c	96	110	11	33	55	88
			Aniline Hydrochloride Added[d]				
5	5a	0.5	190		40	53	93
6	5b	2.0	190		39	59	98
7	5b	16	190		42	50	92
8	5b	0.5	100			7	
9	5b	1.0	100			9	
10	5b	1.5	100			25	
11	5b	2.0	100			32	
12	5b	3.0	100			39	
13	5b	5.0	100			54	
14	5f	0.5	190		35	52	87
15	5f	2.0	190		34	54	88
16	5f	16	190		34	59	93
17	5f	2.0	100			5	
18	5f	3.0	100			11	
19	5f	5.0	100			13	
20	5f	12.0	100			23	
21	5f	16.0	100			39	
22	5f	21.5	100			47	
23	5f	41.3	100			70	

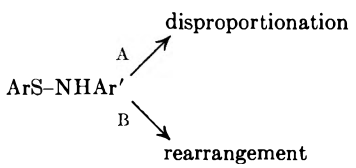
[a] Purified commercial aniline; mole ratio of sulfenanilide to aniline, 1:15. [b] Sulfenanilide prepared from the corresponding sulfenyl chloride. [c] Not detected. [d] Mole ratio of sulfenanilide to aniline hydrochloride, 1:5.1.

Lowering the temperature to 100° slows the rate of rearrangement for **5b** and **5f** sufficiently in the presence of aniline hydrochloride to permit a semiquantitative comparison of the rate of rearrangement for the two sulfenanilides. Figure 2 shows a plot of the per cent yield of sulfides **9b** and **9f** obtained from the thermal rearrangement of sulfenanides **5b** and **5f**, respectively, *vs.* time (entries 8–23, Table III). As is evident from Figure 2, the rate of rearrangement of 4-nitrobenzenesulfenanilide (**5f**) is substantially slower than that of benzenesulfenanilide (**5b**). Electron-donating groups, therefore, facilitate the rate of rearrangement, suggesting that in the transition state for rearrangement sulfur is electron deficient.

The concentration of the added aniline hydrochloride also affects the rate of rearrangement. Figure 3 summarizes this data and shows that as the mole per cent of aniline hydrochloride increases the percentage of **9b** increases.

Discussion

The experimental evidence obtained in this paper confirms our earlier observations that two thermal reactions are characteristic of arenesulfenanilides.[6] The first reaction involves disproportionation of the S–N bond to give sulfenyl and amino radicals (pathway A) which lead to aryl disulfides and azobenzene. The second reaction involves rearrangement (pathway B) leading to 2- and 4-aminodiphenyl sulfides.



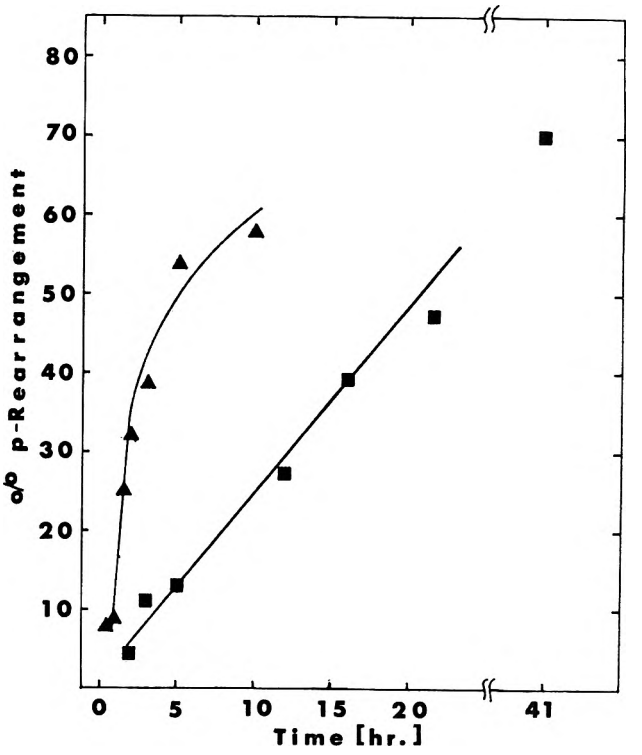


Figure 2.—Per cent yields of 4-aminodiphenyl sulfides **9b** (▲) and **9f** (■) from sulfenanilides **5b** and **5f** at 100° *vs.* time.

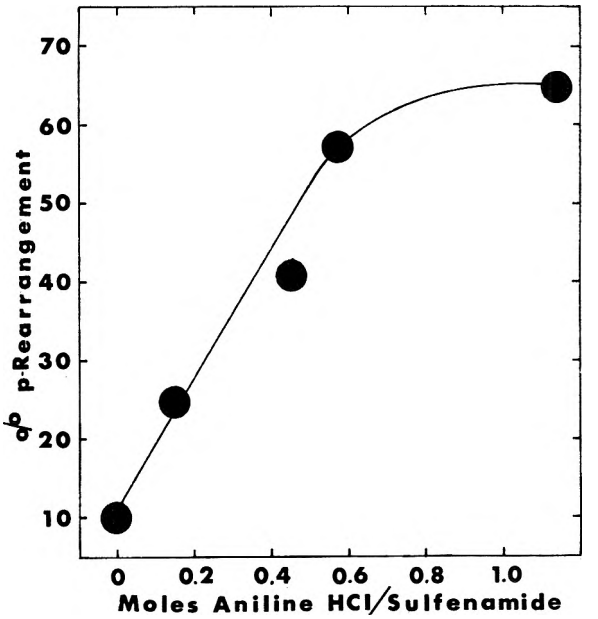


Figure 3.—Per cent yield of 4-aminodiphenyl sulfide **9b** from **5b** at 100° after 1.5 hr *vs.* mole ratio of aniline hydrochloride to sulfenanilide **5b**.

Electron-donating groups favor disproportionation (pathway A) and electron-withdrawing groups favor rearrangement (pathway B). The favoring of pathway A by electron-donating groups is readily explained in terms of stabilization of the resulting sulfenyl radical or lone-pair repulsion which destabilizes the S–N bond.

Rearrangement is favored by addition of aniline hydrochloride. As a consequence of this acid catalysis, both the purity of the solvent and the method of preparation of the sulfenamide have a dramatic effect on the composition of the reaction products. Sulfenanilides, prepared from the corresponding sulfenyl chlorides in which aniline hydrochloride is a by-product, consistently gave higher yields of rearrangement.

Rearrangement was favored only in primary and secondary aromatic amine solvent, and this may in part reflect the lack of acid to catalyze the rearrangement.

Semiquantitative rate studies of sulfenanilides **5b** and **5f** are perhaps the most enlightening as far as a mechanism is concerned. Electron-donating groups accelerated the rate of rearrangement, suggesting that sulfur may be electron deficient in the transition state for rearrangement.

The concentration of added aniline hydrochloride also had an important effect on the rate of rearrangement. Rearrangement increases linearly as the concentration of the aniline hydrochloride increases, which strongly implies that the conjugate acid of the sulfenanilide (**10**) is involved in the rate-determining step. Equations 1 and 2 summarize these results.

$$\mathrm{ArSNHAr' + Ar'NH_3{}^+Cl^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\mathbf{10}}{ArS\overset{+}{N}H_2Ar'\,Cl^-} + Ar'NH_2} \quad (1)$$

$$\mathrm{ArS\overset{+}{N}H_2Ar' \xrightarrow{k_2} \text{rearrangement products}} \quad (2)$$

There is considerable evidence that canonical forms such as **11** make important contributions to the ground-state stabilization of sulfenanilides toward torsion[4] and displacement reactions at the S–N bond.[5] As the

$$\mathrm{ArSNHAr \longleftrightarrow \underset{\mathbf{11}}{Ar\bar{S}{=}\overset{+}{N}HAr}}$$

electronegativity of substituents attached to sulfur increased the importance of **11** increased.[4,5] The decrease in electron density on nitrogen as the electronegativity of groups attached to sulfur increase will result in a lower concentration of the conjugate acid **10** (eq 1). Whether or not eq 1 or 2 is rate determining, if **10** is involved in the transition state electron-withdrawing groups will slow the rate.

The present experimental evidence does not permit a distinction to be made as to whether the arenesulfenanilide rearrangement is general or specific acid catalyzed, *i.e.*, eq 1 or 2 rate determining. Figure 3 would suggest general acid catalysis, but the benzidine[15] and nitramine[16] rearrangements are specific acid catalyzed.

In the following paper, evidence is presented for an intramolecular arenesulfenanilide rearrangement.[14]

Experimental Section

Sulfenanilides **5a**,[17] **5b**,[17] **5c**,[5] **5d**,[5] **5e**,[6] and **5f**[18] were prepared from the corresponding sulfenyl chloride unless otherwise noted. Melting points were obtained on a Fisher-John apparatus. Proton nmr spectra were measured on a Varian A-60A instrument. Infrared spectra were measured on a Perkin-Elmer 457 spectrometer. Gas chromatographic analysis were performed on a Perkin-Elmer 900 gas chromatograph using a 3% OV-17 on 80/100 mesh Chromosorb W (regular) column. Solvents were purified according to literature procedures. Commercial aniline, aniline I, and aniline prepared by hydrogenation of nitrobenzene over 10% palladium on charcoal in ethanol at 40 psi, aniline II, were distilled twice from potassium hydroxide.

General Procedure for the Thermal Rearrangement of Arenesulfenanilides.—The sulfenanilides (approximately 0.008 mol) were heated in an oil bath with an excess of solvent (mole ratio of sulfenanilide to solvent, 1:15) at appropriate temperatures and time intervals in sealed tubes. The reaction mixture was diluted with methylene chloride and filtered, a known weight of standard was added, and the mixture was analyzed by glc by comparison of peak areas with standard solutions of the reactions products. Analysis were performed at least twice and the values were averaged.

General Procedure of Synthesis of 2- and 4-Aminodiphenyl Sulfides (8 and 9).[6]—The 2- and 4-aminodiphenyl sulfides **8** and **9** were prepared by catalytic reduction, over 10% palladium on charcoal in ethanol at 40 psi, of the corresponding crude 2- and 4-nitrodiphenyl sulfides. The 2- and 4-nitrodiphenyl sulfides were prepared by condensation of the sodium salt of the appropriate aryl thiol, prepared by addition of the disulfide or thiol to sodium ethoxide in absolute ethanol, with 2- and 4-chloronitrobenzene. After refluxing for 10 hr the precipitated salts were filtered (solvent removed), dissolved in ether, and filtered. The ether solution was washed twice with 10% sodium hydroxide and twice with water and dried over $MgSO_4$. Removal of the solvent gave the crude nitrodiphenyl sulfide, which was used as described above without purification.

4-Methyl-2′-aminodiphenyl Sulfide (8a).—Reduction of 2.3 g of the nitrodiphenyl sulfide gave after crystallization from pentane 1.5 g (74%) of **8a** as white crystals: mp 47.5–49°; ir (KBr) 3500 and 3390 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 7.0 (m, 8), 4.1 (s, 2, NH_2) and 2.2 (s, 3, CH_3).

Anal. Calcd for $C_{13}H_{13}NS$: C, 72.56; H, 6.05. Found: C, 72.42; H, 6.02.

4-Methyl-4′-aminodiphenyl Sulfide (9a).—Reduction of 4.0 g of the nitrodiphenyl sulfide gave after crystallization from pentane 2.9 g (85%) of **9a** as white crystals: mp 72–73°; ir (KBr) 3480 and 3375 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 7.1 (s, 4), 7.4–6.15 (AB q, 4, J = 8 Hz), 3.6 (s, 2, NH_2), and 2.2 (s, 3, CH_3).

Anal. Calcd for $C_{13}H_{13}NS$: C, 72.56; H, 6.05. Found: C, 72.78; H, 6.27.

2-Aminodiphenyl sulfide (8b)[19] had the following properties: ir (KBr) 3410 (NH_2) and 3340 cm^{-1}; nmr ($CDCl_3$) δ 7.0 (m, 9) and 4.1 (s, 2, NH_2).

4-Aminodiphenyl sulfide (9b)[20] had the following properties: ir (KBr) 3460 and 3360 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 7.2 (s, 5), 7.5–6.7 (AB q, J = 8 Hz), and 3.6 (s, 2, NH_2).

4-Chloro-2′-aminodiphenyl Sulfide (8c).—Reduction of 2.0 g of the nitrophenyl disulfide gave, after molecular distillation (60°, 0.05 mm), 1.4 g (80%) of **8c** as an oil: ir (thin film) 3480 and 3380 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 7.0 (m, 8) and 4.2 (s, 2, NH_2).

Anal. Calcd for $C_{12}H_{10}ClNS$: C, 61.15; H, 4.25. Found: C, 61.32; H, 4.44.

4-Chloro-4′-aminodiphenyl Sulfide (9c).—Reduction of 1.5 g of the nitrodiphenyl sulfide gave, after crystallization from ether–pentane, 1.2 g (90%) of **9c** as light tan crystals: mp 60–61°; ir 3400 and 3310 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 7.1 (m, 4), 7.3–6.4 (AB q, 4, J = 9 Hz), and 3.6 (s, 2, NH_2).

Anal. Calcd for $C_{12}H_{10}ClNS$: C, 61.15; H, 4.25. Found: C, 61.22; H, 4.12.

4-Bromo-2′-aminodiphenyl Sulfide (8d).—Reduction of 5.0 g of the nitrophenyl sulfide gave, after crystallization form ether–pentane, 3.4 g (75%) of **8d** as white crystals: mp 41.5–42.5°; ir (KBr) 3500 and 3390 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 7.1 (m, 8) and 4.2 (broad s, 2, NH_2).

Anal. Calcd for $C_{12}H_{10}BrNS$: C, 51.43; H, 3.57. Found: C, 51.48; H, 3.52.

4-Bromo-4′-aminodiphenyl Sulfide (9d).—Reduction of 3.0 g of the nitrodiphenyl sulfide gave, after crystallization from ether–pentane, 1.6 g (60%) of **9d** as white crystals: mp 69–69.5°; ir (KBr) 3460 and 3380 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 7.1 (m, 8) and 3.8 (broad s, 2. NH_2).

Anal. Calcd for $C_{12}H_{10}BrNS$: C, 51.43; H, 3.57. Found: C, 51.51; H, 3.52.

4-Nitro-2′-aminodiphenyl sulfide (8f)[21] had the following properties: ir (KBr) 3460 and 3360 cm^{-1} (NH_2); nmr (acetone-d_6) δ 8.2 (d, 2) and 7.1 (m, 8).

4-Nitro-4′-aminodiphenyl sulfide (9f)[21] had the following properties: ir (KBr) 3480 and 3280 cm^{-1} (NH_2); nmr (acetone-d_6) δ 8.0 (d, 2), 7.1 (m, 5), and 5.1 (broad s, 2, NH_2).

(15) D. V. Banthorpe, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 2878 (1964).

(16) D. V. Banthorpe, E. D. Hughes, and D. L. H. Williams, *J. Chem. Soc.*, 5349 (1964); D. V. Banthorpe, J. A. Thomas, and D. L. H. Williams, *ibid.*, 6135 (1965).

(17) H. Lecher, F. Holschneider, K. Koberler, W. Speer, and P. Stocklin, *Ber.*, **58**, 409 (1925).

(18) M. L. Moore and T. B. Johnson, *J. Amer. Chem. Soc.*, **57**, 1517 (1935).

(19) E. Bourgeois and P. Huber, *Recl. Trav. Chim. Pays-Bas*, **31**, 30 (1912).

(20) R. Gillespie and R. Passerini, *J. Chem. Soc.*, 3850 (1956).

(21) H. H. Hodgson and W. Rosenberg, *ibid.*, 180 (1930).

4-Chlorobenzenesulfenanilide (5c) *via* the Silver Nitrate Method.[10]—In a 500 ml three-necked flask equipped with magnetic stir bar and nitrogen inlet was dissolved 0.59 g (0.0035 mol) of silver nitrate in 150 ml of absolute ethyl alcohol. To the reaction mixture was added 1.0 g (0.0035 mol) of bis(4-chlorophenyl) disulfide (Columbia Organic Chemicals Co.) in 150 ml of absolute ethyl alcohol. The reaction mixture was allowed to stirr for about 5 min, and 1.3 g (0.014 mol) of aniline was added, and the reaction mixture was allowed to stir under nitrogen for 48 hr. The precipitated salts were filtered from the gray solution, solvent was removed, and the residue was dissolved in ether and filtered. The ether solution was washed twice with 100-ml portions of water and dried over $MgSO_4$. Removal of the solvent gave a solid, which when crystallized from ether–pentane gave 0.46 g (60%) of 5c as white needles: mp 86–88° (lit.[22] mp 84°); ir 3380 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.1 (m, 9) and 5.05 (broad s, 2, NH_2).

(22) H. Tielecke and A. Jumer, East German Patent 17,675 (1959); *Chem. Abstr.*, **55**, P892i (1961).

Registry No.—**5a**, 14933-92-7; **5b**, 14933-91-6; **5c**, 14933-94-9; **5d**, 32338-03-7; **5e**, 27332-21-4; **5f**, 5147-60-4; **8a**, 16452-09-8; **8c**, 37750-29-1; **8d**, 3169-86-6; **9a**, 22865-52-7; **9c**, 32631-29-1; **9d**, 37750-33-7; 4-methyl-2′-nitrodiphenyl sulfide, 20912-17-8; 4-methyl-4′-nitrodiphenyl sulfide, 22865-48-1; 4-chloro-2′-nitrodiphenyl sulfide, 6764-10-9; 4-chloro-4′-nitrodiphenyl sulfide, 21969-11-9; 4-bromo-2′-nitrodiphenyl sulfide, 37750-38-2; 4-bromo-4′-nitrodiphenyl sulfide, 21969-12-0; bis(4-chlorophenyl) sulfide, 5181-10-2.

Acknowledgment.—We thank John R. Ertel for preparing **9d**.

Chemistry of the Sulfur–Nitrogen Bond.[1,2] V. Evidence for an Intermolecular Rearrangement in the Rearrangement of Arenesulfenanilides to *o*- and *p*-Aminodiphenyl Sulfides

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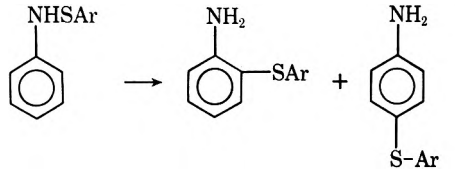
The acid-catalyzed arenesulfenanilide rearrangement has been investigated to determine whether the rearrangement is inter- or intramolecular. The failure of trapping experiments and high ortho/para ratios suggest that the rearrangement is intramolecular. Crossover experiments had little meaning, since sulfenamides exchange with amines. A π-complex or caged radical mechanism, but not a caged ion mechanism, are consistent with these results.

The thermal rearrangement of arenesulfenanilides to 2- and 4-aminodiphenyl sulfides (eq 1) has been established to be quite general.[1] The rearrangement was acid catalyzed and accelerated by electron-donating groups attached to sulfur. Substitution at the para position generally predominated over ortho substitution.



(1)

This rearrangement (eq 1) is a member of an important class of N-substituted aminoaromatic rearrangements which include the benzidine, quinamine, and nitramine rearrangements, among others.[4] The benzidine,[5] quinamine,[6] and nitramine[7] rearrangements are specific acid catalyzed and intramolecular.

In this paper we report the results of an investigation to determine whether the rearrangement is inter- or intramolecular. As we shall see, this has not been an easy task.

(1) Part IV: F. A. Davis, E. R. Fretz, and C. J. Horner, *J. Org. Chem.*, **38**, 690 (1973).

(2) Present in part at the 7th MARM, Philadelphia, Pa., Feb 1972.

(3) (a) National Science Foundation Undergraduate Research Participant, 1971; (b) Undergraduate Research Participant, 1970.

(4) H. J. Shine, "Aromatic Rearrangements," Vol. 6, Elsevier, New York, N. Y., 1967, Chapter 3.

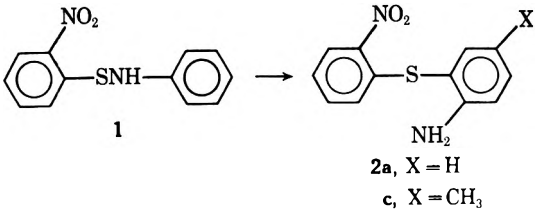
(5) D. H. Smith, J. A. Schwartz, and G. W. Wheland, *J. Amer. Chem. Soc.*, **74**, 2282 (1952).

(6) B. Miller, *ibid.*, **86**, 1127 (1964).

(7) D. V. Banthrope, E. D. Huges, and D. L. H. Williams, *J. Chem. Soc.*, 5349 (1964).

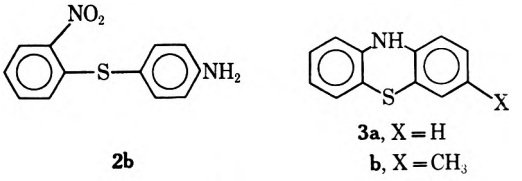
Results and Discussion

In an earlier paper in this series we reported that 2-nitrobenzenesulfenanilide (**1**), when heated in a sealed tube at 190° in aniline, gave aminodiphenyl sulfides **2a** and **2b**, phenothiazine (**3a**), and 2-aminobenzenesulfonanilide (**4a**).[8] With *p*-toluidine as the



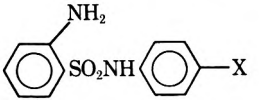
1

2a, X = H
c, X = CH_3



2b

3a, X = H
b, X = CH_3



4a, X = H
b, X = CH_3

solvent **1** gave crossover products **2c**, **3b**, and **4b**.[8] No products from the original sulfenanilide were isolated. Subsequently it was established that phenothiazines

(8) F. A. Davis, R. B. Wetzel, T. J. Devon, and J. F. Stackhouse, *J. Org. Chem.* **36**, 799 (1971).

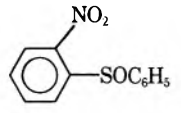
3a,b were formed *via* a thermal Smiles rearrangement of **2a,c**[9] and the sulfonamides, **4a,b**, were formed *via* an intramolecular oxidation–reduction of the 2-nitrobenzenesulfenyl radical formed in homolytic cleavage of the S–N bond.[10,11]

The crossover products isolated when sulfenanilide **1** was heated in *p*-toluidine would appear to be consistent with an intermolecular rearrangement. One possible intermediate would be a sulfenium ion (ArS^+) or ion pair formed by heterolytic cleavage of the S–N bond. The existence of sulfenium ions has been discussed,[12] and they are believed to be intermediates in the formation of diphenyl sulfides from aryl sulfenyl chlorides and aromatic compounds.[13] Since the presence of aniline hydrochloride was found to be necessary for the rearrangement,[1] a sulfenyl chloride, **5**, may also be an intermediate.

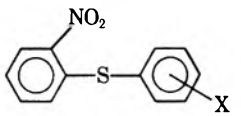
$$ArSNHC_6H_5 + C_6H_5NH_3Cl \longrightarrow \underset{\mathbf{5}}{ArSCl} + 2C_6H_5NH_2$$

A sulfenyl radical is a third possibility, since dienesulfenanilides are well known to undergo homolytic cleavage under these conditions.[10,11] Furthermore, the photolysis of phenyl disulfide gave 2- and 4-mercaptodiphenyl sulfides.[14] A sulfenyl radical is an unlikely intermediate, since under the reaction conditions aryl disulfides in the presence of aromatic amines failed to give significant amounts of 2- and 4-aminodiphenyl sulfides.[11,15]

A widely accepted criterion for an intermolecular mechanism is the ability to trap electrophilic intermediates by scavengers such as benzene or anisole. The related thermal rearrangement of phenyl-2-nitrobenzenesulfenate (**6**) to 2- and 4-hydroxy-2′-nitrodiphenyl sulfides (**7a,b**) has been shown to be intermolecular by trapping the intermediate 2-nitrobenzenesulfenium ion with benzene to give **7c**.[16] The trapping of a sulfenium ion by a suitable scavanger in the arenesulfenanilide rearrangement would be evidence for an intermolecular rearrangement.



6



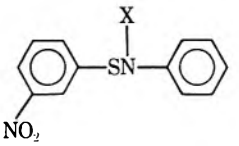
7a, X = 2-OH
b, X = 4-OH
c, X = H

Previous results have shown that the arenesulfenanilide rearrangement (eq 1) is favored in primary and secondary aromatic amine solvents.[1] 3-Nitrobenzene sulfenanilide (**8a**) in aniline gave 27 and 69% yields of aminodiphenyl sulfides **9a** and **10a**, respectively.[1] In *N,N*-diethylaniline or anisole the major product was bis(3-nitrophenyl) disulfide (**11**). These results are summarized in Table I. In anisole 3-nitro-4′-methoxydiphenyl sulfide (**12**), prepared from the corresponding sulfenyl chloride,[17] was not detected by gas chromatography.

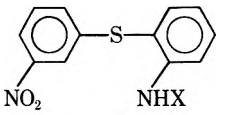
TABLE I
THERMAL REARRANGEMENT OF ARENESULFENANILIDES AT 195° FOR 15.5 HR

Entry	Sulfenanilide[a]	Solvent[b]	Products (yield, %)
1	**8a**[c]	Aniline	**9a** (27), **10a** (69)
2	**8a**	Anisole	**9a** (1), **10a** (4), **11** (74)
3	**8a**	Anisole + $C_6H_5NH_3Cl$[d]	**9a** (32), **10a** (20), **11** (26)
4	**8a**	Anisole + HCl[e]	**9a** (12), **10a** (1), **11** (13), **12** (15)
5	**8a**	*N,N*-Diethylaniline	**10a** (15), **11** (60)
6	**8a**	3-Nitroaniline	**10a** (58)[f]
7	**8a**	2,4-Dichloroaniline	**9a** (~5),[f] **10a** (70)[f]
8	**8a**	*N*-Methylaniline[g]	**10a** (1), **9b** (24), **10b** (75)
9	**8b**	*N*-Methylaniline	**9b** (32), **10b** (53)
10	**8b**	Aniline[h]	**9a** (21), **10a** (42), **9b** (5), **10b** (10)
11	**13a**	Anisole + HCl[e]	**15a** (33), **15a** (27)
12	**13b**	Anisole + HCl[e]	**14b** (23),[c] **15a** (30), **16** (1)
13	**17**	Aniline	**18** (13), **19** (57), **20a** (13), **20b** (29)
14	**17**	Aniline $C_6H_5NH_3Cl$[d]	**20a** (33), **20b** (62)

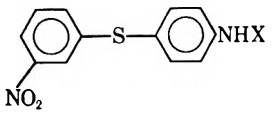
[a] Prepared from the corresponding sulfenyl chloride. [b] Mole ratio of sulfenanilide to solvent, 1:15. [c] Reference 1. [d] Mole ratio of sulfenanilide to aniline hydrochloride, 1:7. [e] See Experimental Section. [f] Isolated yields. [g] Mole ratio of sulfenanilide to *N*-methylaniline, 1:24. [h] Mole ratio of sulfenanilide to aniline, 1:39.



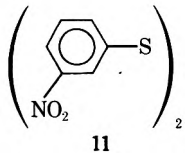
8a, X = H
b, X = CH_3



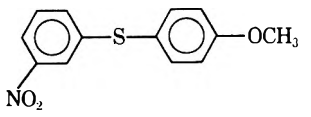
9a, X = H
b, X = CH_3



10a, X = H
b, X = CH_3



11



12

The failure to achieve significant rearrangement or to trap intermediates in these solvents may have resulted from a lack of acid catalysis. A molar ratio of sulfenanilide to aniline hydrochloride of 1:7 in anisole substantially increased the yield of rearrangement for sulfenanilide **8a**, but **12** was not formed. It would appear that these results are not consistent with an intermolecular mechanism involving a sulfenium ion, ion pair, or sulfenyl chloride as intermediates.

(9) F. A. Davis and R. B. Wetzel, *Tetrahedron Lett.*, 4483 (1969).
(10) F. A. Davis and R. P. Johnston, II, *J. Org. Chem.*, **37**, 854 (1972).
(11) F. A. Davis and R. P. Johnston, II, *ibid.*, **37**, 859 (1972).
(12) N. Hkarasch in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, Chapter 32; see also G. K. Helmkamp, D. C. Owsley, W. M. Barnes, and H. N. Cassey, *J. Amer. Chem. Soc.*, **90**, 1635 (1968).
(13) C. M. Buess and N. Kharasch, *J. Amer. Chem. Soc.*, **72**, 3529 (1950); N. Kharasch, *J. Chem. Educ.*, **37**, 585 (1956).
(14) Y. Schaffsma, A. F. Bickel, and E. C. Kooyman, *Tetrahedron*, **10**, 76 (1960).
(15) E. R. Fretz, unpublished results.
(16) D. R. Hogg, J. H. Smith, and P. W. Vipond, *J. Chem. Soc. C*, 273 (1970).
(17) H. Z. Lecher and F. M. Hardy, *J. Org. Chem.* **20**, 475 (1955).

An intramolecular rearrangement must therefore be considered. In order to explain the crossover products obtained when **1** was heated in *p*-toluidine[8] an intramolecular rearrangement requires a displacement on the S–N bond by the amine solvent prior to rearrangement (Scheme I). For sulfenanilide **1** in p-toluidine, therefore, $k_1 > k_2$.

SCHEME I

$$\mathrm{ArSNHAr' + Ar''NH_2} \xrightarrow{K_2} \text{products}$$

$$k_1 \downarrow \uparrow k_{-1}$$

$$\mathrm{ArSNHAr'' + Ar'NH_2} \xrightarrow{K_3} \text{products}$$

Arene sulfenanilides have been shown to undergo a facile exchange with aromatic amine solvents under relatively mild conditions.[18] Electron-withdrawing groups attached to sulfur[18] and electron-donating groups attached to the sulfenamide nitrogen[19] were observed to slow the exchange. Rearrangement was favored by electron-donating groups on sulfur.[1]

A test of the hypothesis that arenesulfenanilides exchange with the solvent and rearrange *via* an intramolecular mechanism according to Scheme I would be the isolation of noncrossover products and mixtures of crossover and noncrossover products when K_3 and/or k_1 are slowed. This may be achieved by proper choice of sulfenanilide and arylamine solvent.

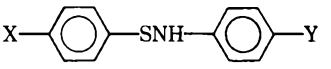
3-Nitrobenzenesulfen-*N*-methylaniline (**8b**), prepared from the corresponding sulfenyl chloride[18] and *N*-methylaniline, rearranges in *N*-methylaniline to give aminodiphenyl sulfides **9b** and **10b** in 32 and 53% yields. In aniline, at a mole ratio of **8b** to aniline of 1:39, sulfenanilide **8b** gave four products: crossover products **9a** and **10a** in 21 and 42% yield and the noncrossover products **9b** and **10b** in 5 and 10% yields (entry 10, Table I). If the rearrangement had been intermolecular, under these conditions only a total of 2.5% of the noncrossover products should have been isolated. It can be argued, however, that the high yield of noncrossover products resulted from the slightly greater nucleophilicity of the *N*-methylaniline compared to aniline. More conclusive evidence for Scheme I was obtained when **8a** was rearranged in *N*-methylaniline. At a molar ratio of 1:24 (sulfenamide to *N*-methylaniline), if the rearrangement were intermolecular, about 4% of the noncrossover products would be expected. Less than 1% of noncrossover products were detected (entry 8, Table I). In 2,4-dichloroaniline or 3-nitroaniline sulfenamide **8a** gave only noncrossover products **9a** and **10a** (entries 6 and 7, Table I).

These results are readily explained in terms of Scheme I. The *N*-methyl group in **8b** slows exchange and may accelerate rearrangement. The rate of exchange is accelerated when *N*-methylaniline is the solvent. With 2,4-dichloroaniline, which is known to exchange with **8a**,[18] or 3-nitroaniline as the solvent the rate of exchange is slowed and $K_2 > K_3$.

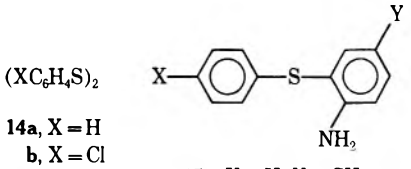
A second generally used method for determining the inter- or intramolecularity of a rearrangement is the use of crossover experiments. Two closely related reactants are rearranged together. If crossover products are obtained the rearrangement is said to be intermolecular.

The arenesulfenanilide rearrangement is favored in aryl amine solvents. However, the use of such solvents for crossover experiments would have little meaning, since sulfenamides exchange with aryl amines.[18] A similar objection applies to the use of anisole and amine hydrochlorides as a solvent system.

Anisole containing gaseous hydrogen chloride suggests that it may be a useful solvent for effecting the arenesulfenanilide rearrangement. Sulfenanilide **8a** in anisole HCl gave, in addition to disulfide **11**, 2-aminodiphenyl sulfide (**9a**) and 3-nitro-4′-methoxydiphenyl sulfide (**12**) as major products. Less than 1% of the 4-aminodiphenyl sulfide **10a** was detected (entry 4, Table I). Similar results were obtained for sulfenanilides **13a,b** which gave disulfides, (**14a,b**), 2-aminodiphenyl sulfides (**15a,b**), and 4-chloro-4′-methoxydiphenyl sulfide (**16**).

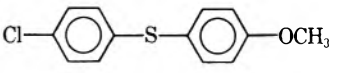


13a, X = H; Y = CH_3
b, X = Cl; Y = H



14a, X = H
b, X = Cl

15a, X = H; Y = CH_3
b, X = Cl; Y = H



16

Sulfenamides are cleaved by hydrogen chloride to the sulfenyl chloride and amine.[20] Apparently the anisole HCl solvent cleaves the S–N bond in the sulfenanilide to give the corresponding sulfenyl chloride. The sulfenyl chlorides attack the solvent to give **12** and **16**, and react with the amine to give a sulfenamide which rearranges or attacks the amine directly to give the 2- and 4-aminodiphenyl sulfides. It is evident from these results that anisole HCl is also unsatisfactory for crossover experiments.[21]

The fact that sulfenanilides **8a** and **13b** and crossover experiments[21] gave almost exclusively the 2-aminodiphenyl sulfides in anisole HCl supports an intramolecular rearrangement under these conditions. A sulfenyl chloride (or sulfenium ion) would be expected to produce more of the 4-aminodiphenyl sulfide if the rearrangement had been intermolecular. The exclusive formation of 3-nitro- and 4-chloro-4′-methoxydiphenyl sulfides (**12** and **16**) tends to support this conclusion. High ortho to para ratios have also been used as evidence for intramolecular rearrangements.[7,23] The observation that the ortho/para ratio increased on addition of aniline hydrochloride to aniline[1] and anisole

(18) F. A. Davis, S. Divald, and A. H. Confer, *Chem. Commun.*, 678 (1971).

(19) F. A. Davis and J. M. Kaminski, manuscript in preparation.

(20) For a recent review see A. Fontana and E. Scoffone, *Mech. React. Sulfur Compounds*, **4**, 14 (1969).

(21) A crossover experiment with sulfenanilides **13a,b** and anisole HCl gave a complex mixture of products which could not be quantitatively analyzed by glc. As expected, crossover 2-aminodiphenyl sulfides were identified in the reaction mixture. However, the 4-aminodiphenyl sulfides were apparently not formed.

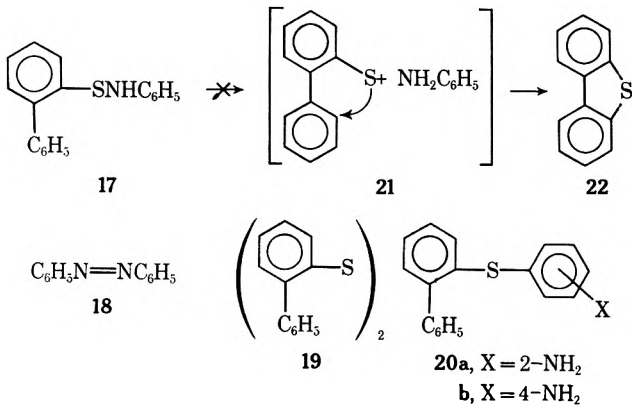
(entry 3, Table I) and the lack of solvent crossover products also supports an intramolecular rearrangement under these conditions.

Despite our inability to obtain more conventional tests for an intramolecular arenesulfenanilide rearrangement the experimental results are in agreement with an intramolecular rearrangement. Assuming then that the rearrangement is intramolecular, it is possible to speculate as to possible mechanisms and to eliminate one possibility.

Previous results suggested that the conjugate acid of the sulfenamide was involved in the transition state for rearrangement and that sulfur was electron deficient.[1] It was not possible to specify whether or not the rearrangement was specific or general acid catalyzed.[1]

At least two types of mechanisms are consistent with the experimental results: the caged radical or caged ion mechanisms and the π-complex mechanism.[22] The first mechanism involves either homolytic or heterolytic cleavage of the conjugate acid of the sulfenanilide to form a radical ($ArS\cdot + H_2NAr$) or ion ($ArS^+ H_2NAr$) in the solvent cage. Recombination of the sulfenyl radical or sulfenium ion in the solvent cage at the positions of highest electron density of the amine fragment would result in the formation of the observed products intramolecularity.

The solvent-caged ion mechanism may, however, be eliminated by the following experimental results. Sulfenanilide **17** prepared from the corresponding sulfenyl chloride and aniline gave, on heating in aniline, four products: azobenzene (**18**), disulfide **19**, and 2- and 4′-aminodiphenyl sulfides, **20a** and **20b**, in 13 and 29% yields, respectively. If a solvent-caged ion, **21**, were involved in the rearrangement of **17** to **20a,b**, some intramolecular combination of this ion to dibenzothiopene (**22**) would have been anticipated. Dibenzothiophene (**22**) was not detected by gas chromatography. Even in the presence of added aniline hydrochloride, which increased rearrangement to nearly 100% **22** was not detected. In a separate experiment 2-phenylbenzenesulfenyl chloride with a trace of anhydrous aluminum chloride gave a greater than 45% yield of **22**.



The π-complex mechanism as advocated by Dewar[22] is also consistent with the experimental results. This mechanism involves the formation of a π-complex between the electron-deficient leaving group (ArS) and the aromatic π system. A series of 1,2 shifts would result in the observed products. One objection to the π-complex mechanism has been the lack of 3-substituted products,[4] and 3-aminodiphenyl sulfides have never been isolated in the arenesulfenanilide rearrangement. As Dewar points out, however, ortho and para substitution are greatly favored by this mechanism over meta substitution.[22]

(22) M. J. S. Dewar in "Molecular Rearrangements," P. De Mayo, Ed., Interscience, New York, N. Y., 1963, Chapter 5.

Experimental Section

Sulfenanilides **8a**,[8] **13a**,[19] and **13b**[1] were prepared from the corresponding sulfenyl chloride unless otherwise noted. Melting points were obtained on a Fisher-Johns apparatus. Proton nmr spectra were measured on a Varian A-60A instrument. Infrared spectra were measured on a Perkin-Elmer 457 spectrometer. Gas chromatographic analyses were performed on a Perkin-Elmer 900 gas chromatograph using a 3% OV-17 on 80/100 mesh Chromosorb W (regular) column. Solvents were purified according to literature procedures.

General Procedure for Thermal Rearrangement of Arenesulfenanilides.—The sulfenanilides (approximately 0.008 mol) were heated in an oil bath with an excess of solvent (mole ratio of sulfenanilide to solvent, 1:15) at 195° in sealed tubes. The reaction mixture was diluted with methylene chloride and filtered, and a known weight of standard was added and analyzed by glc by comparison of peak areas with standard solutions of the reaction products. Analyses were performed at least twice and the values were averaged. Anisole HCl solvent was prepared by bubbling dry HCl at a controlled rate into 5 ml of anisole. After the reaction of the arenesulfenanilide in this solvent had taken place, the reaction mixture was diluted with methylene chloride, washed with 10% sodium hydroxide solution and twice with water, and dried over $MgSO_4$. The dried solution was analyzed as described above.

3-Nitrobenzenesulfen-*N*-methylanilide (8b).—3-Nitrobenzenesulfenyl chloride,[17] prepared from 3-nitrophenyl disulfide (**11**) (10.0 g, 0.032 mol) and dry chlorine gas in 100 ml of dry methylene chloride, was added dropwise over 1 hr to *N*-methylaniline (6.8 g, 0.064 mol) and triethylamine (9.7 g, 0.096 mol) in 100 ml of dry ether cooled to −78° in a Dry Ice–acetone bath in a 1000-ml, three-necked flask equipped with dropping funnel, mechanical stirrer, and nitrogen inlet. After addition the yellow solution was allowed to stir for an additional 0.5 hr at −78°; 100 ml of *n*-pentane was added and the solution was allowed to warm to 0°. After the precipated salts were filtered off the filtrate was washed with water, 2 × 50 ml, and dried over $MgSO_4$. Removal of the solvent gave a yellow oil which was dissolved in ether–pentane and cooled to −78°, and the yellow solid was collected. Crystallization from *n*-pentane give 6.0 g (36%) of yellow plates: mp 48–49°; nmr ($CDCl_3$) δ 3.6 (s, 3, NCH_3), 7.5 (m, 7), and 8.1 (m, 2).

Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 60.00; H, 4.61. Found: C, 60.12; H, 4.74.

Bis(2-phenyl)phenyl Disulfide (19).—2-Mercaptobiphenyl,[23] 10.0 g (0.054 mol), was treated with 10 ml of 10% sodium hydroxide solution and 10 ml of 10% hydrogen peroxide in 100 ml of 1:1 alcohol–water. The white solid was collected and crystallized from ether to give 5.1 g (51%) of white plates: mp 114–116°; nmr ($CDCl_3$) δ 7.2 (m, 3), 7.35 (s, 5), and 7.6 (m, 1).

Anal. Calcd for $C_{24}H_{18}S_2$: C, 72.84; H, 4.86. Found: C, 72.66; H, 4.91.

2-Phenylbenzenesulfenanilide (17).—Sulfenanilide **17** was prepared by addition of 2-phenylbenzenesulfenyl chloride, prepared from 2.0 g (0.0054 mol) of the disulfide in 50 ml of methylene chloride and chlorine, to 2.0 g (0.021 mol) of aniline in 1:1 ether–DMAC at −78° as described above. The crude sulfenanilide was purified by column chromatography on neutral alumina (elution with pentane) to give a white solid, which was crystallized from pentane to give 0.4 g (13%) of white crystals: mp 86–88°; ir (KBr) 3380 cm^{-1} (s, NH); nmr ($CDCl_3$) δ 7.3 (m, 14) and 4.9 (s, 1, NH).

Anal. Calcd for $C_{18}H_{15}NS$: C, 77.98; H, 5.42. Found: C, 77.83; H, 5.31.

General Procedure for Synthesis of 2- and 4-Aminodiphenyl Sulfides.—The 2- and 4-aminodiphenyl sulfides were prepared

(23) D. D. Emrich and W. E. Truce, *J. Org. Chem.*, **25**, 1103 (1960).

as previously described by reduction of the corresponding 2- and 4-nitrodiphenyl sulfides.[1]

2-Amino-5-methyldiphenyl Sulfide (15a).—Reduction of 5.0 g of the nitrodiphenyl sulfide gave an oil which was distilled, bp 125–128° (0.3 mm), to give 1.5 g (35%) of a clear oil which darkened on standing: ir (thin film) 3360 and 3460 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 2.1 (s, 3, NCH_3), 3.9 (s, 2, NH_2), 6.5 (d, 1), and 7.0 (m, 7).

Anal. Calcd for $C_{13}H_{13}NS$: C, 72.56; H, 6.04. Found: C, 72.80; H, 6.24.

2-Phenyl-2′-aminodiphenyl Sulfide (20a).—DMAC was used in the place of ethanol to prepare the nitrodiphenyl sulfide.[1] Reduction of 2.0 g of the nitrodiphenyl sulfide gave, after molecular distillation at 110° (0.1 mm), 0.8 g (43%) of an oil: ir (thin film) 3380 and 3480 cm^{-1} (s, NH_2); nmr ($CDCl_3$) δ 3.8 (s, 2, NH_2) and 7.2 (m, 13).

Anal. Calcd for $C_{18}H_{15}NS$: C, 77.98; H, 5.42. Found: 77.90; H, 5.53.

2-Phenyl-4′-aminodiphenyl Sulfide (20b).—DMAC was used in the place of ethanol to prepare the nitrodiphenyl sulfide.[1] Reduction of 2.4 g of the nitrodiphenyl sulfide gave, after molecular distillation at 100° (0.1 mm), 0.7 g (33%) of an oil which solidified on standing after several weeks: mp 58–60°; ir (thin film) 3400 and 3480 cm^{-1} (m, NH_2); nmr ($CDCl_3$) δ 3.5 (s, 2, NH_2) and 7.0 (m, 13).

Anal. Calcd for $C_{18}H_{15}NS$: C, 77.98; H, 5.42. Found: C, 77.77; H, 5.48.

3-Nitro-4′-methoxydiphenyl Sulfide (12).—Into a 250-ml three-necked flask equipped with magnetic stir bar and nitrogen inlet was placed 10.0 g (0.032 mol) of 3-nitrophenyl disulfide (11) in 100 ml of dry methylene chloride. Dry chlorine gas was passed through the solution for 10 min, followed by dry nitrogen for 20 min. The sulfenyl chloride was cooled to 0° and 10.0 g of anhydrous aluminum chloride followed by 13.8 g (0.128 mol) of anisole were added. The reaction mixture was allowed to stir overnight under nitrogen; 10 ml of ethyl alcohol was added followed by 100 ml of water. The organic layer was separated and dried over $MgSO_4$. Solvent was removed under vacuum (first water pump and then oil pump) to give a dark oil which was chromatographed on Florisil. Elution with pentane–benzene gave a yellow solid which was crystallized from ether–pentane to give 1.6 g (10%) of yellow plates: mp 56–57°; ir (Nujol) 1250 cm^{-1} (s, ether); nmr ($CDCl_3$) δ 3.8 (s, 3, OCH_3), 6.85 (d, 2, J = 9 Hz), 7.1 (s, 4), and 7.35 (d, 2, J = 9 Hz).

Anal. Calcd for $C_{13}H_{11}NO_3S$: C, 62.39; H, 4.41. Found: C, 62.14; H, 4.53.

Thermal Rearrangement of 3-Nitrobenzenesulfen-*N*-methylanilide (8b).—Sulfenanilide **8b** (0.1968 g, 0.00076 mol) in aniline (1.1 g, 0.011 mol) was heated as previously described in a sealed tube. Excess solvent was removed (oil pump) and the dark residue was chromatographed on Florisil. Elution with pentane–benzene gave 0.039 g (20%) of an oil identified as 3-nitro-2′-*N*-methylaminodiphenyl sulfide (**9b**): glc–mass spectrum M 260; ir (thin film) 3400 cm^{-1} ($NHCH_3$); nmr ($CDCl_3$) δ 2.9 (s, 3, NCH_3), 4.8 (broad s, 1, NH), 7.4 (m, 4), and 7.9 (m, 2). Further elution with pentane–benzene gave a yellow solid, which when crystallized from pentane–ether gave 0.12 g (61%) of a yellow solid, mp 82–84°, identified as 3-nitro-4′-*N*-methylaminodiphenyl sulfide (**10b**): ir (KBr) 3420 cm^{-1} (s, NH); nmr ($CDCl_3$) δ 2.9 (s, 3, NCH_3), 4.0 (broad s, 1, NH), 6.6 (d, 2), 7.3 (m, 4), and 7.9 (m, 2).

Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 60.00; H, 4.61. Found: C, 59.97; H, 4.66.

Thermal Rearrangement of 3-Nitrobenzenesulfenanilide (8a) in 2,4-Dichloroaniline.—Sulfenanilide **8a** (0.2019 g, 0.00082 mol) was heated in 2.0 g (0.0123 mol) of 2,4-dichloroaniline in a sealed tube. The excess solvent was removed by sublimation (40°, 0.05 mm) and the dark residue was chromatographed on Florisil. Elution with pentane gave a yellow solid which was sublimed (40°, 0.5 mm) to give 0.01 g (5%) of yellow needles, mp 62–64° (lit.[8] mp 63–64) identified as **9a**. Further elution with pentane–benzene gave a solid which was washed with *n*-pentane to give 0.14 g (70%) of a yellow solid, mp 130–132° (lit.[8] mp 130–131°), identified as **10a**.

Thermal Rearrangement of 3-Nitrobenzenesulfenanilide in 3-Nitroaniline.—Sulfenanilide **8a** (0.1964 g, 0.0008 mol) in 3-nitroaniline (1.66 g, 0.012 mol) was treated as described above. Solvent was removed by sublimation (55°, 0.05 mm) and the dark residue was chromatographed on Florisil. Elution with pentane–benzene gave a solid which was washed with *n*-pentane to give 0.115 g (58%) of a yellow solid, mp 130–131° (lit.[8] mp 130–131°), identified as **10a**.

Dibenzothiophene (22) from 2-Phenylbenzenesulfenyl Chloride.—Into a 250-ml three-necked flask equipped with magnetic stir bar and nitrogen inlet was placed 0.20 g (0.00054 mol) of bis(2-phenyl)phenyl disulfide (19) in 150 ml of *n*-pentane. Dry chlorine gas was passed through the solution for 10 min followed by dry nitrogen for 10 min. The sulfenyl chloride was cooled to 0° and *ca.* 30 mg of anhydrous aluminum chloride was added; the reaction mixture was refluxed for 48 hr, and 10 ml of ethyl alcohol was added. The reaction mixture was washed twice with water and dried over $MgSO_4$. Removal of the solvent gave an oil which was analyzed by gas chromatography, as described above, to give a 45% yield of dibenzothiophene (**22**).

Registry No.—**8a**, 37332-21-4; **8b**, 37692-03-8; **9b**, 37692-04-9; **10b**, 37692-05-0; **11**, 37755-03-6; **12**, 37692-06-1; **13a**, 14933-93-8; **13b**, 14933-94-9; **15a**, 37692-09-4; **17**, 37692-10-7; **19**, 19813-97-9; **20a**, 2688-98-4; **20b**, 37692-13-0; 3-nitrobenzenesulfinyl chloride, 37692-14-1; *N*-methylaniline, 100-61-8; 2-mercaptobiphenyl, 2688-96-2; 2-phenylbenzenesulfenyl chloride, 37692-16-3.

Amitriptyline Metabolites. Synthesis of (*R*,*S*)-(*Z*)- and (*R*,*S*)-(*E*)-*N*-Methyl(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine

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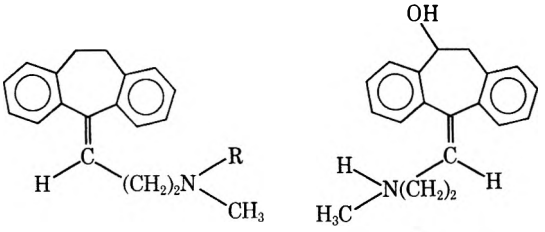
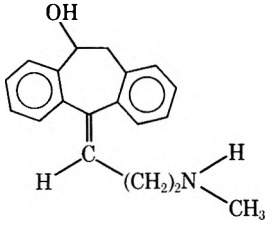
The synthesis of (*R*,*S*)-(*Z*)- and (*R*,*S*)-(*E*)-*N*-methyl(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine, **2** and **3**, respectively, metabolites of the antidepressant drug amitriptyline, is described. Configurational assignments of **2** and **3** are based on an nmr study of (*E*)-*N*-methyl(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (**8**) using tris(dipivalomethanato)europium as a shift reagent.

Amitriptyline (**1a**) and nortriptyline (**1b**) are drugs that are widely used in the treatment of depressive illness. The *Z* and *E* geometrical isomers of *N*-methyl-(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine, **2** and **3**, respectively, are major metabolites of both drugs.[1-3]



1a, R = CH_3
b, R = H

2

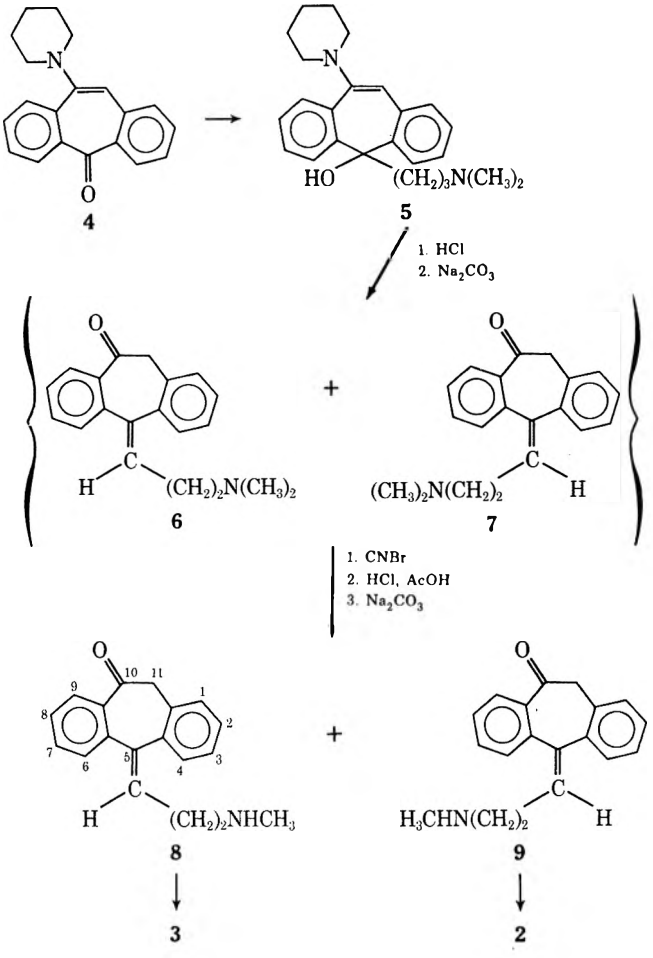


3

In previous reports on the metabolism of **1a** and **1b**, the isolation and spectral characterization of **2** and **3** have been described. However, no assignment of geometrical configuration of these compounds has been made. The recent introduction of the nmr shift reagent, tris(dipivalomethanato)europium,[4] has now made possible the assignment of geometrical configuration of synthetically prepared samples of the racemates of **2** and **3**.

Addition of dimethylaminopropylmagnesium chloride to the known enamine–ketone **4**[5] afforded the crystalline alcohol **5** in 82% yield. Prolonged acid hydrolysis of **5** in 6 *N* hydrochloric acid resulted in hydrolysis of the enamine moiety to a carbonyl function and simultaneous dehydration of the alcohol moiety to give a quantitative yield of the mixed geometric isomers **6** and **7** (Scheme I). In a number of preparations, glpc product analysis showed an average ratio of these geometric isomers to be 81:19. The isomer ratios of these products were also measured by nmr spectroscopy using the relative areas of the *N*-methyl proton peaks of **6** and **7**.[6] In a typical experiment, an isomer ratio of 75:25 was found for the mixture.

SCHEME I



Although the hydrochloride salt of one of the isomers, **6** or **7**, crystallized readily and could be separated in a pure form, no attempt was made to separate and carry either pure isomer to a final product when it was observed that one of the isomers, and probably both, was isomerized on heating an acid. Thus, one of the

(1) (a) H. B. Hucker and C. C. Porter, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **20**, 172 (1961); (b) H. B. Hucker, *Pharmacologist*, **4**, 171 (1962).

(2) R. E. McMahon, F. J. Marshall, H. W. Culp, and W. M. Miller, *Biochem. Pharmacol.*, **12**, 1207 (1963).

(3) L. Bertilsson and B. Alexanderson, *Eur. J. Clin. Pharmacol.*, **4**, 201 (1972).

(4) (a) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969); (b) J. K. M. Saunders and D. H. Williams, *ibid.*, **93**, 641 (1971).

(5) W. Tochtermann, K. Oppenländer, and U. Walter, *Chem. Ber.*, **97**, 1318 (1964).

(6) D. C. Remy and W. A. Van Saun, Jr., *Tetrahedron Lett.*, **No. 27**, 2463 (1971).

TABLE I
CHEMICAL SHIFTS OF THE AROMATIC PROTONS IN (*E*)-*N*-METHYL-(10,11-DIHYDRO-10-OXO-5*H*-DIBENZO[*a*,*d*]CYCLOHEPTENE)-$\Delta^{5,\gamma}$-PROPYLAMINE (8)

Proton	δ ($CDCl_3$), free base	δ ($CDCl_3$), $Eu(dpm)_3$ complex	Δδ
C_1H	7.2–7.5	7.85[a]	0.35–0.65[c]
C_2H	7.2–7.5	7.4–7.7	~0.2
C_3H	7.2–7.5	7.4–7.7	~0.2
C_4H	7.2–7.5	8.09[a]	0.59–0.89[c]
C_6H	7.2–7.5	7.4–7.7[a]	~0.2
C_7H	7.2–7.5	7.61 ± 0.03[b]	0.1–0.4[c]
C_8H	7.2–7.5	7.45 ± 0.03[b]	−0.05–0.25[c]
C_9H	8.15	8.31	0.16

[a] Preferred assignments. [b] Located by spin-decoupling experiments. [c] Represents minimum and maximum downfield displacement.

isomers, **6** or **7**, designated α, 98.9 mol % pure by differential scanning calorimetry, was converted into an equilibrium mixture (85:15 by glpc) on refluxing for 24 hr in 6 *N* hydrochloric acid.

N-Demethylation of the mixed tertiary amines **6** and **7** was effected *via* the von Braun cyanogen bromide method. The cyanamide derivatives were subjected to prolonged hydrolysis in an acetic acid–hydrochloric acid mixture. The isomer ratio of **8** to **9** in this reaction mixture was found to be 69:31 by expanded scale nmr examination of the *N*-methyl proton peaks. The geometric isomers **8** and **9** were successfully separated by crystallization.

Nuclear magnetic resonance spectroscopy has been used successfully in the assignment of configuration to geometric isomers in a series of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenz[*b*,*e*]oxepin[7] and 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin[8] derivatives. In these sets of isomers, the presence of the oxygen or sulfur atom in the central seven-membered ring results in significant differences in the chemical shifts of the vinyl proton[7,8] and aromatic ring protons[8] of the *Z* and *E* isomers.

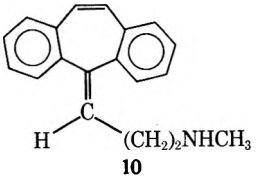
Examination of the nmr spectra of **8** and **9** showed that, whereas there was no significant difference in the chemical shifts of the vinyl protons, there were slight differences in the chemical shifts of the aromatic protons. In an attempt to enhance the difference in chemical shifts of the aromatic protons, the nmr spectra of these isomers (**8** and **9**) were reexamined in the presence of tris(dipivalomethanato)europium, $Eu(dpm)_3$.[4,9]

Analysis of the differential downfield shifts of the aromatic protons resulting from the addition of small amounts of $Eu(dpm)_3$ to a $CDCl_3$ solution of **8** strongly suggested the *E* configuration. The initial findings utilizing a fluorinated shift reagent[10] proved unsatisfactory in that the aromatic protons were not resolved. It seemed reasonable to attribute this failure to the greater complexing capability of the halogenated agent which would result in significant binding with the ketone as well as the nitrogen. Complexation at both sites could well obscure the trends which permitted the configurational assignments in the related 3-substituted *N*,*N*-dimethyl(5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine series.[6] Based on this supposition, the study was repeated with the weaker, and more selective, $Eu(dpm)_3$. Addition of approximately 0.3 mol of rare earth reagent/mol of substrate (**8**) resulted in the appearance of two aromatic protons displaced downfield from the aromatic envelope (7.85 and 8.09). The magnitude of the aromatic ring proton shifts (Table I, Δδ) cannot be determined with any great degree of accuracy since the initial chemical shifts within the overlapping multiplets between δ 7.2 and 7.5 are indeterminate. This problem is further complicated by an overall deshielding of the aromatic envelope by roughly 0.2 ppm. There is no question, however, that the two newly resolved aromatic protons experienced larger than the average displacement as shown in Table I. Since both were doublets with unresolved fine structure, they are assigned to α protons. Together with the already resolved C_9H at δ 8.31 (C_9H is the hydrogen atom peri to the 10-keto group), this accounts for three out of a total of four such protons (*i.e.*, the C_1, C_4, C_6, and C_9H).

Previous studies with other unsymmetrically substituted cyclobenzaprine derivatives in the presence of $Eu(dpm)_3$ have shown that only the protons on the ring cis to the complexing site are shifted significantly downfield. As an example, the chemical shifts of the aromatic protons in (*E*)- and (*Z*)-3-chloro-*N*,*N*-dimethyl(5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine are given in Table II.

Since neither the C_9 proton nor the C_8 and C_7 protons (located within the aromatic envelope by spin decoupling) of **8** were deshielded appreciably, it follows that the doublets are reasonably assigned to the C_1 and C_4 protons and that the side chain in **8** is therefore located trans relative to the ketone.

Reduction of the ketone groups of **8** and **9** with sodium borohydride completed the syntheses of (*R*,*S*)-(*E*)- and (*R*,*S*)-(*Z*)-*N*-methyl(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine, **3** and **2**, respectively. Beside being isomerically pure by tlc and nmr, both **2** and **3** were free from traces of **10** which could arise from dehydration.[2,11] The 10,11-vinyl hydrogens of **10** show a sharp singlet at δ 6.83 ($CDCl_3$); this absorption was completely absent in the spectra of **2** and **3**.



10

Experimental Section

Melting points were determined on a Thomas-Hoover "Unimelt" capillary melting point apparatus and are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were determined on Varian A-60A and HA-100 spectrometers in $CDCl_3$, and all shifts are relative to tetramethylsilane as an internal standard. Where isomer ratios were measured by nmr using the relative areas of the *N*-methyl protons of each isomer, the *N*-methyl proton region of the nmr spectrum was examined using a 50-Hz sweep width. Relative areas were measured with a planimeter. Gas–liquid partition chromatography (glpc) was carried out with a

(7) Chas. Pfizer & Co., British Patent 1,018,995 (1966).

(8) M. Rajšner, E. Srátek, J. Metyšova, and M. Protiva, *Collect. Czech. Chem. Commun.*, **34**, 1963 (1969).

(9) "Eu-Resolve," Ventron Corp.

(10) R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971).

(11) A. deLeenheer and A. Heyndrickx, *J. Pharm. Sci.*, **60**, 1403 (1971).

TABLE II

CHEMICAL SHIFTS OF THE AROMATIC PROTONS IN (*E*)- AND (*Z*)-3-CHLORO-*N*,*N*-DIMETHYL(5*H*-DIBENZO[*a*,*d*]CYCLOHEPTENE)-$\Delta^{5,\gamma}$-PROPYLAMINE

	E (trans) isomer			*Z* (cis) isomer		
Proton	δ (CCl_4), free base	δ (CCl_4), Eu(dpm)$_3$ complex[a]	Δδ	δ (CCl_4), free base	δ (CCl_4), Eu(dpm)$_3$ complex	Δδ
C_1H	7.07[b]	7.11	0.04	7.13–7.25	7.46	0.21–0.33
C_2H	7.12	7.11	−0.01	7.13–7.25	7.46	0.21–0.33
C_4H	7.23	7.11	−0.12	7.13–7.25	8.37	1.12–1.24
C_6H	7.15–7.25	7.72	0.47–0.57	7.13–7.25	7.31	0.12 ± 0.06
C_7H	7.15–7.25	7.45	0.20–0.30	7.13–7.25	7.18	<0.1
C_8H	7.15–7.25	7.45	0.20–0.30	7.13–7.25	7.18	<0.1
C_9H	7.15–7.25	7.45	0.20–0.30	7.13–7.25	7.18	<0.1

[a] Approximately 0.2 mol Eu(dpm)$_3$/mol of substrate. [b] Parts per million relative to internal tetramethylsilane.

4 mm (i.d.) × 6 ft glass 5% QF-1 on acid-washed dimethylchlorosilane-treated Chromosorb G column, 100–120 mesh. Thin layer chromatography (tlc) was perhaps the most useful analytical method in studying purity of the final products **2** and **3**. Tlc's were performed on Analtech fluorescent silica gel G plates; spots were detected by uv, exposure to iodine, Dragendorff's reagent, and charring with sulfuric acid and heat (100° for 5–15 min). R_f^1 and R_f^2 values refer to the systems: $CHCl_3$–CH_3OH–concentrated NH_4OH (60:8:1, v/v/v) and cyclohexane–CH_3OH–diethylamine (7:2:1, v/v/v), respectively.[12]

The conversion of amine salts into the free base form, for nmr, ir, tlc, and glc analyses, was carried out in a standard manner. The salt was dissolved in water and treated with an excess of a saturated sodium carbonate solution. The precipitate was extracted into benzene or ether, washed with water, dried over magnesium sulfate, and filtered. The solvent was removed on a rotary evaporator at a final temperature of about 80°.

N,*N*-**Dimethyl-3-(5-hydroxy-10-piperidino-5*H*-dibenzo[*a*,*d*]-cyclohepten-5-yl)propylamine (5).**—To a cooled, stirred solution of 10.0 g (0.0346 mol) of ketone **4**[5] in 150 ml of dry THF was added dropwise 40 ml of a 1.92 *M* solution of dimethylaminopropylmagnesium chloride in THF. The solution was stirred overnight at room temperature. The THF was removed and the residue was dissolved in benzene. Water was added slowly while stirring until a clear benzene phase and a gelatinous residue formed. The benzene was decanted, and the residue was extracted with hot benzene. The combined benzene extracts were evaporated leaving a white crystalline residue that was recrystallized from absolute ethanol to give 10.7 g (82%) of **5**, mp 169.5–171°.

Anal. Calcd for $C_{25}H_{32}N_2O$: C, 79.74; H, 8.57. Found: C, 79.49; H, 8.54.

Mixed Geometric Isomers of *N*,*N*-Dimethyl-3-(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (6 and 7).—A solution of 6.0 g of **5** in 100 ml of 6 *N* HCl was refluxed for 14 hr. The solution was evaporated to dryness, and the residue was converted into a mixture of the free bases, C=O band 1684 cm^{-1} (liquid film). Glpc separates the two geometric isomers, designated α and β; a ratio of 80:20 was found for this sample. Integration of the areas of the *N*-methyl protons observed in the nmr spectrum of this sample gave a ratio of 75:25 for the two isomers: nmr ($CDCl_3$) δ 2.12 (s, $N(CH_3)_2$), 2.16 (s, $N(CH_3)_2$) (combined $N(CH_3)_2$ = 6 H), 2.2–2.5 (m, $-CH_2CH_2-$, 4 H), 3.78 and 4.45 (double d, J_{gem} = 13 Hz $-CH_2CO-$, 2 H), 6.21 (t, *J* = 7 Hz, vinyl CH, 1 H), 7.15–7.52 and 8.0–8.2 (m, aromatic CH).

One of the hydrochloride salts of *N*,*N*-dimethyl-3-(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (designated the α form) crystallized readily from the mixture and was separated in pure form by recrystallization from ethanol–ether, mp 221–224° dec (reported[13] mp 222–226°). The free base of the α form was crystallized from hexane, mp 71–73°. Differential scanning calorimetry (dsc) indicated the sample to be 98.9 mol % pure: R_f^1 0.89, R_f^2 0.83.

Anal. Calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.54; H, 7.35; N, 4.81.

A 2.0-g (0.00688 mol) sample of this free base, α form, mp 71–73°, was reduced with 1.30 g (0.0374 mol) of sodium borohydride dissolved in 40 ml of methanol. After refluxing for 1 hr, the methanol was removed and the residue was recrystallized from hexane to give one of the geometrically pure forms, designated α, of (*R*,*S*)-*N*,*N*-**dimethyl-3-(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine:** mp 95.5–97.5°; nmr ($CDCl_3$) δ 2.05 (s, $N(CH_3)_2$, 6 H), 2.2 to 3.5 (m, aliphatic CH, 7 H), 5.0 (broad s, OH, 1 H), 5.91 (t, *J* = 7 cps, vinyl CH, 1 H), 7.1–7.7 (m, aromatic CH); R_f^1 0.70.

Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 4.77; N, 7.90. Found: C, 81.67; H, 4.67; N, 7.93.

Acid Isomerization of the α Form of *N*,*N*-Dimethyl-3-(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine.—A sample of the free base, α form, mp 71–73°, was dissolved in 6 *N* HCl. After refluxing for 24 hr, the solution was evaporated and the hydrochloride salt residue was converted into the free base. Glpc analysis of the mixture showed both isomers to be present and in a ratio of 85:15.

Mixed Geometric Isomers of *N*-Methyl-3-(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (8 and 9).—To a magnetically stirred solution of 2.5 g (0.0236 mol) of cyanogen bromide in 5 ml of benzene was added dropwise over 0.5 hr a solution of the mixed geometric isomers **6** and **7** (4.27 g, 0.0147 mol, 75:25 isomer ratio by nmr) dissolved in 15 ml of benzene. The solution was stirred overnight at room temperature. The benzene was decanted and a small amount of orange residue was washed with benzene. The combined benzene extracts were washed with two 100-ml portions of 3 *N* HCl and three 100-ml portions of water. After evaporation of the benzene, the residue was dissolved in a mixture of 75 ml glacial acetic acid, 20 ml of water, and 25 ml of concentrated HCl. This solution was stirred and refluxed for 16 hr. The solution was evaporated to dryness, and the residue was converted into a mixture of the free bases **8** and **9** with sodium carbonate solution, ir (liquid film) 3358 (NH) and 1690 cm^{-1} (C=O). Integration of the areas of the *N*-methyl protons observed in the nmr spectrum of this sample gave a ratio of 69:31 for the two isomers: nmr ($CDCl_3$) δ 1.2[2] (s, NH, 1 H), 2.2–2.9 (m, $-CH_2CH_2-$, with a singlet at 2.36 (NCH_3) having a shoulder at 2.30 (NCH_3), 7 H), 3.79 and 4.41 (double d, J_{gem} = 13 Hz, $-CH_2CO-$, 2 H), 6.23 (t, *J* = 7 Hz, vinyl CH, 1 H), and 7.2–7.6 and 8.0–8.2 (m, aromatic CH, 8 H).

Separation of the Geometric Isomers 8 and 9.—A mixture of the secondary amines **8** and **9** (1.57 g, isomer ratio 69:31 by nmr) was dissolved in 20 ml of benzene. Dry HCl gas was passed into the solution until no further precipitation occurred. The mixture was stirred to give a semisolid residue A and a clear benzene supernatant B. The benzene phase was decanted from the solid.

Residue A.—The semisolid residue crystallized on being triturated with benzene. Recrystallization of this material from isopropyl alcohol–ether gave *N*-**methyl-3-(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine hydrochloride,** α form, mp 219–224° dec, R_f^1 0.66, R_f^2 0.49 (free base).

Anal. Calcd for $C_{19}H_{19}NO \cdot HCl$: C, 72.72; H, 6.42; N, 4.46; Cl, 11.30. Found: C, 72.09; H, 6.55; N, 4.27; Cl, 11.19.

After being converted into the free base, expanded scale nmr examination showed a single *N*-methyl proton absorption peak at δ 2.36. High-resolution nmr spectroscopy using the shift

(12) E. C. Munksgaard, *Acta Pharmacol. Toxicol.*, **27**, 129 (1969).

(13) Hoffmann-La Roche and Co., Netherlands Patent Application 68,10177.

reagent tris(dipivalomethanato)europium has established that this α form has the *E* configuration (see text): nmr (100 MHz, $CDCl_3$) δ 2.37 (s, NCH_3, 3 H), ~2.40 (m, $CH_2C=$, 2 H), 2.71 (t, *J* = 7 Hz, NCH_2, 2 H), 3.78 (d, *J* = 13 Hz, 11 axial CH, 1 H), 4.42 (d, *J* = 13 Hz, 11 equatorial CH, 1 H), 6.22 (t, *J* = 7.5 Hz, vinylic CH, 1 H) 7.2–7.5 (m, aromatic CH, 7 H), 8.15 (d with fine structure, *J* = 8 Hz, C_9H, 1 H); nmr in presence of ~0.3 mol of Eu(dpm)$_3$ ($CDCl_3$) 4.13 (d, *J* = 13 Hz, 11 axial CH, 1 H), 4.42 (d, *J* = 13 Hz, 11 equatorial CH, 1 H), ~5.4 (broad, $CH_2C=$, 2 H), ~7.5 (broad, NCH_3, CH_2N, HC=, 6 H) 7.4–7.7 (m, aromatic H, 5 H), 7.85 (broadened d, *J* ≈ 8 Hz, C_1H, 1 H), 8.09 (broadened d, *J* ≈ 7–8 Hz, C_4H, 1 H), 8.31 (broadened d, *J* ≈ 8 Hz, C_9H, 1 H).

Supernatant B.—The supernatant benzene phase was concentrated to about 10 ml and allowed to stand. The solution was decanted from a small amount of oil that precipitated. This process was carefully repeated to give about 5 ml of a clear benzene solution. The benzene was evaporated to give 0.33 g of (*Z*)-*N*-methyl-3-(10,11-dihydro-10-oxo-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine hydrochloride as a viscous oil that could not be crystallized. After being converted into the free base, expanded scale nmr examination showed a single *N*-methyl proton absorption peak at δ 2.30; nmr ($CDCl_3$) δ 1.21 (s, NH, 1 H), 2.2–2.9 (m, $-CH_2CH_2-$, with a singlet at 2.30 (NCH_3), 7 H), 3.78 and 4.40 (double d, J_{gem} = 13 Hz, $-CH_2CO-$, 2 H), 6.21 (t, *J* = 7 Hz, vinyl CH, 1 H), and 7.2–7.6 and 8.0–8.2 (m, aromatic CH, 8 H).

(*R*,*S*)-(*E*)-*N*-Methyl(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (3).—To a solution of 1.56 g of the E ketone 8 dissolved in 25 ml of absolute methanol was added a solution of 1.56 g of sodium borohydride dissolved in 3 ml of water. The solution was stirred and refluxed for 1.5 hr. The methanol was evaporated, and the residue was dissolved in benzene. The benzene solution was washed with water, dried, and filtered, and the solvent was evaporated to give 1.56 g of the (*R*,*S*)-*E* amino alcohol **3**: ir (KBr) 3400 (s, broad, OH), 3300 (m, broad, NH), 1555 (w), 675 (w), 560 (w), and 540 (w) cm^{-1}. A comparison of the infrared spectra of (*R*,*S*)-(*E*)-**3** and (*R*,*S*)-(*Z*)-**2** showed that the bands at 675, 560, and 540 cm^{-1} were stronger in the *E* spectrum: R_f^1 0.57, R_f^2 0.31; nmr ($CDCl_3$, 10% w/v) δ 1.26 (S, NH, 1 H), 2.0–2.52 (m, with peaks at 2.03 and 2.19 (NCH_3)), 2.74–3.68 (broad, $-CH_2CHOH-$, 2 H), 4.66–5.1 (broad, OH, 1 H), 5.85 (t, vinyl CH, 1 H, *J* = 7 Hz), and 7.0–7.4 (m, aromatic CH). The hydrogen maleate salt was prepared and crystallized from isopropyl alcohol, mp 156–157.5°.

Anal. Calcd for $C_{19}H_{21}NO \cdot C_4H_4O_4$: C, 69.85; H, 6.37; N, 3.54. Found: C, 69.70; H, 6.62; N, 3.60.

Attempts to analyze this salt by differential thermal analysis (dta), differential scanning calorimetry (dsc), and phase solubility analysis were unsuccessful.

A crystalline neutral naphthalene-1,5-disulfonate salt was prepared and recrystallized from methanol, mp 242°.

Anal. Calcd for $(C_{19}H_{21}NO)_2 \cdot C_{10}H_8O_6S_2$: C, 68.06; H, 5.95; N, 3.31; S, 7.57. Found: C, 67.67; H, 5.97; N, 3.22; S, 7.50.

On attempted analysis by dta, this salt showed a sharp endotherm at 242° (in air) (234° *in vacuo*), followed by a very sharp exotherm of crystallization to give presumably norcyclobenzaprine naphthalene-1,5-disulfonate which then melted at 309°.

Phase solubility analysis of the (*R*,*S*)-(*E*)-naphthalene-1,5-disulfonate salt showed it to be 99.8% pure.

(*R*,*S*)-(*Z*)-*N*-Methyl(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine (2).—In a manner similar to that described for reduction of the *E* isomer **8**, the *Z* isomer **9** (0.33 g) was reduced to **2** using 0.10 g of sodium borohydride: ir (KBr) 3400 (s, broad, OH), 3300 (m, broad, NH), 675 (m), 560 (w), and 540 (w) cm^{-1}. A comparison of the infrared spectra of (*R*,*S*)-(*E*)-**3** and (*R*,*S*)-(*Z*)-**2** showed that the OH stretching band at 3400 was stronger in the *Z* spectrum. The band at 1555 cm^{-1}, seen in the spectrum of **3**, is not present in the spectrum of **2**: R_f^1 0.52, R_f^2 0.24; nmr ($CDCl_3$, 10% w/v) δ 1.26 (s, NH, 1 H), 2.0–2.6 (m, with peaks at 2.21 (NCH_3) and 2.39), 2.82–3.7 (broad, $-CH_2CHOH-$, 2 H), 4.66–5.1 (broad, OH, 1 H), 5.85 (t, vinyl CH, 1 H, *J* = 7 Hz), and 7.0–7.4 (m, aromatic). The (*R*,*S*)-*Z* isomer **2** did not form a crystalline hydrogen maleate salt on long standing. The hydrogen oxalate salt was prepared and recrystallized from absolute ethanol, mp 135–137° (foaming).

Anal. Calcd for $C_{19}H_{21}NO \cdot C_2H_2O_4$: C, 68.28; H, 6.28; N, 3.79. Found: C, 67.93; H, 6.50; N, 3.52.

Attempts to analyze this salt by dta and dsc were unsuccessful.

Registry No.—**2**, 37439-87-5; **2** hydrogen maleate, 37439-88-6; **3**, 37439-89-7; **3** hydrogen maleate, 37439-90-0; **3** naphthalene-1,5-disulfonate salt, 37439-91-1; **4**, 37439-92-2; **5**, 37439-93-3; **6**, 37439-94-4; **7**, 37440-21-4; **8**, 37508-15-9; **8** HCl, 37440-24-7; **9**, 37440-22-5; (*R*,*S*)-*N*,*N*-dimethyl-3-(10,11-dihydro-10-hydroxy-5*H*-dibenzo[*a*,*d*]cycloheptene)-$\Delta^{5,\gamma}$-propylamine, 37440-23-6.

Acknowledgments.—The authors are indebted to Mr. K. Streeter, Mr. Y. Lee, and Mr. R. Boos and their associates for the microanalyses, dta, and dsc data, Dr. George Smith for the phase solubility analyses, Mr. A. Augenblick for the glpc analyses, and Mr. W. Riley McGaughran for the infrared and 60-MHz nmr spectra.

N-Hydroxypteridines Structurally Analogous to Oncogenic *N*-Hydroxypurines. Covalent Hydration of 1-Hydroxy-2-oxo-1,2-dihydropteridine[1]

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1-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydropteridine has been synthesized and its properties compared with the analogous 3-hydroxypurine derivative. A technique was devised for the catalytic reduction of 5-nitrocytosine 3-oxide to the requisite 5-aminocytosine 3-oxide necessary for the synthesis of the 1-hydroxy-2-oxo-1,2-dihydropteridine. The latter undergoes facile covalent hydration, including addition of methanol and ethanol.

The biological importance of pteridines and the existence of oncogenic[2] purine *N*-oxides suggested that consideration should be given to the possible chemical and biological properties of structurally analogous pteridine *N*-oxide derivatives. Few pteridine *N*-oxides are known[3,4] and the only one structurally analogous to the oncogenic 3-hydroxyxanthine (**1**, R = H) is 1-hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-6,7-dimethylpteridine[3] (6,7-dimethyl **2**, R = H).

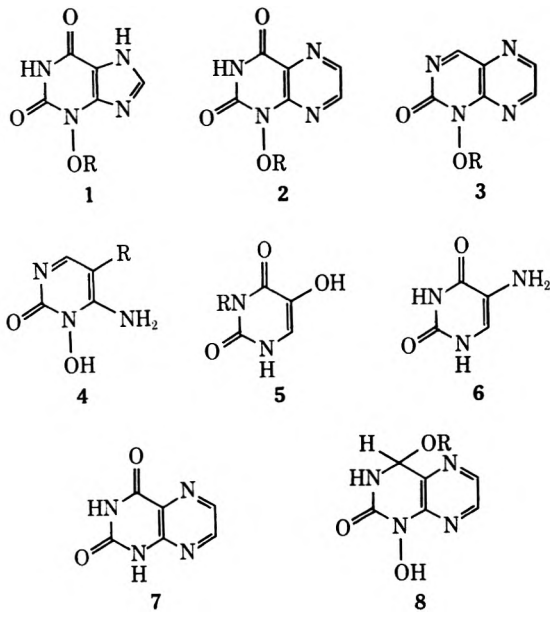
The desired 1-hydroxy-2,4-dioxo-1,2,3,4-tetrahydro-

(1) This investigation was supported in part by funds from the National Cancer Institute, Grant No. CA 08748, and the Atomic Energy Commission, Contract No. AT(11-1)-3521.

(2) K. Sugiura, M. N. Teller, J. C. Parham, and G. B. Brown, *Cancer Res.*, **30**, 184 (1970).

(3) R. M. Cresswell, H. K. Maurer, T. Strauss, and G. B. Brown, *J. Org. Chem.*, **30**, 408 (1965).

(4) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press, New York, N. Y., 1971, p 52.



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pteridine (2, R = H) and its *O*-benzyl derivative (2, R = $C_6H_5CH_2$) were prepared from condensation of 1-hydroxy- or 1-benzyloxy-5,6-diaminouracil[3,5] with glyoxal.

The synthesis of 1-hydroxy-2-oxo-1,2-dihydropteridine (**3**, R = H) required the synthesis of a series of new intermediates. That synthesis involved the nitration of the cytosine 3-oxide,[6] in concentrated sulfuric acid at room temperature with potassium nitrate, to give **4** (R = NO_2) in good yield and high purity. Reduction of the nitro group without reducing the *N*-oxide function was accomplished by catalytic hydrogenation with palladium on charcoal in water. The 5-aminocytosine 3-oxide (**4**, R = NH_2) tends to be oxidized when in contact with air and, immediately after the completion of hydrogenation, 1 equiv of 1 *N* HCl was added to the mixture to stabilize the amino derivative. Hydrogenation in 1 *N* HCl, to avoid the air oxidation after hydrogenation, was found to give a considerably lower yield because of the unexpected formation of 5-hydroxyuracil 3-oxide (**5**, R = OH) and at least six other minor by-products. The identity of **5** was confirmed by elemental analysis, nmr, and by its reduction to the known 5-hydroxyuracil.[7] Sodium dithionite was found to be an excellent selective reducing agent for reducing nitrosouracil *N*-oxides,[3,5] but was not as satisfactory for reducing nitrocytosine *N*-oxide, since it yielded both **4** (R = NH_2) and 5-aminouracil (**6**). The latter may arise by a mechanism similar to that proposed for the deamination of cytosine with sodium bisulfite.[8,9]

1-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydropteridine (2, R = H) can exist in many tautomeric forms, but the neutral species is predominantly the dioxo form, as indicated by the similarity of the ultraviolet spectrum of 2 (R = H) in neutral solution to those of 2,4-dihydroxypteridine (**7**), known to exist predominately in dioxo form,[10] and of 1-benzyloxy-2,4-dioxo-1,2,3,4-tetrahydropteridine (2, R = $C_6H_5CH_2$). Comparison of the ultraviolet spectra of the neutral species of 3-hydroxyxanthine derivatives with those of the parent xanthines showed[11] that introduction of the *N*-hydroxy group at the 3 nitrogen caused a bathochromic shift of 6 ± 1 nm in the main absorption band. The neutral species of 2,4-dihydroxypteridine and of its 1-hydroxy derivative shows a similar difference.

The nmr spectrum of 1-hydroxy-2-oxo-1,2-dihydropteridine (**3**, R = H) disclosed an unusually facile covalent hydration.[12] The crystals obtained from water correspond to a monohydrate. An nmr spectrum in DMSO suggested an equilibrium mixture of **3** (R = H) and **8** (R = H).[11b] The only signals expected for **3** (R = H) were a pair of doublets with coupling constants of ~2–3 Hz, a singlet for the aromatic proton, and a deuterium-exchangeable and relatively broad signal for the NOH proton. There are also broad aliphatic resonance at τ 4.41 and deuterium-exchangeable protons with signals at τ −0.18, 1.52, and 3.42, features not to be expected for the species **3** (R = H). The broad signal at τ 4.41, which became a sharp singlet upon the addition of D_2O, indicated that the protons influencing the broadening of the peak were exchanged. It was, therefore, concluded that the formation of **8** (R = H) was the cause of the additional signals. As in other cases of covalent hydration the addition reaction was acid catalyzed. The complete covalent hydration of **3** (R = H) to **8** (R = H) occurred when DCl was added to it in DMSO, as shown by the disappearance of all signals attributed to the anhydrous species.[11b]

Boiling of **3** (R = H) in methanol or ethanol yielded corresponding addition products **8** (R = Me or Et), which were isolated in crystalline form. The nmr spectrum of **8** (R = Me)[11b] indicated the presence of a single pure species. Doublets at τ 4.65 (J = 6 Hz) and 1.11 (J = 6 Hz) are assigned to the 4-H and 3-H. The nmr spectrum of the ethoxy isomer[11b] was similar to that for **3** (R = Me) except that the two doublets of H-6 and H-7 in the region τ 1.50–1.73 were converted to a multiplet when D_2O was added. This suggested that the ethanol adduct equilibrated with D_2O rapidly to form a new additional species of D_2O adduct. Under such conditions, the methanol adduct was stable, since the addition of D_2O, DCl, or NaOD caused only exchange of the labile protons, and did not dissociate the adduct.

The ultraviolet spectra of 1-hydroxy-2-oxo-1,2-dihydropteridine (**8**, R = H) in both neutral and basic aqueous solution are almost identical with those of the methanol adduct in neutral or in basic methanol, respectively. Since the methanol adduct is stable in methanol, the close similarity of its ultraviolet spectra in methanol to that of 1-hydroxy-2-oxo-1,2-dihydro-

(5) T.-C. Lee, G. Stöhrer, M. N. Teller, A. Myles, and G. B. Brown, *Biochemistry*, **24**, 4463 (1971).

(6) T. J. Delia, M. J. Olsen, and G. B. Brown, *J. Org. Chem.*, **30**, 2766 (1965).

(7) D. Davidson and O. Bandisch, *Ber.*, **58**, 1685 (1925).

(8) H. Hayatsu, Y. Wataya, and K. Kai, *J. Amer. Chem. Soc.*, **92**, 724 (1970).

(9) R. Shapiro, R. E. Servis, and M. Welcher, *ibid.*, **92**, 422 (1970).

(10) W. Pfleiderer, *Chem. Ber.*, **90**, 2582 (1957).

(11) (a) J. C. Parham, T. G. Winn, and G. B. Brown, *J. Org. Chem.*, **36**, 2639 (1971). (b) Nmr spectra of **8**, R = H, with and without DCl, and of **8**, R = Me or Et, with and without D_2O, will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-73-703. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(12) A. Albert and N. L. F. Amarago, *Advan. Heterocycl. Chem.*, **4**, 1 (1965).

pteridine in water indicates that the latter exists in the covalently hydrated form in aqueous solution.

2-Hydroxypteridine is known[13] to form a covalent hydration adduct stable only in acid and neutral media. The present data show that the covalent hydration adduct of the *N*-hydroxy derivative could also be observed in a nonaqueous medium, and furnishes another example of the influence of the *N*-hydroxy group in increasing[14] the susceptibility of the molecule to attack by nucleoplasm

The 1-hydroxy-2,4-dioxo-1,2,3,4-tetrahydropteridine (**2**, R = H) formed stable *N*-acetoxy, mesyloxy, or tosyloxy derivatives (**2**, R = Ac, Ms, or Ts). From **3** similar derivatives were obtained, but nmr evidence indicated that they were in the covalently hydrated forms corresponding to **8**. Rapid hydrolysis of those intermediates prevented their isolation in a pure state.

Even under mild conditions, such as in aqueous solution at pH's near 7 and at room temperature, 3-acetoxyxanthine (**1**, R = Ac) and related compounds undergo a "3-acyloxypurine 8-substitution" reaction[15-18] which involves replacement of the 3-acetoxy group by hydrogen and substitution at C-8 by nucleophiles such as water, chloride ion, or methionine. Unlike the purine *N*-oxide derivatives, the analogous acetoxy-, mesyloxy-, or tosyloxypteridines (**2** or **3**, R = Ac, Ms, or Ts) are quite stable even under more vigorous conditions. The failure of esters of **2** and **3** (R = Ac, Ms, or Ts) to undergo rearrangement can be attributed to the relatively π-deficient character of the pyrazine moiety, as compared to the π-excessive state of the imidazole. The ring system of **2** or **3** must be inefficient in transmitting a π electron from the pyrazine ring *via* delocalization to the N–O position to facilitate the cleavage of that bond in a manner similar to that which can occur with 3-acetoxyxanthine (**1**, R = Ac).[17,18]

The possible relationship of the 3-acyloxypurine 8-substitution reaction to the oncogenicity[2] of **1**, R = H, has been considered.[18,19] From the absence of a counterpart to that reaction in the analogous pteridines, it would not now be suggested that they would be oncogenic.

Experimental Section

Uv absorption spectra were determined with a Unicam SP800 recording spectrophotometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The nmr spectra were determined with a Varian A-60 spectrometer in DMSO-d_6 with the use of tetramethylsilane as an internal reference. The melting points are uncorrected. Paper chromatography, ascending, on Whatman No. 1 paper was used to check the purity of each of the compounds prepared. The pK_a's were determined in 0.01 *M* buffers[20] by methods described.[21] For Dowex-50 chromatography BioRad AG-50, 8X, 200–400 mesh [H$^+$] resin was used, in a column 4.5 × 26 cm, unless otherwise specified.

1-Benzyloxy-1,2,3,4-tetrahydro-2,4-dioxopteridine.—1-Benzyloxy-5,6-diaminouracil, prepared[3,22] by reduction of 1-benzyloxy-5-nitrosouracil (5.60 g) with sodium dithionite, was added to a boiling solution of glyoxal (1.20 g) in water (100 ml) in small portions. After 1 hr the hot suspension was filtered and the insoluble material was washed twice with 100 ml of boiling water. The combined filtrates yielded the benzyloxypteridine (720 mg) on cooling. Concentration of the mother liquors yielded an additional 250 mg. The yield based on nitrosouracil was 970 mg (18%), mp 212° (from 50% EtOH).

Anal. Calcd for $C_{13}H_{10}N_4O_3$: C, 57.78; H, 3.73; N, 20.73. Found: C, 57.67; H, 3.75; N, 20.56. Uv max at (pH 5.0) (neutral species) nm ($\epsilon \times 10^{-3}$), 232 (12.9), 245 (10.0) inflection, 282 (3.39), 329 (6.61). Chromatography of the filtrate from benzyloxypteridine solution over a column of Dowex-50 eluting with water yielded 2,4-dihydroxypteridine[23] (800 mg, 25%), uv max at pH 5.9 (neutral species), nm ($\epsilon \times 10^{-3}$), 230 (10.0), 324 (6.92); at pH 10.1 monoanion, 235 (10.5), 270 (8.91), 347 (4.90).

1-Hydroxy-2,4-dioxo-1,2,3,4-tetrahydropteridine.—5,6-Diamino-1-hydroxyuracil[3] from the reduction of 6-amino-1-hydroxy-5-nitrosouracil (1.92 g) with sodium dithionite was added to a glyoxal solution (650 mg in 25 ml of water) which was preheated for 5 min to permit the glyoxal to dissolve. After gentle refluxing for 1.5 hr the insoluble solid (500 mg) was separated and washed twice with 10 ml of boiling water. The filtrates were passed over a Dowex-50 [H$^+$] column which was eluted with water that was concentrated to yield 1-hydroxypteridine (1.0 g, overall yield 50%). Recrystallization from water (30 ml) gave needles, mp 321° dec.

Anal. Calcd for $C_6H_4N_4O_3$: C, 40.00; H, 2.24; N, 31.10. Found: C, 40.01; H, 2.25; N, 31.00. Uv max at pH 3.0 (neutral species), nm ($\epsilon \times 10^{-3}$), 232 (11.5), 252 (7.50) inflection, 332 (6.72); at pH 7.9 monoanion, 234 (9.79), 261 (10.2), 302 (6.96); at pH 12.0 dianion, 238 (8.53), 271 (19.8), 307 (3.46) inflection; $pK_{a_1} = 6.50 \pm 0.05$, $pK_{a_2} = 9.35 \pm 0.05$.

1-Acetoxy-2,4-dioxo-1,2,3,4-tetrahydropteridine.—The 1-hydroxypteridine (200 mg) was boiled with a mixture of acetic anhydride (2 ml) and acetic acid (1.5 ml) for 2 hr and cooled. This yielded the acetoxypteridine (220 mg, 89%) as fine crystals, mp 255°.

Anal. Calcd for $C_8H_6N_4O_4$: C, 43.25; H, 2.72; N, 25.22. Found: C, 43.22; H, 2.72; N, 24.98. Uv max at pH 5.0 (neutral species), nm ($\epsilon \times 10^{-3}$), 229 (11.2), 323 (7.94).

1-Mesyloxy-2,4-dioxo-1,2,3,4-tetrahydropteridine.—1-Hydroxy-2,4-dioxo-1,2-dihydropteridine (85 mg) with mesyl chloride (0.1 ml) in pyridine (1.0 ml) was stirred at room temperature for 2 hr. This was absorbed on a Dowex-50 [H$^+$] column, and eluted with water to give 1-hydroxy-2,4-dioxopteridine (13 mg) followed by the 1-mesyloxypteridine (85 mg, 70%), mp 130°. The mesyloxypteridine is stable in water at room temperature but does hydrolyze to the hydroxypteridine upon heating.

Anal. Calcd for $C_7H_6N_4O_5S$: C, 32.57; H, 2.34; N, 21.70. Found: C, 32.68; H, 2.36; N, 21.85. Uv max at pH 5.0 (neutral species), nm ($\epsilon \times 10^{-3}$), 229 (11.2), 315 (6.76).

2,4-Dioxo-1-tosyloxy-1,2,3,4-tetrahydropteridine.—The 1-hydroxypteridine (180 mg) and 1 *N* NaOH (1.5 ml) were added to a suspension of tosyl chloride (290 mg) in a mixture of water (2 ml) and ethanol (3 ml), and stirred at 90° for 15 min and at room temperature overnight. A white precipitate (320 mg, 96%) was washed with water, ethanol, and ether, mp 224° dec.

Anal. Calcd for $C_{13}H_{10}N_4O_5S$: C, 46.72; H, 3.02; N, 16.76. Found: C, 46.78; H, 3.09; N, 16.60. Uv max at pH 5.0 (neutral species), nm ($\epsilon \times 10^{-3}$), 234 (21.9), 315 (6.17).

5-Nitrocytosine 3-Oxide.—Finely ground potassium nitrate (2.22 g, 0.022 mol) was slowly added with stirring to a solution of cytosine 3-oxide[6] (2.90 g, 0.02 mol) in 10 ml of concentrated H_2SO_4. The solution was warmed to 30° for 30 min, then added to 200 g of crushed ice, and carefully neutralized with 50% NaOH to pH 6 at a temperature below 10°. A yellow precipitate was collected, washed repeatedly with water, and dried (2.95 g, 86%), mp 220°. The bright yellow nitrocytosine 3-oxide gave a dark orange-brown color with ferric chloride.

Anal. Calcd for $C_4H_4N_4O_4$: C, 27.92; H, 2.34; N, 32.55. Found: C, 27.78; H, 2.28; N, 32.35. Uv max at pH 2.0 (neutral species), nm ($\epsilon \times 10^{-3}$), 245 (5.77) inflection, 270 (6.63),

(13) Y. Inone and D. D. Perrin, *J. Chem. Soc.*, 2600 (1962).
(14) R. M. Cresswell and G. B. Brown, *J. Org. Chem.*, **28**, 2560 (1963).
(15) U. Wölcke, N. J. M. Birdsall, and G. B. Brown, *Tetrahedron Lett.*, 785 (1969).
(16) N. J. M. Birdsall, T.-C. Lee, and U. Wölcke, *Tetrahedron*, **27**, 5961 (1971).
(17) N. J. M. Birdsall, U. Wölcke, T.-C. Lee, and G. B. Brown, *ibid.*, **27**, 5969 (1971).
(18) N. J. M. Birdsall, J. C. Parham, U. Wölcke, and G. B. Brown, *ibid.*, **24**, 3 (1972).
(19) G. Stöhrer and G. B. Brown, *Science*, **167**, 1622 (1970).
(20) D. D. Perrin, *Aust. J. Chem.*, **16**, 572 (1963).
(21) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962.
(22) W. Klötzer, *Monatsh. Chem.*, **95**, 265 (1964).
(23) C. K. Cain, M. F. Mallette, and E. C. Taylor, *J. Amer. Chem. Soc.*, **68**, 1996 (1946).

330 (9.73); at pH 10 monoanion, 240 (7.86) inflection, 276 (8.98), 347 (12.7).

Reduction of 5-Nitrocytosine 3-Oxide to 5-Aminocytosine 3-Oxide. A. By Sodium Dithionite.—Sodium dithionite (12.2 g, 70 mmol) was added, in small portions at 25°, to a solution of 5-nitrocytosine 3-oxide (3.44 g, 20 mmol), stirred at the same temperature for 0.5 hr, and the mixture was absorbed on a Dowex-50 [H^+] column and eluted with water (800 ml). Further inorganic material and a small amount of starting material was removed with 1 *N* hydrochloric acid (300 ml). With 2 *N* hydrochloric acid (400 ml) 5-aminocytosine 3-oxide hydrochloride (1.01 g, 28%) was obtained; further elution with 2 *N* hydrochloric acid (1200 ml) gave a small amount of unknown by-products.

B. By Catalytic Hydrogenation in 1 *N* Hydrochloric Acid.—A suspension of 5-nitrocytosine 3-oxide (1.72 g, 10 mmol) with 10% palladium on charcoal in 1 *N* hydrochloric acid (250 ml) was hydrogenated at 1 atm for 2 days, at which time 3 equiv of hydrogen had been absorbed. The filtrate was evaporated to dryness *in vacuo*, and the residue was dissolved in 5 ml of water and chromatographed over a Dowex-50 [H^+] column. By elution with water, and stepwise with 1 *N* to 4 *N* hydrochloric acid, two major products were isolated and six minor products were detected. The major product eluted by water was the 5-hydroxyuracil 3-oxide derivative: uv max (pH 4) 275 (pH 11) 299, 232 nm; (500 mg) nmr τ 3.05, 3.45 (NH), broad absorption between 0.67 and 0.0 (NH + 3 H).

Anal. Calcd for $C_4H_4N_2O_4$: C, 33.34; H, 2.80; N, 19.44. Found: C, 33.37; H, 2.78; N, 19.45.

Its identity was confirmed by reduction to the known 5-hydroxyuracil. The desired 5-aminocytosine 3-oxide (340 mg, 18.0%) was eluted with 2 *N* hydrochloric acid.

C. By Catalytic Hydrogenation in Water.—5-Nitrocytosine 3-oxide (3.44 g, 20 mmol) in water (500 ml) with 10% palladium on charcoal (800 mg) was hydrogenated for 2 days. To minimize air oxidation 20 ml of 1 *N* hydrochloric acid was added immediately after the hydrogenation. The catalyst was separated, the filtrate was absorbed on Dowex-50 [H^+], and elution with 1 *N* hydrochloric acid yielded 5-aminocytosine 3-oxide (3.4 g, 95%). This darkened on standing and was stored cold and used as soon as possible without further purification.

Reduction of 5-Hydroxyuracil 3-Oxide.—To 5-hydroxyuracil 3-oxide (30 mg) in 1 *N* hydrochloric acid (10 ml), powdered zinc (100 mg) was added with stirring. After 3 days at 25° 5-hydroxyuracil (10 mg) was obtained as a white precipitate. Its identity was confirmed by comparison of the uv spectrum with that of an authentic sample.[7]

1-Hydroxy-2-oxo-1,2-dihydropteridine.—Glyoxal (400 mg) was depolymerized by heating under reflux in water (50 ml) until the solid was dissolved. The clear solution was allowed to cool to 50°, 5-aminocytosine 3-oxide hydrochloride (1.02 g) was added, and the solution was stirred at 50–60° for 2.5 hr. A white precipitate formed, and at room temperature the *N*-hydroxypteridine **3** (719 mg, 70%) was collected as light gray needles from water, mp 267° dec.

Anal. Calcd for $C_6H_4N_4O_2 \cdot H_2O$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.59; H, 3.29; N, 30.79. Uv max at pH 5.0 (neutral species), nm ($\epsilon \times 10^{-3}$), 227 (6.76) inflection, 241 (7.59), 289 (4.27) inflection, 311 (7.41); pH 12 (anion) 258 (15.1), 275 (17.4), 415 (3.31). Nmr (DMSO) τ 4.41 (broad, 4-H of **8**, R = H), 3.42 (broad, 4-OH of **8**, R = H), 1.78, 1.62 (doublet pair, J = 3 Hz, 6-H + 7-H of **8**, R = H), 1.52 (broad, 3-H of **8**, R = H), 1.29, 1.07 (doublet pair, J = 3 Hz, 6-H + 7-H of **3**, R = H), 0.57 (singlet, 4-H of **3**, R = H), −0.18 (broad, 1-H of **8**, R = H), −0.41 (broad, 1-H, **3**, R = H) Nmr (DCl added) 4.41 (singlet, 4-H of **8**, R = H), 1.78, 1 (doublet pair, J = 3 Hz, 6-H + 7-H of 8, R = H).

The Reaction of Methanol (or Ethanol) with 1-Hydroxy-2-oxo-1,2-dihydropteridine.—1-Hydroxy-2-oxo-1,2-dihydropteridine (100 mg) was boiled with methanol (10 ml) until the solid dissolved (1 hr), and the solution was evaporated. The nmr of the residue indicated the addition of methanol at the 3,4 bond. The 1-hydroxy-4-methoxy-2-oxo-1,2,3,4-tetrahydropteridine crystallized from methanol as needles, mp 176° dec.

Anal. Calcd for $C_7H_8N_4O_3$: C, 42.86; H, 4.11; N, 28.56. Found: C, 42.70; H, 4.20; N, 28.63. Uv max in methanol, nm ($\epsilon \times 10^{-3}$), 228 (6.76) inflection, 242 (7.99), 290 (5.53) inflection, 312 (6.64); in 0.01 *N* methanolic NaOH, 260 (11.3), 278 (12.5), 415 (2.09). Nmr (DMSO) τ 6.70 (singlet, CH_3), 4.65 (doublet, J = 6 Hz, 4-H), 1.75, 1.58 (doublet pair, J = 3 Hz, 6-H + 7-H), 1.11 (broad doublet, J = 6 Hz, 3-H), −0.22 (singlet, 1-H). Nmr (D_2O, NaOD, or DCl added) 6.70 (singlet, CH_3) 4.65 (singlet, 4-H), 1.75, 1.58 (doublet pair, J = 6 Hz, 6-H + 7-H).

Similar treatment of the 1-hydroxy-2-oxo-1,2-dihydropteridine with ethanol gave 1-hydroxy-4-ethoxy-2-oxo-1,2,3,4-tetrahydropteridine, mp 176° dec (from hexane).

Anal. Calcd for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.80; N, 26.66. Found: C, 45.80; H, 4.91; N, 26.58. Nmr (DMSO) τ 8.86 (triplet, J = 7 Hz, CH_3), 6.42 (quartet, J = 7 Hz, CH_2), 4.44 (doublet, J = 4 Hz, 4-H), 1.71, 1.53 (doublet pair, J = 3 Hz, 6-H + 7-H), 1.10 (doublet, J = 4 Hz, 3-H), −0.33 (broad, 1-H). Nmr (D_2O added) 8.86 (triplet, J = 7 Hz, CH_3), 6.42 (quartet, J = 7 Hz, CH_2), 4.41 (singlet, 4-H), 4.31 (singlet, 4-H of **8**, R = D), 1.50–1.73 (multiplet, 6-H + 7-H of **8**, R = Et and R = D).

Registry No.—**2** (R = benzyl), 37440-26-9; **2** (R = H), 37440-27-0; **2** (R = Ac), 37440-28-1; **2** (R = mesyl), 37440-29-2; **2** (R = tosyl), 37440-30-5; **3**, 37440-31-6; **4** (R = NO_2), 37440-39-4; **4** (R = NH_2), 37440-40-7; **4** (R = NH_2, HCl), 37440-41-8; **5** (R = OH), 37440-32-7; **8** (R = Me), 37440-33-8; **8** (R = Et), 37440-34-9; 1-benzyloxy-5,6-diaminouracil, 37440-35-0; glyoxal, 107-22-2; 2,4-dihydroxypteridine, 525-77-9; 5,6-diamino-1-hydroxyuracil, 37440-37-2; cytosine 3-oxide, 37440-38-3.

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Sterically Controlled Syntheses of Optically Active Organic Compounds. XVIII. Asymmetric Syntheses of Amino Acids by Addition of Hydrogen Cyanide to the Schiff Bases[1]

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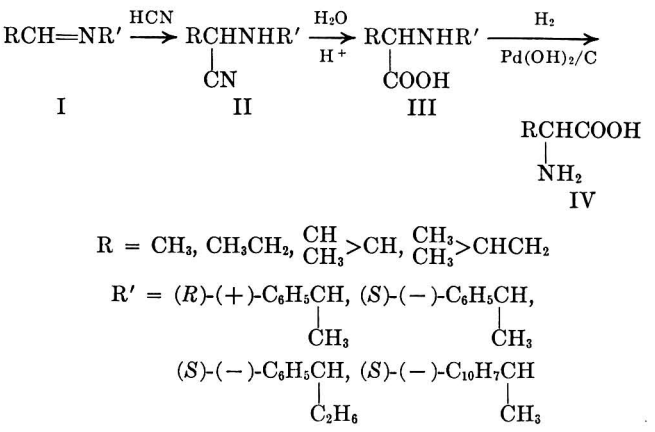
Addition reactions of hydrogen cyanide to Schiff bases which were prepared from several aliphatic aldehydes and optically active benzylic amines were studied. The addition products were hydrolyzed and hydrogenolyzed to form optically active amino acids. The synthetic yields of amino acids were in a range of 9–58% and the optical purities of amino acids without fractionation of optical isomers were in a range of 22–58%. When (*R*)-α-alkylbenzylamines were used, (*R*)-amino acids were obtained. The fractionation of optical isomers during isolation and purification was examined.

Partially optically active *N*-alkyl-α-aminopropionitrile was prepared by the Strecker reaction from optically active α-methylbenzylamine, acetaldehyde and hydrogen cyanide,[2] or from the same amine with racemic lactonitrile.[3] The *N*-α-methylbenzylaminoacetonitrile was hydrolyzed and hydrogenolyzed to form optically active alanine.[2,3] From the reaction mixture, highly optically active alanine (optical purity 89–98%) was isolated by crystallization in which fractionation of optical isomers would take place.[4]

Addition reactions to the carbon–nitrogen double bonds have been studied.[5,6] Carbon–nitrogen double bonds react with hydrogen cyanide to form α-amino nitriles.[7–15] Hydrolysis of the amino nitriles yielded α-amino acids.

Recently, Patel and Worsley[16] reported the asymmetric synthesis of several α-amino acids (mostly unnatural) by addition of hydrogen cyanide to the carbon–nitrogen double bond of Schiff bases that were prepared from optically active α-methylbenzylamine and various aldehydes. The optical purities of amino acids they reported were very high (98–99%). The high optical purity could have resulted from fractionation which occurred during the crystallization and the washing procedure employed in the synthesis.

In this investigation, the addition reactions of hydrogen cyanide to azomethine compounds (I) which were prepared from various optically active benzylic amines and aliphatic aldehydes were studied in order to (1) examine the fractionation problem in the previous study,[16] (2) examine the effect of optically active benzylic amines on the optical purity of the synthesized amino acids, and (3) synthesize natural amino acids. The amines used were (*R*)-(+)- and (*S*)-(−)-α-methylbenzylamine, (*R*)-(+)-α-ethylbenzylamine, and (*R*)-(+)-α-(1-naphthyl)ethylamine. The aldehydes



used were acetaldehyde, propionaldehyde, isobutyraldehyde, and isovaleraldehyde, which resulted in the formation, respectively, of the natural amino acids, alanine, butyrine, valine, and leucine.

The addition reaction of hydrogen cyanide to the Schiff bases was carried out in absolute ethanol for 20 hr at room temperature; however, the addition of hydrogen cyanide to the Schiff base was carried out at −10°. The reaction products that contain *N*-alkylaminonitriles (II) were hydrolyzed by refluxing in 6 *N* hydrochloric acid. The resulting *N*-alkylamino acids (III) were hydrogenolyzed with palladium hydroxide on charcoal in order to remove the *N*-α-alkylbenzyl group. The resulting amino acids (IV) were converted to their corresponding DNP derivatives by treatment with 2,4-dinitrofluorobenzene. The DNP amino acids were purified by the use of Celite column chromatography[17] without fractionation of optical isomers.[18] These DNP derivatives were used to measure the optical purities of the resulting amino acids. The overall yields, specific rotations, and optical purities of alanine, butyrine, valine, and leucine that were synthesized using various optically active amines are listed in Table I.

The overall yield of amino acids is in a range of 19–58%. Valine, which is the most sterically hindered, had the lowest yield, and alanine, which is the least sterically hindered, had the highest yield. The effect

(1) Contribution No. 227 of the Institute for Molecular and Cellular Evolution.

(2) K. Harada, *Nature (London)*, **200**, 1201 (1963).

(3) K. Harada and S. W. Fox, *Naturwissenschaften*, **51**, 106 (1964).

(4) K. Harada, T. Okawara, and K. Matsumoto, *Bull. Chem. Soc. Jap.*, in press.

(5) K. Harada in "The Chemistry of the Carbon–Nitrogen Double Bond," S. Patai, Ed., Interscience, London, 1970, p 255.

(6) J. P. Anselme in "The Chemistry of the Carbon–Nitrogen Double Bonds," S. Patai, Ed., Interscience, London, 1970, p 299.

(7) G. E. P. Smith, Jr., and F. W. Bergstrom, *J. Amer. Chem. Soc.*, **56**, 2095 (1934).

(8) R. Tiollais, *Bull. Soc. Chim. Fr.*, **14**, 959 (1947).

(9) A. Dornow and S. Lupfert, *Chem. Ber.*, **89**, 2718 (1956).

(10) G. H. Harris, B. R. Harriman, and K. W. Wheeler, *J. Amer. Chem. Soc.*, **68**, 846 (1946).

(11) J. Collazos, *Chim. Ind. (Paris)*, **86**, 47 (1961).

(12) F. Adlickes, *J. Prakt. Chem.*, **161**, 271 (1943).

(13) C. C. Porter and L. Hellerman, *J. Amer. Chem. Soc.*, **61**, 754 (1939).

(14) H. A. Lillevik, R. L. Hossfeld, H. V. Lindstrom, R. T. Arnold, and R. A. Gortner, *J. Org. Chem.*, **7**, 164 (1942).

(15) C. C. Porter and L. Hellerman, *J. Amer. Chem. Soc.*, **66**, 1652 (1944).

(16) M. S. Patel and M. Worsley, *Can. J. Chem.*, **48**, 1881 (1970).

(17) J. C. Perrone, *Nature (London)*, **167**, 513 (1951); A. Court, *Biochem J.*, **58**, 70 (1954).

(18) K. Harada and K. Matsumoto, *J. Org. Chem.*, **32**, 1790 (1967).

TABLE I

ASYMMETRIC SYNTHESES OF AMINO ACIDS BY ADDITION OF HYDROGEN CYANIDE TO THE SCHIFF BASES

Aldehyde		CH_3CHO			CH_3CH_2CHO		
Reaction	Amine[a]	DNP-Ala[b] $[\alpha]^{25}D$ (c)	Optical purity[c]	Overall yield,[d] %	DNP-But[b] $[\alpha]^{25}D$ (c)	Optical purity[c]	Overall yield,[d] %
1a	(*R*)-(+)-Me	−56.8 (2.0)	40	54	−47.5 (1.7)	48	49
1b		−64.1 (1.8)	45	40	−55.0 (1.9)	56	37
1c		−116.8 (1.6)	81	25	−93.5 (1.6)	95	14
1d		−9.5[e] (2.7)	95[e]	17	−14.8[e] (1.8)	100[e]	14
2	(*S*)-(−)-Me	+58.1 (2.0)	41	58	+48.9 (1.8)	49	43
3	(*R*)-(+)-Et	−76.0 (1.7)	53	52	−54.8 (1.6)	55	41
4	(*R*)-(+)-Naph	−53.4 (1.9)	37	54	−52.6 (1.5)	53	45

$(CH_3)_2CHCHO$			$(CH_3)_2CHCH_2CHO$		
DNP-Val[b] $[\alpha]^{25}D$ (c)	Optical purity[c]	Overall yield,[d] %	DNP-Leu[b] $[\alpha]^{25}D$ (c)	Optical purity[c]	Overall yield,[d] %
−34.2 (1.4)	31	21	−14.1 (2.3)	24	40
−52.2 (0.7)	48	12	−20.1 (2.3)	34	23
−66.8 (1.2)	61	9	−24.3 (2.6)	41	
−16.3[e] (1.7)	74[e]	10	−9.0[e] (2.0)	78[e]	14
+32.2 (1.2)	30	19	+13.8 (2.9)	23	37
−52.3 (1.5)	48	19	−17.5 (4.4)	30	35
−48.4 (1.5)	44	22	−13.0 (4.9)	22	34

[a] (*R*)-(+)-Me, (*R*)-(+)-α-methylbenzylamine; (*S*)-(−)-Me, (*S*)-(−)-α-methylbenzylamine; (*R*)-(+)-Et, (*R*)-(+)-α-ethylbenzylamine; (*R*)-(+)-Naph, (*R*)-(+)-α-(1-naphthyl)ethylamine. [b] These specific rotations of DNP amino acids were measured in 1 *N* NaOH. [c] Optical purity defined as $[\alpha]D$ obsd/$[\alpha]D$ of the compound × 100. DNP-(*S*)-(+)-alanine, $[\alpha]D$ +143.9° (1 *N* NaOH); DNP-(*S*)-(+)-butyrine, $[\alpha]D$ +98.8° (1 *N* NaOH); DNP-(*S*)-(+)-valine, $[\alpha]D$ +109.1° (1 *N* NaOH); DNP-(*S*)-(+)-leucine, $[\alpha]D$ +59.5° (1 *N* NaOH). [d] The yields are calculated from aldehydes. [e] Specific rotations and optical purities are measured as amino acid hydrochlorides.

TABLE II

ELEMENTAL ANALYSES OF AMINO ACIDS AND *N*-ALKYLAMINO ACIDS

			Calcd, %			Found, %		
Compd	Mp, °C	Formula	C	H	N	C	H	N
N-R-Ala[a]	273–276 (sublime)	$C_{11}H_{15}NO_2$	68.37	7.82	7.25	68.49	7.95	7.17
N-R-But[a]	247–250 (sublime)	$C_{12}H_{19}NO_2$	69.54	8.27	6.76	69.22	8.40	6.65
N-R-Val[a]	265–270 (sublime)	$C_{13}H_{19}NO_2$	70.56	8.65	6.33	70.21	8.79	6.34
N-R-Leu[a]	255–258 (sublime)	$C_{14}H_{21}NO_2$	71.46	8.99	5.95	71.53	9.12	6.05
Ala		$C_3H_9NO_2$	40.44	7.92	15.72	40.56	7.88	15.78
But		$C_4H_9NO_2$	46.59	8.80	13.58	46.94	8.80	13.66
Val		$C_5H_{11}NO_2$	51.26	9.46	11.96	51.06	9.42	11.98
Leu		$C_6H_{13}NO_2$	54.94	9.99	10.68	54.72	9.95	10.63

[a] R: (*R*)-(+)-α-methylbenzyl.

of various optically active amines on the overall yield is not clear. The effect of amines on the optical purities of amino acid is also not large; however, the optical purities of amino acids prepared by the use of (*R*)-(+)-α-ethylbenzylamine are always the largest. This result agrees with the data that were obtained by other Strecker-type syntheses of amino acids using the same amines under similar conditions.[4] DNP-leucine is difficult to crystallize and the elimination of 2,4-dinitrophenol from the DNP-ylated reaction mixture by sublimation before Celite column chromatography is probably not complete. Therefore, the specific rotations and optical purities of leucine (measured as DNP-leucine) listed in Table I could be thought to be lower than those of the actual values. Elemental analyses of some of the *N*-alkylamino acids and also alanine, butyrine, valine, and leucine are shown in Table II.

In reaction series 1a, Table I, partially optically active alanine, butyrine, valine, and leucine were

prepared by the use of (*R*)-(+)-α-methylbenzylamine and the optical purities of these DNP amino acids were measured without fractionation of optical isomers as in the previous studies.[18] In reaction series 1b, 1c, and 1d, Table I, several washing and isolation procedures that were used by Patel and Worsley[16] were examined.

In reaction 1b, the isolated compound III was washed with absolute alcohol after isolation by the use of a Dowex 50 column. It was found that some of the optically active diastereomeric mixture (III) dissolved easily in absolute alcohol, especially for *N*-alkylvaline and *N*-alkylleucine. The alcohol-washed III was hydrogenolyzed and the optical purities of the resulting amino acids were measured with the DNP-ylation technique without further fractionation of optical isomers. Therefore, the increase of optical purities in reaction 1b compared with 1a in Table I can be attributed to the washing of the isolated diastereomeric mixtures.

In reaction 1c, the diastereomeric mixture III was isolated after adjusting the pH to 6 by the addition of alcohol, instead of by using ion-exchange resin. The isolated compounds were then hydrogenolyzed and the optical purities of amino acids were measured without fractionation. The increase of optical purity in reaction 1c compared with 1a in Table I can be attributed to fractionation during crystallization in the isolation procedure.

In reaction 1d, amino acids which were obtained by the hydrogenolysis of reaction 1c were dissolved in 1 *N* hydrochloric acid. After the solution was evaporated to dryness, the residual amino acid hydrochlorides were dissolved in a small amount of absolute ethanol and the amino acid hydrochlorides were precipitated by addition of ether. The optical purities of amino acid hydrochlorides were measured directly without converting them to DNP derivatives. Therefore, the increase of optical purity of reaction 1d compared with 1c can be attributed to fractionation during crystallization of the amino acid hydrochlorides.

These artificially designed fractionations of optically active isomers by washing and crystallization of the diastereomeric mixture and by crystallization of the partially optically active amino acid hydrochlorides indicate strongly that the high optical purities obtained in the earlier study[16] are due to the fractionation during the isolation and purification procedures.[18a]

Experimental Section

All hydrogenolysis reactions were carried out by the use of a Parr 3910 shaker type hydrogenation apparatus at room temperature. All optical activity measurements were carried out on a JASCO-ORD-UV 5 spectropolarimeter.

The specific rotations of optically active amines follow: (*R*)-(+)-α-methylbenzylamine, $[\alpha]^{25}D$ −39.0° (*c* 5, benzene); (*S*)-(−)-α-methylbenzylamine, $[\alpha]^{25}D$ −38.5° (*c* 5, benzene); (*S*)-(−)-α-ethylbenzylamine, $[\alpha]^{25}D$ +21.1° (*c* 6, benzene); (*R*)-(−)-α-(1-naphthyl)ethylamine, $[\alpha]^{25}D$ +91.0° (*c* 7, benzene).

Preparation of the Schiff Base I.—To the solution of benzylic amine (0.01 mol) in 15 ml of anhydrous benzene was added a solution of an aldehyde (0.01 mol) in 15 ml of benzene under ice cooling. The solution was kept in ice water for 5 min with occasional shaking. Then the solution was kept at room temperature for 20 min. To the mixture, 5.0 g of anhydrous sodium sulfate was added to remove precipitated water. The benzene solution was kept for another 12 hr at room temperature. The mixture was filtered to remove sodium sulfate and the filtrate was evaporated under reduced pressure at a temperature below 45° using a water bath. The pale yellow syrup (Schiff base) was used in the addition reactions.

α-Aminonitriles (II).—The Schiff base I was dissolved in 20 ml of absolute ethanol. The solution was chilled to −10° and then 2 ml (0.05 mol) of liquid hydrogen cyanide was added. The reaction mixture was shaken to mix the reactants homogeneously. Then the container was sealed and the reaction mixture was allowed to stand at room temperature for 20 hr. The reaction mixture was colorless to pale yellow after standing. After the reaction was over, excess hydrogen cyanide and ethanol were removed under reduced pressure using a sodium hydroxide trap. The residual syrup (aminonitrile, II) was processed further by hydrolysis.

***N*-Alkylamino Acids (III).**—The α-aminonitrile II was refluxed with 20 ml of 6 *N* hydrochloric acid for 12 hr. The hydrolyzate was extracted with ether to remove colored ether-soluble material. The hydrochloric acid was evaporated to dryness under reduced pressure. Absolute ethanol (20 ml) was added to the residue, the solution was kept at 0° for 3 hr, and the solution was filtered to remove ammonium chloride. The ethanol was evaporated under reduced pressure. The residue was dissolved in a small amount of water, and the solution was applied to a Dowex 50 column (H^+ form, 1.9 × 23 cm) and was eluted with 1.5 *N* aqueous ammonia after water washing. The fractions containing the amino acid were combined and the solution was evaporated under reduced pressure. Half of the *N*-alkylalanine, *N*-alkylbutyrine, *N*-alkylvaline, and *N*-alkylleucine, where the *N*-alkyl group is an (*R*)-(+)-α-methylbenzyl group, was recrystallized from ethanol and water for elemental analysis. The results are shown in Table II. Half of the other *N*-alkylamino acids were hydrogenolyzed without isolation to avoid fractionation of optical isomers.

Optically Active Amino Acid IV.—*N*-Alkylamino acid III was dissolved in a mixture of ethanol and water (70 ml, 1:1), and the solution was hydrogenolyzed by the use of palladium hydroxide on charcoal (0.5 g) for 12 hr. After the reaction was over, a part of the amino acid was converted to DNP amino acid in the usual manner.[19] The resulting DNP amino acid was purified and isolated by the use of a Celite column treated with a pH 7 citrate–phosphate buffer.[17] The DNP amino acid was used for measurement of optical purity of amino acid. The other part of the amino acid was recrystallized from water and ethanol for elemental analysis. The elemental analyses of alanine, butyrine, valine, and leucine, which were prepared by the use of (*R*)-(+)-α-methylbenzylamine, are shown in Table II.

Fractionation of Optical Isomers during the Isolation and Purification Processes. Reaction 1b.—After acid hydrolysis, the *N*-alkylamino acid III was isolated by the use of a Dowex 50 column as described earlier. The *N*-alkylamino acids III (a diastereomeric mixture) were washed with varying amounts of absolute alcohol (*N*-alkylalanine, 15 ml; *N*-alkylbutyrine, 15 ml; *N*-alkylvaline, 3 ml; *N*-alkylleucine, 3 ml). *N*-Alkylvaline and *N*-alkylleucine are rather soluble in absolute alcohol and only 3 ml of ethanol was used for washing. The alcohol-washed *N*-alkylamino acids were dissolved in an ethanol–water mixture (1:1) and hydrogenolyzed. The optical purities were measured as DNP derivatives after purification using Celite column chromatography.

Reaction 1c.—After acid hydrolysis of II, the hydrochloric acid was evaporated under reduced pressure. The residue was dissolved in 7–16 ml of water and the pH was adjusted to 6 with pyridine. To this solution, an equal volume of absolute ethanol was added to precipitate the *N*-alkylamino acid III. Crystallized III was hydrogenolyzed and DNP-ylated to measure the optical purity of amino acid as described above.

Reaction 1d.—The amino acid IV, which was obtained by the method described in reaction 1c, was dissolved in 10 ml of 1 *N* hydrochloric acid, and the solution was evaporated to dryness. The residue was dissolved in 1.5–3 ml of absolute ethanol. To this was added 3–8 ml of ether to precipitate amino acid hydrochloride. The optical purities were measured as amino acid

(18a) NOTE ADDED IN PROOF.—Recent study showed that the optical purity of amino acid prepared by the method described in ref 16 was 60% by using nmr technique: J. C. Fiaud and A. Horeau, *Tetrahedron Lett.*, 2565 (1971).

(19) F. Sanger, *Biochem. J.*, **39**, 507 (1945); K. R. Rao and H. A. Sober *J. Amer. Chem. Soc.*, **76**, 1328 (1954).

hydrochloride instead of as DNP derivatives. The results of reactions 1b, 1c, and 1d are shown in Table I.

Registry No.—I (R = Me, R′ = (*R*)-(+)-Me), 37696-13-2; I (R = Me, R′ = (*S*)-(−)-Me), 37696-14-3; I (R = Me, R′ = (*R*)-(+)-Et), 37696-15-4; I (R = Me, R′ = (*R*)-(+)-Naph), 37696-16-5; I (R = Et, R′ = (*R*)-(+)-Me), 37696-17-6; I (R = Et, R′ = (*S*)-(−)-Me), 37696-18-7; I (R = Et, R′ = (*R*)-(+)-Et, 37696-19-8; I (R = Et, R′ = (*R*)-(+)-Naph), 37696-20-1; I (R = *i*-Pr, R′ = (*R*)-(+)-Me), 6397-96-2; I (R = *i*-Pr, R′ = (*S*)-(−)-Me), 6397-97-3; I (R = *i*-Pr, R′ = (*R*)-(+)-Et), 37696-23-4; I (R = *i*-Pr, R′ = (*R*)-(+)-Naph), 37696-24-5; I (R = *i*-Bu, R′ = (*R*)-(+)-Me), 27482-979; I (R = *i*-Bu, R′ = (*S*)-(−)-Me), 27482-980; I (R = *i*-Bu, R′ = (*R*)-(+)-Et), 37696-27-8; I (R = *i*-Bu, R′ = (*R*)-(+)-Naph), 37696-28-9; *N*-(*R*)-(+)-Me-Ala (DL), 37696-29-0; *N*-(*R*)-(−)-Me-But (DL), 37696-30-3; *N*-(*R*)-(+)-Me-Val (DL), 37696-31-4; *N*-(*R*)-(+)-Me-Leu (DL), 37696-32-5; D-Ala, 338-69-2; D-But, 2623-91-8; D-Val, 640-68-6; D-Leu, 328-38-1; D-Ala (DNP), 10580-45-7; D-But (DNP), 6367-34-6; D-Val (DNP), 37696-35-8; D-Leu (DNP), 37696-36-9.

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Structure and Conformation of Chalcone Photodimers and Related Compounds

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Based on combined evidence from various techniques, we report here the configurational assignments and the conformational preferences of the two chalcone (benzalacetophenone) photodimers. Mass spectra and nmr data have provided much of the evidence for the configurational assignments, while dipole moment data and conformational energy estimates have been used in the conformational work. Detailed analysis of mass and nmr spectra has allowed to assign the β-truxinic structure to the low-melting (mp 126°) photodimer and the α-truxillic structure to the high-melting (mp 226°) photodimer. These results modify previous reports which assigned the δ-truxinic structure to the low-melting isomer. The conformational properties of these molecules have been investigated by comparing the experimental dipole moments with contour maps of calculated dipole moments as a function of the internal rotation angles, and with conformational energy maps. Our results show that these structurally crowded molecules experience drastic restrictions of the conformational space available, so that they exist in well-defined, thermodynamically preferred conformations.

Owing to the widespread activity in the field of photodimerization reactions, structural studies on compounds containing cyclobutane rings recently attracted wide interest. Furthermore, photodimerization of unsaturated compounds often yields crowded cyclobutanes which may possess interesting conformational properties.

In the following, we report a study of the structure and conformational preferences of the two chalcone photodimers. Although the above compounds have been long known,[1] their stereochemistry has not been worked out in detail and we have combined several techniques to investigate the various aspect of the problem.

Evidence for a correct configurational assignment is here obtained by combining the mass and nmr data relative to the two photodimers, and comparing these data with those relative to a number of related compounds of known structure. The (novel) chlorinated derivatives of the two chalcone photodimers proved useful both in the elucidation of the mass spectra and in the interpretation of the dipole moment data.

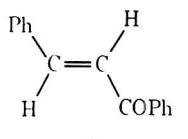
Dipole moment data and conformational energy estimates have been used to detect the conformational preferences of the photodimers.

Dipole moment data, being conformation dependent, may prove very useful in conformational studies but often do not provide unequivocal information, since different conformations may be calculated to have the same dipole moment value.[2] We have therefore found it desirable to generate a conformational energy contour map for each compound and to show that the calculated dipole moment corresponding to the energetically allowed region (preferred conformation) fits the experimental dipole moment.

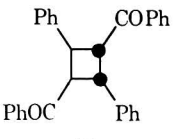
Structural Assignments

Irradiation of chalcone (I) is known to produce a dimer the structure of which depends on the reaction phase employed.[1]

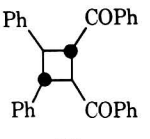
The high-melting (mp 226°) isomer, produced by solid-state irradiation, has been assigned[3] a structure II, while the low-melting (mp 126°) isomer, produced in solution, has been assigned[3] a structure III.



I



II



III

These assignments, however, were based on a complex series of chemical reactions in which the possibility of isomerizations was not eliminated, so that they appear tentative[4] at best.

(1) H. Stobbe and K. Bremer, *J. Prakt. Chem.*, **123**, 1 (1929).

(2) G. Montaudo, S. Caccamese, and P. Finocchiaro, *J. Amer. Chem. Soc.*, **93**, 4202 (1971).

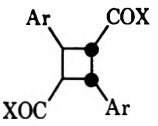
(3) P. Adler, Thesis, Rostock, 1938; *Chem. Abstr.*, **37**, 345 (1943).

(4) R. O. Kan, "Organic Photochemistry," McGraw-Hill, New York, N. Y., 1966, p 167.

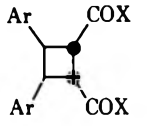
The problem has later received little attention, and the earlier[3] assignments have been incorporated in the most recent literature[5] without being subject to further scrutiny.

We have therefore reexamined the stereochemical problem by combining the mass and nmr data relative to the two photodimers and comparing these data with those relative to a number of structurally related compounds (Chart I).

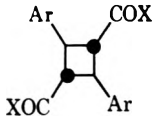
CHART I



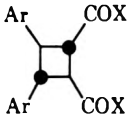
II, Ar = C_6H_5; X = C_6H_5
V, Ar = C_6H_5; X = CH_3
VI, Ar = p-ClC_6H_4; X = CH_3
VII, Ar = p-ClC_6H_4; X = C_6H_5
IX, Ar = C_6H_5; X = OH



IV, Ar = C_6H_5; X = C_6H_5
VIII, Ar = p-ClC_6H_4; X = C_6H_5
XI, Ar = C_6H_5; X = OH



X, Ar = C_6H_5; X = OH



XII, Ar = C_6H_5; X = OH

Our results confirm the α-truxillic structure (II) of the high-melting isomer, but assign a β-truxinic structure (IV) to the low-melting isomer, contrary to the earlier report of a δ-truxinic structure (III).

Fragments arising from cyclobutane ring cleavage in the mass spectra of II and VII or IV and VIII, respectively, should allow us to differentiate between the head-to-tail (truxillic) and head-to-head (truxinic) structures. In fact, the three fragments XIII, XIV, and XV should be present in the case of a truxinic structure, but only XIV is expected in the case of a truxillic structure.

$[XC_6H_4CHCHC_6H_4X]\cdot^+$ XIII $[XC_6H_4CHCHCOC_6H_5]\cdot^+$ XIV

$[C_6H_5COCHCHCOC_6H_5]\cdot^+$ XV

X = H, Cl

The mass spectrum of VIII shows fragments XIII and XIV at m/e (rel intensity) 248 (8) and 242 (100), respectively. The third fragment XV is absent because of the primary loss of benzoyl from the molecular ion. Similarly, the mass spectrum of IV shows fragments XIII and XIV at m/e 180 (28), 179 (39), 178 (26) and 208 (50), 207 (65), respectively, which confirm the truxinic (head-to-head) structure of photodimers IV and VIII. On the contrary, the mass spectrum of VII shows *only* the fragment XIV at m/e (rel intensity) 242 (30) produced by the fragmentation of a truxillic (head-to-tail) structure. In the mass spectrum of II (the parent compound of VII), beside fragment XIV at m/e (rel intensity) 208 (66), 207 (84), fragment XIII is also present at m/e (rel intensity) 180 (4), 179 (12).

However, fragment XIII is generated here starting from XIV by a rearrangement process[6,7] with loss of carbon monoxide. Remarkably, in the case of the chlorinated derivative VII, the latter process does not provide a fragment with the same m/e value of XIII, so that the diagnosis of a truxillic structure for the photodimers II and VII is unequivocal.

Furthermore, the mass spectra of V and VI show clearly that cyclobutane cleavage generates only fragment XVI, characteristic of a head-to-tail structure [for compound V at m/e (rel intensity) 146 (37), 145 (62) and for compound VI at m/e (rel intensity) 180 (67), 179 (30)]. Remarkably, no rearrangement process with loss of carbon monoxide occurs in the latter compounds.

$[XC_6H_4CHCHCOCH_3]\cdot^+$ XVI X = H, Cl

Further insight on the stereochemistry of these compounds is provided by nmr data. The high-melting chalcone photodimer (II) shows a broad singlet for the cyclobutyl protons in the nmr spectrum (Figure 1). However, addition of $Eu(fod)_3$ shift reagent removes the four-proton degeneracy, revealing a typical AA'BB' pattern (Figure 1) very similar to that of

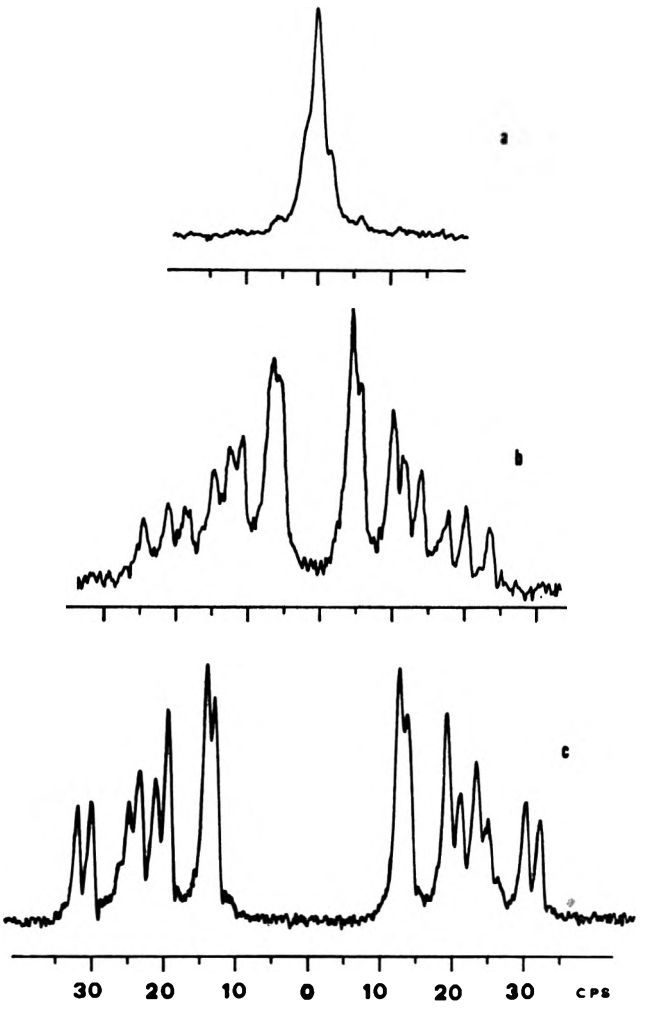


Figure 1.—Nmr spectra (cyclobutyl protons) of (a) benzalacetophenone photodimer II in $CDCl_3$; (b) benzalacetophenone photodimer II in $CDCl_3$ plus $Eu(fod)_3$; $Eu(fod)_3$/substrate = 0.25 mol/mol; (c) benzalacetone photodimer V in $CDCl_3$.

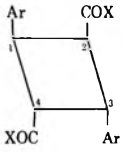
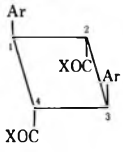
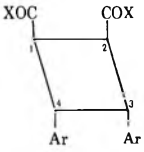
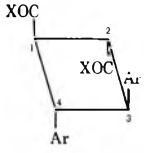
(5) H. Wynberg, M. B. Groen, and R. N. Kellogg, *J. Org. Chem.*, **35**, 2828 (1970).

(6) J. H. Beynon, G. R. Lester, and A. E. Williams, *J. Phys. Chem.*, **63**, 1861 (1959).

(7) J. H. Bowie, R. Grigg, D. H. Williams, S. O. Lawesson, and G. Schroll, *Chem. Commun.*, 403 (1965).

TABLE I

NMR DATA FOR CYCLOBUTANE RING PROTONS

	Ar	X	Compd	Chemical shifts, ppm $H_{2,4}$	$H_{1,3}$	$H_{1,2}$	$H_{3,4}$	Coupling constants, Hz $^3J_{2,3}$	$^3J_{1,2}$	$^4J_{1,3}$
	C_6H_5	OH	IX[a]	3.80	4.22			6.3	11.7	
	C_6H_5	CH_3	V	3.85	4.60			6.6	11.4	
	p-ClC_6H_4	CH_3	VI	3.86	4.61					
	C_6H_5	C_6H_5	II	4.90	4.90			6.0	11.9	
	p-ClC_6H_4	C_6H_5	VII	4.83	4.83					
	C_6H_5	OH	X[a]	3.22	3.78			9.3	9.3	
	C_6H_5	OH	XI[a]			3.96	4.57	7.85		−0.65
	C_6H_5	C_6H_5	IV			4.05	4.68	7.9		−0.4
	p-ClC_6H_4	C_6H_5	VIII			3.93	4.56			
	C_6H_5	OH	XII[a]			3.24	3.62	8.9		0.9

[a] Pyridine spectrum.

benzalacetone photodimer (V), for which a α-truxillic structure has already been demonstrated.[8,9]

The pattern of the signals for the cyclobutyl protons of the low-melting chalcone photodimer (IV) is also typical of an AA'BB' system, which requires either a plane or a twofold axis of symmetry in the molecule.

The spectral patterns of the chloro derivatives VI, VII, and VIII, closely resemble those of the respective parent compounds (Table I).

From the relationship between the magnitude of the vicinal coupling constants and dihedral angles (Karplus equation) it should be possible to determine the stereochemistry of the cyclobutyl ring substituents by deriving the values of the cis and trans vicinal couplings (^3J) from the analysis of the spectra. However, vicinal couplings in cyclobutyl systems have been found to be sensitive to substituents and strain effects.[10-13] Furthermore, they vary over a sufficient range so that some overlap between the values occurs.[10-13]

On the contrary, both theoretical[14] and experimental[10,11,12,15] evidence has been provided showing that the cis diagonal couplings (^4J) are positive, while the trans diagonal couplings have a negative sign in cyclobutyl systems.

Under these circumstances, we have attempted to obtain unequivocal stereochemical assignments by comparing the nmr cyclobutyl protons data of the chalcone photodimers with those relative to four dimers derived from *trans*-cinnamic acid (Table I, compounds IX, X, XI, XII) and to the benzalacetone photodimer (Table I, compound V), for which the cyclobutyl protons appear as a symmetric AA'BB' system. The $^3J_{1,2}$, $^3J_{2,3}$, $^4J_{1,3}$ coupling constants for compounds in Table I were obtained from the analysis of their AA'BB' subspectra.[16-18]

The α-truxillic structure of the high-melting chalcone photodimer (II) results from the close agreement of the $J_{1,2}$ and $J_{2,3}$ coupling constants with those corresponding to the α-truxillic acid (IX) and to the benzalacetone photodimer (Table I, compound V, Figure 1). The alternative ϵ-truxillic structure (X) can be ruled out since $J_{1,2}$ and $J_{2,3}$ should be equal in this case. It is interesting to note that no stereochemical deductions[5] could be based on the comparison of the chemical shift values of compound II with those of the other α-truxillic compounds (Table I), or on the appearance of its undoped spectrum (Figure 1). In fact, substitution of the hydroxyl or methyl group with a phenyl provokes in II a sensible downfield shift of the methine protons geminal to the carbonyls,[19] so that the system appears as a broad singlet at 4.90 ppm. Conformational factors seem to be responsible for

(8) J. Dekker and T. G. Dekker, *J. Org. Chem.*, **33**, 2604 (1968).
(9) G. Montaudo and S. Caccamese, *J. Mol. Struct.*, **12**, 488 (1972).
(10) V. Georgian, L. Georgian, and A. V. Robertson, *Tetrahedron*, **19**, 1219 (1963).
(11) C. H. Krauch, S. Farid, and G. O. Schenck, *Chem. Ber.*, **99**, 625 (1966).
(12) I. Fleming and D. H. Williams, *Tetrahedron*, **23**, 2747 (1967).
(13) L. Paolillo, H. Ziffer, and O. Buchardt, *J. Org. Chem.*, **35**, 38 (1970).
(14) M. Barfield, *J. Amer. Chem. Soc.*, **93**, 1066 (1971).
(15) A. Gamba and R. Mondelli, *Tetrahedron Lett.*, 2133 (1971).
(16) D. M. Grant R. C. Hirst, and H. S. Gutowsky, *J. Chem. Phys.*, **38**, 470 (1963).
(17) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. I, Pergamon Press, London, 1965, p 347.
(18) E. Lustig, E. P. Ragelis, N. Duy, and J. A. Ferretti, *J. Amer. Chem. Soc.*, **89**, 3953 (1967).
(19) The signal at 3.80 ppm in the α-truxillic acid can be assigned to the 2,4-cyclobutyl protons (Table I), based on the fact that the methine proton in isopropyl phenyl ketone resonates at 3.58 ppm.[20] This applies also to the benzalacetone photodimer, This assignment was confirmed by the analysis of some lanthanide-induced shifts data which could not be fitted on the alerntive hypothesis.[21]
(20) "High Resolution NMR Spectra Catalog, Vol. 2, Varian Associates, Palo Alto, Calif., 1963, Spectrum No. 559.
(21) G. Montaudo and S. Caccamese, to be published.

TABLE II

DIPOLE MOMENT DATA[a] IN BENZENE AT 25° OF CHALCONE PHOTODIMERS AND RELATED COMPOUNDS

Compd	a_ϵ	a_n	μ, D
IV	2.17	0.326	2.66
VIII	2.95	0.296	3.44
II	1.26	0.338	1.88
VII	1.57	0.292	2.39
V[b]	1.34	0.188	1.76

[a] $a_\epsilon = [(\epsilon_{12} - \epsilon_1)/w_2]_{w_2 \to 0}$, $a_n = [(n_{12}^2 - n_1^2)/w_2]_{w_2 \to 0}$; ϵ is the dielectric constant of the solution; ϵ_{12} is the dielectric constant of the solution, w_2 is the weight fraction of solute, n_1 is the refractive index of the solvent, and n_{12} is the refractive index of the solution; final formula of the Guggenheim procedure (see ref 2), $\mu = [0.009208 M_2 (a_\epsilon - a_n)]^{1/2}$. [b] Reference 9.

this downfield shift, as will be discussed in the next section.

Also the β-truxinic structure of the low-melting chalcone photodimer (IV) results from the close agreement (Table I) of the $^3J_{2,3}$ and $^4J_{1,3}$ coupling constants with those corresponding to the β-truxinic acid (XI) (the AA'BB' spectral patterns of the two compounds are practically superimposable). The alternative δ-truxinic structure (III) can be ruled out because of the negative sign of the $^4J_{1,3}$ constant (which indicates a trans-1,3 structure) instead of the positive value of $^4J_{1,3}$ expected for a cis-1,3 structure.

Conformational Properties

The intriguing conformational properties of the two chalcone photodimers II and IV become evident when one considers that such crowded molecules are likely to experience a drastic restriction of the conformational space available to the internal rotation of the cyclobutane substituents.

However, from the inspection of the structural models in Figure 2 one may easily realize that these molecules have several independent conformational parameters and that they are complex systems, difficult to deal with.

In spite of their complexity, the conformational properties of the two photodimers can be properly investigated by comparing the experimental dipole moments (DM) with contour maps of calculated DM as a function of the internal rotation angles, and with conformational energy contour maps.[9,22] We need a simplifying assumption to start our analysis. We shall assume a planar form for the cyclobutane ring in compounds II and IV, as found in the solid state for several 1,2,3,4-tetrasubstituted cyclobutyl derivatives.[23,24] Later, it will be seen how we can actually verify the validity of this assumption.

The experimental DM values for the compounds investigated are collected in Table II. Inspection of the structural models in Figure 2 reveals that the overall DM of the photodimers varies with the molecular conformation, since a variation of the internal rotation angles ϑ_1 and ϑ_2 causes a change in the relative orientation of the two carbonyl groups.

Contour maps of the calculated DM as a function of ϑ_1 and ϑ_2 are reported in Figures 3 and 4 for the

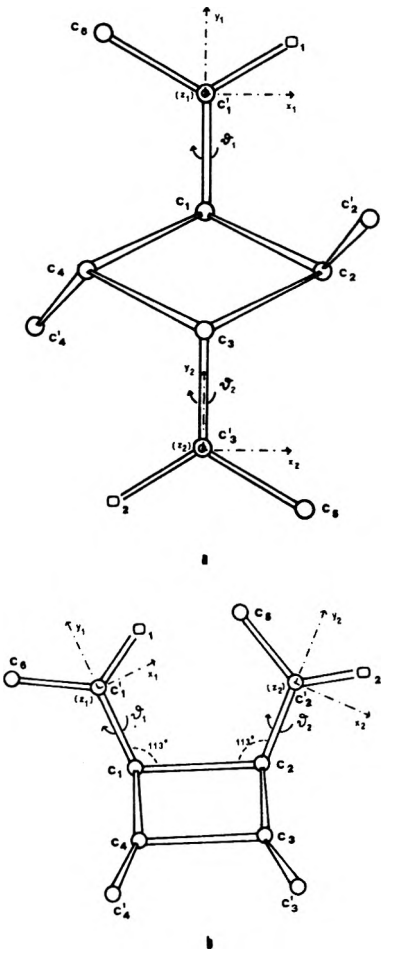


Figure 2.—Structural models and internal rotation angles of compound II (a) and compound IV (b).

photodimers II and IV, respectively. Dipole moments were calculated, for each pair of ϑ_1 and ϑ_2 values, adding vectorially the bond moments resolved into their x, y, and z components. The individual moment contributed by each carbonyl group was taken as 2.96 D[25] and its direction was assumed to be that of the C–O bond. Interatomic distances and bond angles were deduced from pertinent literature data and the cyclobutane ring was assumed to be planar.[23,24] The contour maps were generated starting from the conformations in Figure 2 and rotating the carbonyl groups clockwise; for compound II (Figure 2a) the two C–O bonds lie in parallel planes with respect to the xy (paper) plane at 45° with the $C_1'C_1C_2$ and $C_3'C_3C_4$ planes, respectively; for compound IV (Figure 2b) the two C–O bonds lie in the paper plane.

The experimental DM values for compounds II (1.88 D) and IV (2.66 D) are well below the DM values corresponding to the completely free rotation of the benzoyls (II, 3.62 D; IV 4.54 D, respectively), indicating that these molecules are likely to experience restricted rotation. However, at this stage, DM data alone are insufficient to solve unequivocally the conformational problem, since the experimental DM values of II and IV can be fitted over large regions of the maps of calculated DM in Figures 3 and 4. We have therefore attempted to complement these data with some *a priori* conformational energy estimates.

(22) G. Montaudo, P. Finocchiaro, P. Maravigna, and C. G. Overberger, *Macromolecules*, **5**, 197 (1972).

(23) C. Chang, R. F. Porter, and S. H.Bauer, *J. Mol. Struct.*, **7**, 89 (1971).

(24) T. N. Margulis, *J. Amer. Chem. Soc.*, **93**, 2193 (1971).

(25) G. Montaudo, P. Finocchiaro, and P. Maravigna, *ibid.*, **93**, 4214 (1971).

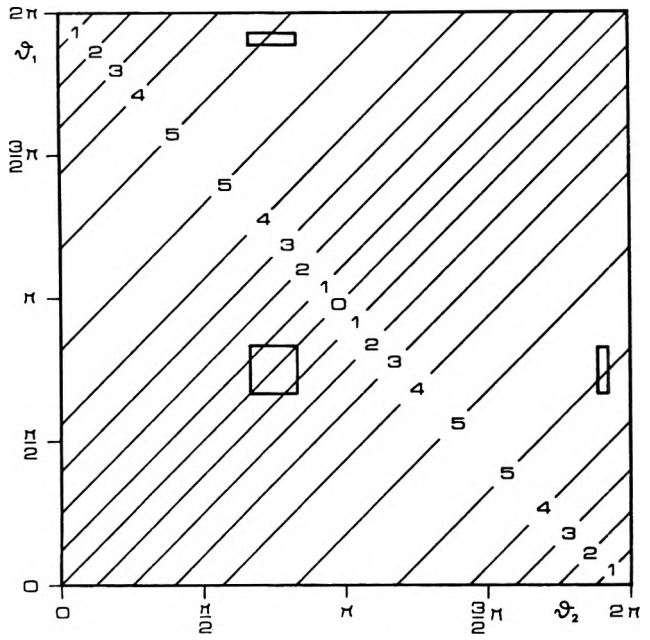


Figure 3.—Contour map of calculated dipole moment as a function of ϑ_1 and ϑ_2 internal rotation angles and, overlapped, conformationally allowed area for compound II.

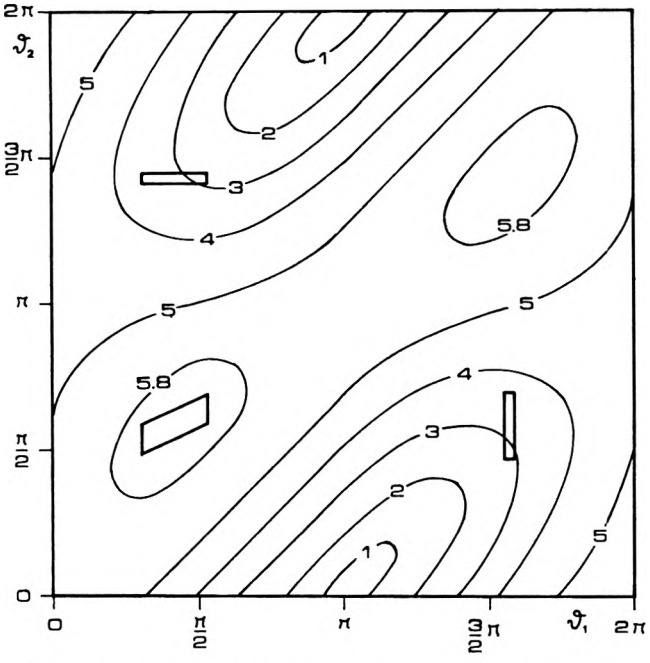


Figure 4.—Contour map of calculated dipole moment as a function of ϑ_1 and ϑ_2 internal rotation angles and, overlapped, conformationally allowed area for compound IV.

The contour maps of conformational energy relative to compounds II and IV are shown overlapping the dipole moments maps in Figures 3 and 4, respectively.[26] Only nonbonded interactions were included in this estimate. Coefficients for the pairwise Lennard-Jones potential interaction were taken from Schott and Scheraga.[27] Angular deformations, torsional potentials, and electrostatic interactions were not evaluated, so that an "exclusion map"[28] has actually been obtained and only the line delimiting the energetically allowed area is shown in the figures. The maps were generated using Dreiding models, an approximation justified by the above assumptions.[29]

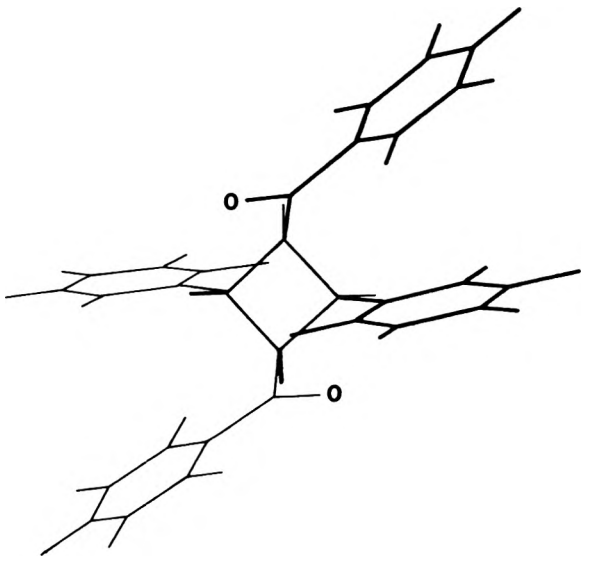


Figure 5.—Preferred conformation of compound II viewed along an axis normal to the cyclobutane ring.

On evaluating our results, it should be noted that for the photodimer II the experimental DM value (1.88 D, Table II) can be fitted over a wide region of the DM contour map, but only two narrow regions of the conformational space are available to the molecule on energetic grounds (Figure 3).[31] Furthermore, only one of these regions ($\vartheta_1 \cong 145$, $\vartheta_2 \cong 145$) is compatible with the experimental DM value and it is therefore chosen as the preferred conformation (Figure 5). Remarkably, the benzalacetone photodimer V, which possess an α-truxillic structure as the chalcone photodimer II, has been found[9] to exist in the same conformation as II, and has a measured DM value of 1.76 D.[9] The preferred conformation of photodimer II (Figure 5) also accounts for the downfield shift observed in the nmr of II, as compared to V, of the methine protons geminal to the carbonyls. In fact, the phenyl groups are held in such a position to operate a deshielding effect on the methine protons (Figure 5). The conformational preference of the chlorinated photodimer VII should be identical with that of the parent compound II, since the chloro atoms are in a para position.

The individual moments contributed by the chlorine atoms in compound VII should cancel each other if the cyclobutane ring is fixed in the planar form. A small

(26) Actually, these molecules have four internal rotation angles. However, for compound II the rotation of the two phenyl groups is severely hindered (thermodynamically restricted rotation) so that they can be considered nearly fixed in the positions shown in Figure 5. In compound IV the internal rotation of the two phenyls does not interfere with that of the benzoyl groups. However, the two rings hinder each other; in Figure 6 they are represented in one of the two *equivalent* positions that they can assume (the other is enantiomeric).

(27) R. A. Schott and H. A. Scheraga, *J. Chem. Phys.*, **45**, 2091 (1966); **46**, 4410 (1967).

(28) P. J. Flory, "Statistical Mechanics of Chain Molecules," Interscience, New York, N. Y., 1969, p 253, and references cited therein.

(29) The energetically allowed regions in Figures 5 and 6 are slightly underestimated, since angular deformations of the bonds were neglected in generating the maps. Furthermore, the wideness of the allowed area is also function of the value of the carbonyl–phenyl torsional angle. On the basis of the existing literature data,[30] we have selected a value of 30°, which also permits generation of the widest allowed area possible. It should be remarked that, given the extremely narrow regions energetically allowed, the assumptions made in generating the energy maps are unlikely to affect significantly the accuracy of our analysis.

(30) A. G. Pinkus and H. C. Custard, *J. Phys. Chem.*, **74**, 1042 (1970), and references cited therein.

(31) Actually, three regions are shown as allowed in Figure 3, but the two regions centered at $\vartheta_1 \cong 350$, $\vartheta_2 \cong 145$ and $\vartheta_1 \cong 145$, $\vartheta_2 \cong 350$, respectively, are enantiomeric.

difference (0.51 D, Table II) is actually measured between the two compounds, which seems to indicate either a certain degree of puckering or a libration of the ring around the planar form. Alternatively, one could attribute the DM difference to local field effects generated by the polar chlorine atoms. We favor the idea that to consider the cyclobutane ring as being planar is sufficiently accurate in the present case.

The conformational preference of the β-truxinic photodimer IV can be assigned by an analysis entirely similar to that carried out in the case of II. Data in Figure 4 show that the energetically allowed regions are very narrow; only one of them ($\vartheta_1 \cong 75$, $\vartheta_2 \cong 260$)[32] is compatible with the experimental DM value (Table II) and it is therefore chosen as the preferred conformation (Figure 6). Interestingly, in the two rotamers of this conformation, the two vicinal benzoyls are enantiotopic and therefore must exchange.

Also in this case the conformational preference of the chlorinated derivative VIII should be identical with that of the parent compound IV. However, the overall DM value here is influenced by the chlorine substitution and the conformational preference of VIII cannot be simply deduced by comparing its experimental DM value with that of the unsubstituted photodimer II.

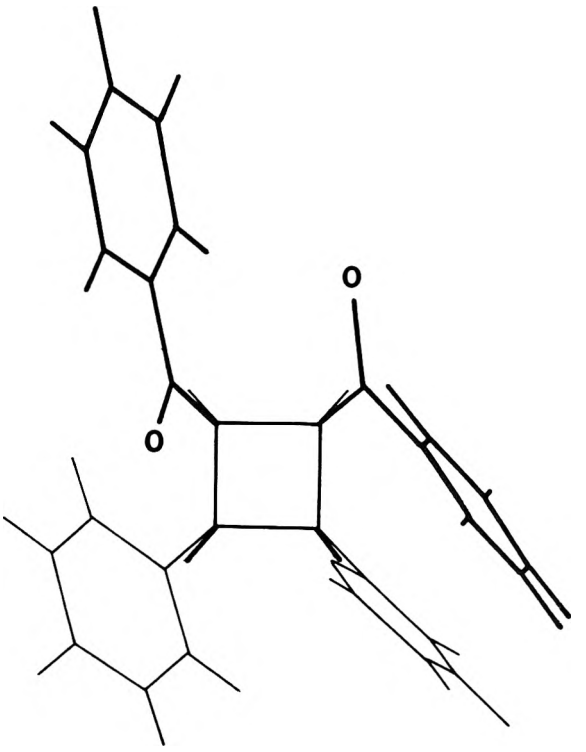


Figure 6.—Preferred conformation of compound IV viewed along an axis normal to the cyclobutane ring.

Experimental Section

Uv spectra were recorded in 95% ethanol on a Hitachi Perkin-Elmer EPS-3T spectrophotometer. The ir spectra were determined in Nujol using a Perkin-Elmer 237 spectrophotometer. The nmr spectra were obtained in deuteriochloroform (unless otherwise indicated) with a Varian A-60D instrument using tetramethylsilane as the internal standard. They are reported in parts per million on the δ scale. $Eu(fod)_3$ (Sievers reagent[33]) obtained from Alfa Inorganics was used without further purification. The mass spectra were obtained at 70 eV by direct injection into the ion source of a Varian MAT CH 7 mass spectrometer. The dielectric constants were measured in benzene (99.9% Schuchardt, dried over molecular sieves) at 25 ± 0.02° with a DM 01 Dipolmeter WTW working at 2 MHz. For the refractive index measurements a differential refractometer BP 2000 V Brice-Phoenix was used, which measured the difference in refractive index between a solution and benzene as solvent, at 25°. From these data, dipole moments have been calculated by a technique previously described.[2] Molecular weight determinations were obtained by vapor phase osmometry, in *o*-dichlorobenzene at 130° using a Mechrolab 302 thermoelectric osmometer. Melting points (uncorrected) were obtained in glass capillary tubes sealed under vacuum.

Synthetic Procedures.—The following α,β-unsaturated ketones were prepared according to the literature: benzalacetone,[34] *p*-chlorobenzalacetone,[35] benzalacetophenone,[34] *p*-chlorobenzalacetophenone.[36] According to the literature also these acids were prepared: α-truxillic acid,[37] ε-truxillic acid,[38] β-truxinic acid,[39] δ-truxinic acid.[40]

The irradiation experiments were carried out using a Q 1200 Quarzlampengesellschaft (Hanau, West Germany) medium-pressure mercury lamp. For solid-state photodimerization the powdered compounds were irradiated in air from 30 cm with a Pyrex-jacketed lamp, to cut off lower wavelengths. For solution photodimerization, the solution of the compounds, previously bubbled with nitrogen, was exposed to the radiation of the unfiltered lamp in a Pyrex flask placed at a distance of 40–50 cm. Reaction was monitored during irradiation by uv spectra. Using this irradiation apparatus, the following photodimers were prepared: *trans,cis,trans*-1,3-diacetyl-2,4-diphenylcyclobutane (V),[40] *trans,cis,trans*-1,3-dibenzoyl-2,4-diphenylcyclobutane (II),[1] *trans,cis,trans*-1,4-diphenyl-2,3-dibenzoylcyclobutane (IV).[1]

***trans,cis,trans*-1,3-Diacetyl-2,4-di(4-chlorophenyl)cyclobutane (VI).**—*p*-Chlorobenzalacetone (10 g) was irradiated in the solid state. After 60 days, the brownish material was dissolved in acetone and chromatographed over silica gel. Elution with hexane–acetone (9:1) afforded several central fractions which showed no fluorescence to Wood light by tlc. Evaporation of the solvent and recrystallization from hexane gave 100 mg of a compound melting at 194–196°: ν_{CO} 1700 cm^{-1}; mol wt calcd for $C_{20}H_{18}Cl_2O_2$, 361.3; found, 358.0.

***trans,cis,trans*-1,3-Dibenzoyl-2,4-di(4-chlorophenyl)cyclobutane (VII).**—*p*-Chlorobenzalacetophenone (5 g) was irradiated in the solid state. After 22 days, the yellow-orange product was crystallized from an ethanol–dioxane mixture as white crystals (400 mg): mp 257–259°; ν_{CO} 1671 cm^{-1}; mol wt calcd for $C_{30}H_{22}Cl_2O_2$, 485.4; found, 470.1.

***trans,cis,trans*-1,4-Di(4-chlorophenyl)-2,3-dibenzoylcyclobutane (VIII).**—A solution of *p*-chlorobenzalacetophenone (7 g) in 25 ml of chloroform was irradiated, adding a crystal of iodine, for 9 days in a Pyrex flask. The solvent was evaporated as the yellow-orange residue, treated with a mixture of acetone–hexane, and chromatographed over silica gel. Elution with hexane–acetone (9:1) afforded several fractions, tested by tlc. Similar fractions were collected and concentrated. On standing, 300 mg of a white powder precipitated. Recrystallization from ethanol gave white crystals: mp 113–114°; ν_{CO} 1689, 1666 cm^{-1}; mol wt calcd for $C_{30}H_{22}Cl_2O_2$, 485.4; found, 478.2.

All the compounds studied analyzed correctly by elemental analysis.

Mass Spectra.—Only significant peaks are reported (m/e > 164). For chlorinated compounds only the lowest ions of the isotopic clusters are given: VI, 360, 342, 317, 302, 180, 165, 145; VII, 484, 466, 379, 365, 242, 214, 207, 179, 165; II, 416, 398, 311, 296, 208, 207, 180, 179, 178, 165; VIII, 484, 466, 379, 248, 242, 214, 207, 179, 178, 165; IV, 416, 398, 311, 296, 208, 207, 180, 179, 178, 165.

(32) Actually, three regions are shown as allowed in Figure 4, but the two regions centered at $\vartheta_1 \cong 75$, $\vartheta_2 \cong 260$ and $\vartheta_1 \cong 260$, $\vartheta_2 \cong 75$, respectively, are enantiomeric.

(33) R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971).

(34) H. Gilman and A. H. Blatt, Ed., "Organic Syntheses," 2nd ed, Wiley, New York, N Y., 1941, pp 77–78.

(35) R. E. Lutz, T. A. Martin, J. F. Codington, T. M. Amacker, R. K. Allison, N. H. Leake, R. J. Rowlett, J. D. Smith, and J. W. Wilson, *J. Org. Chem.*, **14**, 982 (1949).

(36) E. Weitz and A. Scheffer, *Chem. Ber.*, **54**, 2327 (1921).

(37) A. Schönberg, "Preparative Organic Photochemistry," Springer-Verlag, Berlin, 1968, p 85.

(38) R. Stoermer and E. Emmel, *Chem. Ber.*, **53**, 497 (1920).

(39) R. Stoermer and F. Scholtz, *ibid.*, **54**, 85 (1921).

(40) A. Butenant, L. Karlson-Poschmann, G. Failer, U. Schiedt, and E. Biekert, *Justus Liebigs Ann. Chem.*, **575**, 123 (1952).

Nmr.—II, 4.90 (4 H), 7.23 (16 H), 7.77 (4 H); IV, 4.05–4.68 (4 H), 7.30 (16 H), 7.99 (4 H); V, 1.61 (6 H), 3.85–4.60 (4 H), 7.25 (10 H); VI, 1.70 (6 H), 3.86–4.61 (4 H), 7.33 (8 H); VII, 4.83 (4 H), 7.25 (14 H), 7.75 (4 H); VIII, 3.93–4.56 (4 H), 7.34 (14 H), 7.85 (4 H).

Registry No.—II, 24825-08-9; IV, 37676-14-5; V, 16607-22-0; VI, 37676-16-7; VII, 37676-17-8; VIII, 37676-18-9; IX, 490-20-0; X, 528-38-1; XI, 528-34-7; XII, 528-33-6; *p*-chlorobenzalacetone, 3160-40-5.

Neighboring-Group Participation in Carbohydrate Chemistry. IV.[1] Neighboring-Group Reaction of the 6-Benzamido Group in a Nucleophilic Displacement of a 5-Mesylate[2]

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The neighboring-group reaction of the 6-benzamido group in the nucleophilic displacement of a 5-mesylate was demonstrated. Refluxing of an *N,N*-dimethylformamide solution of 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-methylsulfonyl-α-D-glucofuranose (**12**) with anhydrous potassium acetate gave a complex reaction mixture from which the following three products were isolated and characterized: 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose (**15**, 5%), 2-phenyloxazoline derivatives of 6-amino-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose (**14b**, 41%), and 6-amino-3,6-dideoxy-1,2-*O*-isopropylidene-β-L-*threo*-hex-3-enofuranose (**22**, 18%). Heating of an ethanolic solution of **12** with 1 mol of sodium ethoxide gave **14b** (58%).

The neighboring-group participation of a carboxamido group in the nucleophilic displacement of an alkyl and/or aryl sulfonate bound to a vicinal carbon atom is an extensively studied reaction[3,4] which has been frequently utilized in carbohydrate chemistry for the synthesis of various amino sugar derivatives.[3,4] Either the carbonyl oxygen or the nitrogen atom of the carboxamido group (**1**) can function as the nucleophile in the reaction,[5] giving an oxazoline (**2**) or an aziridine (**3**) derivative as an intermediate. Whether the participation of the carboxamido group will occur with the formation of the five- (**2**) or three-membered ring intermediate (**3**) seems to be controlled by stereochemical factors. However, in some *N*-aryl substituted amides, an electronic factor may play an important role as well.[6] A recent report has described the participation of the *N,N*-dialkyl carboxamido group with the possible formation of an imino-α-lactone (**5**) or an α-lactam (**6**) intermediate.[7]

The apparent lack of participation of the 6-benzamido group when methyl 2,6-dibenzamido-2,6-dideoxy-3-*O*-methyl-5-*O*-methylsulfonyl-β-D-glucofuranoside (**7**) was treated with sodium benzoate in *N,N*-dimethylformamide, or sodium acetate in ethanol,[8] was rather surprising. Equally puzzling was the absence of participation of the 6-benzamido group in the reaction of 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-methylsulfonyl-α-D-glucofuranose (**12**) and 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-5-*O*-methylsulfonyl-α-D-glucofuranose (**13**) with sodium ethoxide in ethanol at elevated and/or room temperature.[9] Since the obtained syrups, which could not be purified, did not exhibit the NH absorption peak in the 3300–3200-cm^{-1} region in the infrared spectrum, Hough, *et al.*,[9] concluded that an ethyleneimine derivative was not formed. They assumed instead that elimination of the 5-*O*-methylsulfonyl group with a hydrogen atom from C-6 had occurred, since this was known to be a facile reaction.[10] The formation of the corresponding oxazoline derivative **14b** was not mentioned. The unexplainable absence of participation of the 6-benzamido group in the displacements described above prompted us to reinvestigate the whole problem. The obtained results are presented in this paper.

Results and Discussion

As a model substance for our studies, 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-methylsulfonyl-α-D-glucofuranose (**12**)[9] was employed.

Refluxing of an *N,N*-dimethylformamide solution of **12** with anhydrous potassium acetate for 1 hr gave a complex reaction mixture, from which, after both column and preparative thin layer chromatography using 4:1 ether–benzene and 95:5 benzene–methanol solvent mixtures, three products were isolated and characterized.

The first product (**14**, 41%) was a white, crystalline solid, mp 132–133°, for which the infrared spectrum did not show an absorption peak in the 3300-cm^{-1} region, typical for the amide NH (NH stretch).[11a] However, there was a strong absorption band at 1650 cm^{-1}, indicative of either an amide carbonyl group (C=O stretch)[11a] or a carbon–nitrogen double bond (C=N stretch).[11b,12] Two bands at 1602 and 1580

(1) Part III: M. Miljković, D. Miljković, A. Jokić, V. Andrejević, and E. A. Davidson, *J. Org. Chem.*, **37**, 2536 (1972).

(2) This work was supported by a grant (AM12074) from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

(3) L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 127, 143 (1967).

(4) B. Capon, *Quart. Rev. Chem. Soc.*, **18**, 71 (1964).

(5) T. Taguchi and M. Kojima, *J. Amer. Chem. Soc.*, **81**, 4316 (1959).

(6) H. W. Heine, P. Love, and J. L. Bove, *ibid.*, **77**, 5420 (1955).

(7) M. Miljković, D. Miljković, A. Jokić, V. Andrejević, and E. A. Davidson, *J. Org. Chem.*, **36**, 3218 (1971).

(8) W. Meyer zu Reckendorf, *Tetrahedron*, **19**, 2033 (1963); *Angew. Chem.*, **75**, 573 (1963); L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 137 (1967).

(9) D. H. Buss, L. D. Hall, and L. Hough, *J. Chem. Soc.*, 1616 (1965).

(10) R. E. Gramera, T. R. Ingle, and R. L. Whistler, *J. Org. Chem.*, **29**, 878 (1964).

(11) (a) N. B. Colthup, L. H. Daly, and S. E. Wiberley, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964, p 263; (b) p 232; (c) p 224; (d) p 309.

(12) W. Meyer zu Reckendorf and W. A. Bonner, *Chem. Ber.*, **95**, 1917 (1962).

cm^{-1} could be interpreted as the "quadrant stretching" vibrations of a benzene ring conjugated with an unsaturated carbon atom (C=O or C=N group).[11c] A band at 1260 cm^{-1} was indicative of the presence of a –COC= grouping,[13] and at 1347 and 1180 cm^{-1} there were two strong bands ascribed to the methylsulfonyl group (asymmetric and symmetric SO_2 stretch).[11d] Since the nmr spectrum of **14** indicated the presence of only one methylsulfonyl group (three-proton singlet at δ 3.11), the loss of the other methylsulfonyl group, which was neither eliminated nor displaced by acetate (a conclusion based on the ir and the nmr spectrum of **14**), could be explained only if the compound **14** were either an aziridine **14a** or an oxazoline **14b** derivative of L-idose. These two derivatives could readily be formed by intramolecular displacement of the 5-*O*-methylsulfonyl group by the amide nitrogen or oxygen atom. The microanalytical data were in excellent agreement with the molecular formula for **14** ($C_{17}H_{21}NO_7S$).

Since the nmr spectrum of **14** did not show a resonance absorption in the 1.6–2.0-ppm region, characteristic of the methylene and methyne protons of an aziridine,[14] structure **14a** was excluded.

The assigned structure, **14b**, was proven by subjecting **14** to a mild acid hydrolysis with aqueous 75% acetic acid, expecting that under these experimental conditions the oxazoline ring should open,[15,16] whereas the 1,2-*O*-isopropylidene group should remain unchanged.[17] Treatment of **14** with aqueous 75% acetic acid at room temperature for 22 hr gave a product **15**, the infrared spectrum of which showed strong absorption bands at 3425 and 1650 cm^{-1}. The first peak was apparently due to the presence of an amide NH group (NH stretch), whereas the second peak resulted from the presence of an amide carbonyl group (C=O stretch). The presence of the doublet at 1600 and 1580 cm^{-1} was indicative of the existence of conjugation of the benzene ring with an unsaturated carbon atom, presumably C=O[11c] (benzoyl group). The infrared as well as the nmr data strongly suggest that **15** is 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose. This was chemically proven by comparing **15** with authentic 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose synthesized independently from 1,2-*O*-isopropylidene-β-L-idofuranose (**16**) according to the following scheme. Treatment of an acetone solution of **16** with freshly fused zinc chloride and 85% phosphoric acid gave 1,2:5,6-di-*O*-isopropylidene-β-L-idofuranose (**17**)[18] (48%), which upon mesylation with methanesulfonyl chloride in pyridine afforded the corresponding 3-*O*-methylsulfonyl derivative **18** (94%). Selective hydrolysis of the 5,6-*O*-isopropylidene group in **18** with 75% aqueous acetic acid at room temperature gave 1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose (**19**) (90%), which upon tosylation of the primary C-6 hydroxyl group with *p*-toluenesulfonyl chloride in pyridine afforded the 6-*O*-*p*-tolylsulfonyl derivative **20** (63%). An ethanolic solution of **20** on treatment with an ethanolic solution of dry ammonia at room temperature gave **21**, which was not further purified, but directly benzoylated with 1 mol of benzoyl chloride. The benzoylated product, after chromatography on silica gel (elution with an 85:15 benzene–methanol solvent mixture) and recrystallization from benzene–methanol, proved to be identical (mixture melting point, ir and nmr spectra) with compound **15**.

The second product (5%) isolated from the original reaction mixture was a white, crystalline solid, mp 198°, identical with the synthetically obtained 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose (**15**), described above (mixture melting point, ir and nmr spectra).

The third product (**22**, 18%) was also a white, crystalline solid, mp 82.5–83°. This compound did not show an absorption band in the 3300-cm^{-1} region in the infrared spectrum, which is typical for the amide NH stretching, again suggesting that the 6-benzamido group originally present in **12** was chemically altered. The strong absorption band at 1650 cm^{-1}, the doublet at 1602 and 1580 cm^{-1}, and the peak at 1248 cm^{-1} were all indicative of the presence of an oxazoline ring, since the first peak could be assigned to the C=N stretch, the doublet to the "quadrant stretching" vibrations of the benzene ring conjugated with C=N, and the last peak to the presence of the –COC= grouping. In addition to a five-proton multiplet at δ 8.1–7.2 ppm and a six-proton singlet at 1.46, due to the presence of phenyl and isopropylidene group, there were three groups of resonance peaks in the nmr spectrum of **22**, in the relative ratio 1:3:2. The one-proton "complex" doublet at δ 6.13 ppm ($J_{1,2}$ = 5.8 Hz) was apparently due to the anomeric proton H-1, the two-proton quartet at 4.16 ($J_{5,6}$ = 9.0 and $J_{6,6'}$ = 3.0 Hz) corresponds to the C-6 methylene protons, whereas the group of peaks in the 5.4–5.0-ppm region (three protons) was probably due to the H-2, H-3, and H-5 protons [a peak at δ 5.35 (H-3), triplet at 5.20 ($J_{5,6}$ = 9.0 Hz, H-5), and an unresolvable resonance signal around 5.30 (H-2)]. These spectroscopic data, as well as the striking similarity of the nmr spectrum of **22** with the nmr spectrum of 6-*O*-acetyl-5-*O*-benzoyl-3-deoxy-1,2-*O*-isopropylidene-β-L-*threo*-hex-3-enofuranose,[19] strongly suggest that **22** is the 2-phenyloxazoline derivative of 6-amino-3,6-dideoxy-1,2-*O*-isopropylidene-β-L-*threo*-hex-3-enofuranose. The microanalytical data were in excellent agreement with the proposed structure (**22**). The complexity of the anomeric proton doublet in **22** is possibly caused by virtual coupling to H-3 which, based on these and previously reported examples,[1,19] seems to be typical for the 1,2-*O*-isopropylidene-1,2-dihydro-4-substituted furans.

Heating of an ethanolic solution of **12** with 1 mol of

(13) W. Seeliger, E. Aufderhaar, W. Diepers, R. Feinauer, R. Nehring, W. Thier, and H. Hellman, *Angew. Chem.*, **78**, 913 (1966).

(14) S. J. Brois, *J. Org. Chem.*, **27**, 3532 (1962); N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963, Spectrum No. 372; L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 199, and references cited therein; F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 362.

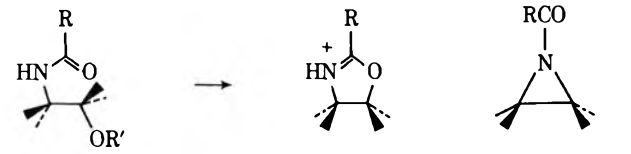
(15) J. A. Frump, *Chem. Rev.*, **71**, 483 (1971).

(16) The opening of the aziridine ring, as in **14a**, under these experimental conditions is highly unlikely. If, however, it does occur, the product should be 5-benzamido-5-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose and/or its 6-*O*-acetyl derivative.

(17) A. N. DeBelder, *Advan. Carbohyd. Chem.*, **20**, 237 (1965), and references cited therein.

(18) N. Baggett and R. W. Jeanloz, *J. Org. Chem.*, **28**, 1845 (1963).

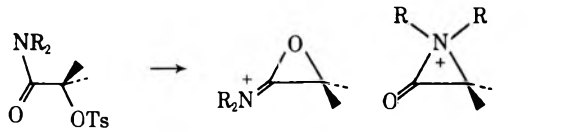
(19) M. Miljković, A. Jokić, and E. A. Davidson, *Carbohyd. Res.*, **17**, 155 (1971).



1, R′ = Ts, Ms
R = alkyl, aryl

2, R = alkyl, aryl

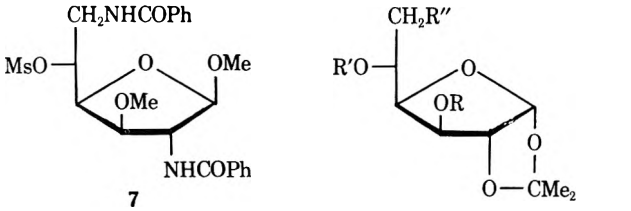
3, R = alkyl, aryl



4, R = alkyl

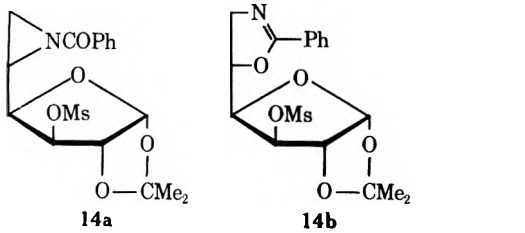
5, R = alkyl

6, R = alkyl



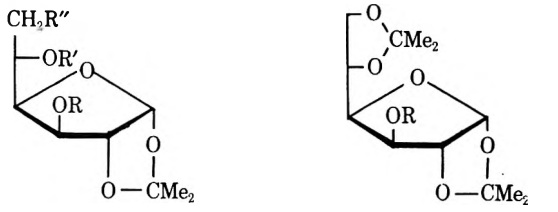
7

8, R = R′ = H; R″ = OH
9, R = R′ = H; R″ = *p*-$CH_3C_6H_4SO_3$
10, R = R′ = H; R″ = NH_2
11, R = R′ = H; R″ = C_6H_5CONH
12, R = R′ = Ms; R″ = C_6H_5CONH
13, R = H; R′ = Ms; R″ = C_6H_5CONH



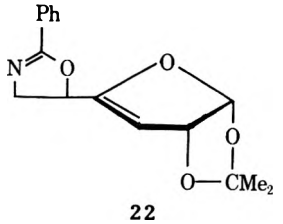
14a

14b



15, R = Ms; R′ = H; R″ = C_6H_5CONH
16, R = R′ = H; R″ = OH
19, R = Ms; R′ = H; R″ = OH
20, R = Ms; R′ = H; R″ = $CH_3C_6H_4SO_2$
21, R = Ms; R′ = H; R″ = NH_2

17, R = H
18, R = Ms



22

sodium ethoxide at 60° for 1 hr gave the oxazoline derivative **14b** in 58% yield (mixture melting point, ir, and [α]D identical with those of the 2-phenyloxazoline derivative of 6-amino-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose, described earlier). As opposed to findings of Hough, *et al.*,[9] the oxazoline derivative **14b** was easy to isolate from the crude reaction mixture by chromatography on silica gel (elution with 3:1 benzene–acetone solvent mixture).

The results presented above clearly demonstrate that the nucleophilic displacement of 5-methylsulfonate in **12** does proceed *via* the participation of the 6-benzamido group. The formation of the oxazoline derivative when an *N*,*N*-dimethylformamide solution of **12** is refluxed with anhydrous sodium acetate, or when an ethanolic solution of **12** is heated at 60° with sodium ethoxide, is evidently a strongly favored reaction, in comparison with the formation of the N-acylated aziridine derivative. The direct displacement product, 5-*O*-acetyl-6-benzamido-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose, was not isolated, although its presence in the reaction mixture was not excluded since several other products present in low yield were not characterized.

Experimental Section

General.—The silica gel used for all column chromatographies was E. Merck (Darmstadt, Germany) silica gel, grain size <0.08 mm. The melting points are uncorrected. Optical rotations were determined with a Cary 60 spectropolarimeter in a 1.0-cm cell. The ir spectra were recorded with Perkin-Elmer infrared spectrophotometers, Models 337 and 267; the nmr spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Chemical shifts (δ) are expressed in parts per million.

Treatment of 6-Benzamido-6-deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-methylsulfonyl-α-D-glucofuranose (12) with Potassium Acetate in Refluxing *N*,*N*-Dimethylformamide.—An *N*,*N*-dimethylformamide solution (70 ml) containing 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-methylsulfonyl-α-D-glucofuranose (**12**, 1.0 g, 2.09 mmol) and anhydrous potassium acetate (1.00 g, 12 mmol) was heated at reflux for 60 min. The reaction mixture was cooled to room temperature and diluted with water (150 ml) and the solution was extracted with three 200-ml portions of benzene. The combined benzene extracts were washed with water and dried over anhydrous magnesium sulfate, the benzene was removed *in vacuo*, and the oily residue (716 mg) was chromatographed on silica gel (100 g). Elution with 4:1 ether–benzene gave three fractions.

The first fraction (166 mg) after rechromatography on silica gel (16 g) and elution with 95:5 benzene–methanol afforded the unsaturated product **22** (108 mg, 18%), which was recrystallized from ether–hexane (needles): mp 82.5–83°; $[\alpha]^{27}D$ −136° (*c* 0.42, $CHCl_3$); ir ($CHCl_3$) 1650 (C=N stretch), 1635 (shoulder, C=C stretch), 1602 and 1580 ("quadrant stretching" vibrations of the benzene ring conjugated with C=N), and 1248 cm^{-1} (–COC= group); nmr ($CDCl_3$) δ 8.1–7.2 (m, 5, phenyl), 6.13 (d, $J_{1,2}$ = 5.8 Hz, 1, H-1), 5.35 (H-3), *ca.* 5.30 (H-2), 5.20 (t, $J_{5,6}$ = 9.0 Hz, 1, H-5), 4.16 (q, $J_{5,6}$ = 9.0 and $J_{6,6'}$ = 3.0 Hz, 2, H-6 and H′-6), 1.46 (s, 6, Me of Ip).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96; N, 4.88. Found: C, 66.80; H, 6.01; N, 4.77.

The second fraction, comprising less than 10% yield, contained at least three components and was not studied further.

The third fraction (397 mg) was rechromatographed on silica gel (30 g). Elution with 95:5 benzene–methanol gave two components, which were further purified by preparative thin layer chromatography using the same solvent mixture (95:5 benzene–methanol) for development. The first product was recrystallized from ether to give 332 mg (41%) of pure **14b** (white needles): mp 132–133°, $[\alpha]^{27}D$ −55° (*c* 0.65, $CHCl_3$); ir ($CHCl_3$) 1650 (C=N stretch), 1635 (shoulder, C=C stretch), 1602 and 1580 ("quadrant stretching" vibrations of the benzene ring conjugated with C=N), 1347 and 1180 (asymmetric and symmetric SO_2 stretch), and 1260 cm^{-1} (–COC= group); nmr ($CDCl_3$) δ 8.1–7.2 (m, 5, phenyl), 6.08 (d, $J_{1,2}$ = 4.3 Hz, 1, H-1), 5.16 (d, $J_{3,4}$ = 3.0 Hz, 1, H-3), 4.73 (complex t, $J_{5,6}$ = 7.0 Hz, 1, H-5), 4.70 (d, $J_{1,2}$ = 4.3 Hz, 1, H-2), *ca.* 4.3–3.6 (m, 2, H-6 and H′-6), 3.1 (s, 3, Ms), 1.50 and 1.33 (two s, 6, Me from Ip).

Anal. Calcd for $C_{17}H_{21}NO_7S$: C, 53.26; H, 5.52; N, 3.65; S, 8.37. Found: C, 53.39; H, 5.44; N, 3.74; S, 8.24.

The second component, **15**, after recrystallization from benzene–methanol (needles, 45 mg, 5%) showed mp 197.5–198°; $[\alpha]^{27}D$ −30° (*c* 0.20, $CHCl_3$); ir (KBr) 3425 (OH and NH stretch), 1650 (amide C=O stretch), 1590 and 1570 ("quadrant stretching" vibrations of the benzene ring conjugated with C=O), 1335 and 1185 (asymmetric and symmetric SO_2 stretch); nmr (pyridine-d_5) δ 8.3–7.3 (m, 5, phenyl), 6.30 (d, $J_{1,2}$ = 4.0 Hz, 1, H-1), *ca.* 5.8 (broad s, 1, H-3), 5.33 (d, $J_{1,2}$ = 4.0 Hz, 1, H-2), 5.0–4.6 (broad peak, H-4, H-6, and H′-6), 4.10 (t, $J_{5,6}$ = 6.0 Hz, 1, H-5), 3.73 (s, 3, Ms), 1.43 and 1.28 (two s, 6, Me from Ip).

Anal. Calcd for $C_{17}H_{23}NO_8S$: C, 50.87; H, 5.78; N, 3.49; S, 7.98. Found: C, 51.10; H, 6.06; N, 3.37; S, 8.09.

1,2:5,6-Di-*O*-isopropylidene-β-L-idofuranose (17).—To a solution (30 ml) of 1,2-*O*-isopropylidene-β-L-idofuranose (**16**) (2.000 g) in anhydrous acetone, freshly powdered and melted $ZnCl_2$ (133 mg) was added. After the solution was cooled, 5 drops of 85% H_3PO_4 was added and the reaction mixture was stirred at room temperature for 22 hr. A saturated solution of $NaHCO_3$ (20 ml) was then added, the precipitated salts were removed by filtration, and the filtrate was concentrated *in vacuo*. The white, crystalline (needles) material which separated was removed by filtration (206 mg of **17**), and the aqueous filtrate was extracted with three 50-ml portions of chloroform. The combined extracts were washed with water and dried over anhydrous Na_2SO_4, and the chloroform was removed *in vacuo*. The residue (2.160 g) after chromatography on silica gel (90 g) and elution with 4:1 benzene–acetone gave 921 mg of **17**, an overall yield of 1.127 g (48%). The further purification of **17** was effected by recrystallization from ether–cyclohexane, mp 155–156°, $[\alpha]^{27}D$ −32° (*c* 1.0, $CHCl_3$).[20]

1,2:5,6-Di-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose (18).—A pyridine solution (50 ml) containing 1,2:5,6-di-*O*-isopropylidene-β-L-idofuranose (**17**) (350 mg, 1.35 mmol) was cooled to −10° and methanesulfonyl chloride (1.0 ml, 13.5 mmol) was added dropwise. The reaction mixture was kept at −10° for 10 min, and then for 17 hr at room temperature. The excess methanesulfonyl chloride was destroyed by addition of methanol (10 ml) to the cooled reaction mixture. Removal of the pyridine–methanol solvent mixture *in vacuo* afforded a crystalline mass, which was dissolved in water (30 ml). The water solution was extracted with three 50-ml portions of chloroform and the combined extracts were washed successively with water, 2% H_2SO_4, and again with water. After drying over anhydrous Na_2SO_4, chloroform was removed *in vacuo*, and the yellowish, crystalline residue (460 mg) was chromatographed on silica gel (30 g). Elution with 3:2 hexane–ethyl acetate and recrystallization from ether gave 427 mg (94%) of pure **18**: mp 138.5–139.5°; $[\alpha]^{27}D$ −27° (c 1.0, $CHCl_3$); ir ($CHCl_3$) 1352 and 1180 cm^{-1} (asymmetric and symmetric SO_2 stretch); nmr ($CDCl_3$) δ 6.03 (d, $J_{1,2}$ = 4.0 Hz, 1, H-1), 5.05 (d, $J_{3,4}$ = 2.2 Hz, 1, H-3), 4.80 (d, $J_{1,2}$ = 4.0 Hz, 1, H-2), 4.5–3.6 (unresolved group of peaks, 4, H-4, H-5, H-6, and H′-6), 3.10 (s, 3, Me from Ms), 1.53, 1.48, 1.39, and 1.36 (four s, 12, Me from Ip).

Anal. Calcd for $C_{13}H_{22}O_8S$: C, 46.15; H, 6.56; S, 9.48. Found: C, 46.32; H, 6.43; S, 9.54.

1,2-*O*-Isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose (19).—A solution of **18** (520 mg) in 75% aqueous acetic acid (80 ml) was kept at room temperature for 15 hr. The solvent was then removed *in vacuo* and the solid residue was chromatographed on silica gel (16 g). Elution with 85:15 benzene–methanol gave 416 mg (90%) of 1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose (**19**), which after recrystallization from benzene–methanol afforded pure **19**: colorless needles, mp 125–125.5°; $[\alpha]^{27}D$ −22° (*c* 1.0, ethanol); ir (KBr) 1338 and 1180 (asymmetric and symmetric SO_2 stretch); nmr (pyridine-d_5) δ 6.27 (d, $J_{1,2}$ = 4.0 Hz, 1, H-1), 5.66 (d, $J_{3,4}$ = 3.0 Hz, 1, H-3), 5.27 (d, $J_{1,2}$ = 4.0 Hz, 1, H-2), 3.43 (s, 3, Me from Ms), 1.43 and 126 (two s, 6, Me from Ip).

Anal. Calcd for $C_{10}H_{18}O_8S$: C, 40.27; H, 6.08; S, 10.75. Found C, 40.32; H, 5.99; S, 10.84.

1,2-*O*-Isopropylidene-3-*O*-methylsulfonyl-6-*O*-*p*-tolylsulfonyl-β-L-idofuranose (20).—To a pyridine solution (3 ml) of 1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose (**19**) (298 mg, 1.0 mmol) cooled to −10°, a cold pyridine solution (3 ml) containing *p*-toluenesulfonyl chloride (210 mg, 1.1 mmol) was added, and the reaction mixture was allowed to stand at room temperature for 22 hr. The solution was cooled to 5°, water (10 ml) was added, and solvents were removed *in vacuo*. The residue was dissolved in water (30 ml) and extracted with three 40-ml portions of chloroform. The combined chloroform extracts were successively washed with water, 2% H_2SO_4, and again with water and dried over anhydrous Na_2SO_4, and the chloroform was removed *in vacuo*. The residue (a colorless syrup, 353 mg) was chromatographed on silica gel (45 g). Elution with 85:15 benzene–methanol gave 286 mg (63%) of pure **20**: $[\alpha]^{27}D$ −18° (c 1.0, $CHCl_3$); nmr ($CDCl_3$) δ 6.00 (d, $J_{1,2}$ = 4.0 Hz, 1, H-1), 5.03 ("complex" doublet, $J_{3,4}$ = 2.2 Hz, 1, H-3), 4.85 (d, $J_{1,2}$ = 4.0 Hz, 1, H-2), 4.5–4.1 (unresolved multiplet, 4, H-4, H-5, H-6 and H′-6), 3.11 (s, 3, Me from Ms), 2.47 (s, 3, Me from Ts), 1.50 and 1.33 (two s, 6, Me from Ip).

Anal. Calcd for $C_{17}H_{24}O_{10}S_2$: C, 45.12; H, 5.34; S, 14.17. Found: C, 44.94; H, 5.27; S, 13.91.

6-Amino-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose (21) and 6-Benzamido-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose (15).—A cold solution of dry ammonia in ethanol was added to an ice-cold ethanolic solution of **20** (80 mg, 0.27 mmol). After 1 hr, the solution was warmed to room temperature and allowed to stand for 16 hr. Evaporation of ethanol *in vacuo* afforded **21** (81 mg), which was not purified, but dissolved in pyridine and benzoylated with benzoyl chloride (34 mg, 0.27 mmol). After the mixture had been kept at room temperature for 28 hr, methanol (20 ml) was added and the solvents were evaporated *in vacuo*. Water was added to the oily residue, and the mixture was extracted with three 30-ml portions of ether. The combined ether extracts were washed with water, 2% H_2SO_4, and water and dried over anhydrous Na_2SO_4, and the ether was removed *in vacuo*. The residue (colorless oil, 38 mg) was chromatographed on silica gel (9 g); elution with 85:15 benzene–methanol afforded 14 mg of pure crystalline 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose, mp 194–196°, which after two recrystallizations from benzene–methanol showed mp 198°; this product was identical with compound **15** (mixture melting point, ir and nmr spectra).

Treatment of the 2-Phenyloxazoline Derivative of 6-Amino-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose (14b) with 75% Aqueous Acetic Acid.—A solution (10 ml) of **14b** (50 mg) in 75% aqueous acetic acid was kept at room temperature for 44 hr. Water (50 ml) was then added and the reaction mixture was washed with three 50-ml portions of ether. The aqueous layer, which contained all of the material, was evaporated *in vacuo*. The residue (55 mg, white powder) was dissolved in 20 ml of cold water, and saturated sodium bicarbonate solution (10 ml) was added. The solution was then extracted with three 50-ml portions of ethyl acetate, and the combined extracts were dried over anhydrous Na_2SO_4. The ethyl acetate was removed *in vacuo* and the white, crystalline product (32 mg, mp 190–192°) was recrystallized from benzene–ethyl acetate, whereby the melting point was raised to 197.5–198°. This product was identical with compound **15** and with 6-benzamido-6-deoxy-1,2-*O*-isopropylidene-3-*O*-methylsulfonyl-β-L-idofuranose synthesized from **16** (mixture melting point, ir and nmr spectra).

Treatment of 6-Benzamido-6-deoxy-1,2-*O*-isopropylidene-3,5-di-*O*-methylsulfonyl-α-D-glucofuranose (12) with Sodium Ethoxide in Ethanol.—Finely powdered compound **12** (60 mg, 0.125 mmol) was suspended in freshly distilled absolute ethanol (4 ml) and a 0.5 *N* ethanolic solution of NaOEt was added to the suspension (1 ml, 0.5 mmol). The undissolved solid went into solution after several minutes. The reaction mixture was heated at 60° for 1 hr, cooled to 5°, and neutralized with 0.01 *N* HCl. The aqueous solution was extracted with three 50-ml portions of benzene, and the combined benzene extract was washed twice with water and then dried over anhydrous Na_2SO_4. The benzene was removed *in vacuo* and the residue (40 mg, colorless oil) was chromatographed on silica gel (10 g). Elution with 3:1 benzene–acetone afforded 28 mg (58%) of a colorless syrup which crystallized on trituration with ether–hexane. Recrystallization from ether–hexane gave colorless needles (23 mg), mp 130–131°, which were identical [mixture melting point, ir spectrum, and $[\alpha]^{27}D$ −55° (c 0.22, $CHCl_3$)] with the 2-phenyloxazoline derivative **14b**.

Registry No.—**12**, 2592-51-0; **14b**, 37750-67-7; **15**, 37750-68-8; **16**, 29747-91-9; **17**, 13100-30-6; **18**, 37750-71-3; **19**, 29747-89-5; **20**, 37750-73-5; **21**, 19286-06-7; **22**, 37676-08-7.

(20) Baggett and Jeanloz[18] reported the following physical constants for **17**: mp 153–154°; $[\alpha]^{22}D$ −22° (*c* 0.60, water), and $[\alpha]^{23}D$ −25° (c 0.55, acetone).

The Structures of Nepetaefolin, Nepetaefuran, and Nepetaefuranol

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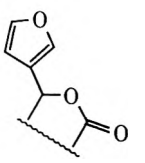
The stereostructures **1**, **2**, and **11** have been deduced for nepetaefolin, nepetaefuran, and nepetaefuranol, respectively, on the basis of chemical evidence, including a correlation *via* leonotin with marrubiin. The facile conversion of **1** to **2** was noted and the interconversion of **2** and **11** was achieved. The spiro epoxide moiety of **1** and **2** was found to undergo anchimerically assisted hydrolysis (*e.g.*, **7**) and hydrochlorination (*e.g.*, **9**), whereas a δ-lactone in these structures remained intact. Metaperiodate oxidation of nepetaefuranol to a nor ketone **16**, followed by elimination to give an α,β-unsaturated ketone **17**, revealed the substitution pattern in the highly functionalized ring B of these labdanoid diterpenes, and pyridine-d_5 shifts assisted configurational assignments. Confirmation of the structural designation was provided by conversion of the reduction product **10** from nepetaefuran to leonotol (**25**), which has also been derived from leonotin (**20**) of established structure and stereochemistry.

The genus *Leonotis*, frequently associated with *Cannabis* through the colloquial term "dagga," is widely distributed throughout South Africa and tropical regions of America, and is reputed to possess a variety of medicinal properties.[2] Along with a pharmacological study of extracts of the species *Leonotis nepetaefolia R.Br.* (Labiatae),[3] we have pursued chemical investigations of constituents of the leaves and stems of this plant. We now report the structural elucidation of nepetaefolin, an unusual prefuranoid diterpene, together with two closely related diterpenes, nepetaefuran and nepetaefuranol.[4]

Nepetaefolin (1) and Nepetaefuran (2).—Extraction of the dried leaves of *L. nepetaefolia* with acetone, followed by crystallization of the residue from ethanol, furnished crude nepetaefolin (**1**), $C_{22}H_{28}O_7$, in *ca.* 0.2% yield.[5] Rigorous purification of **1** could be effected by chromatography on alumina, which also provided varying amounts of a second diterpene, nepetaefuran (**2**), isomeric with **1**. When methanol was used as the extraction solvent or when extraction was carried out upon plant material which had been stored for an extended period (longer than 6 months), the yield of nepetaefolin was much diminished and that of nepetaefuran correspondingly increased. In fact, it was quickly recognized that nepetaefolin is a somewhat unstable substance and is transformed to **2** under mild conditions, including exposure to ethanolic chloroform. However, nepetaefuran was present in the plant extracts under all extraction conditions and, so far as can be discerned, is an authentic secondary metabolite.

The change **1** → **2** is accompanied by the disappearance of olefinic proton signals at 5.04 and 6.52 ppm in the nmr spectrum of **1** and the emergence of new resonances (1 H each) at 6.29, 7.27, and 7.38 ppm. The latter were recognized as characteristic of a mono-β-substituted furan common to a variety of diterpenes, including members of the labdane group such as lambertianic acid (**3**).[6] Further support for the presence of the furan moiety in **2** came from the mass spectrum, which showed a base peak at *m/e* 81 corresponding to the fragment A.[7] A strong ir absorption at 1612 cm^{-1}

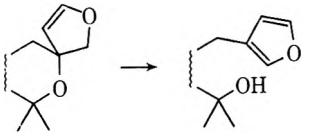
A



D

and an AB quartet at 3.96 and 4.24 ppm (J = 10 Hz) in the nmr spectrum of **1** had also disappeared in this reaction. Moreover, whereas nepetaefolin contained no OH groups, nepetaefuran was found to possess a single hydroxyl function which, from its resistance to acetylation, was judged to be tertiary. The conversion of **1** to **2** thus constitutes elimination from a 3,3-disubstituted 2,3-dihydrofuran, as shown in Scheme I. As expected, acid catalysis greatly facilitates this process.

SCHEME I



B C

In agreement with the partial structures B and C assigned to **1** and **2**, respectively, catalytic hydrogenation of nepetaefolin gave a dihydro derivative **4**, whereas nepetaefuran furnished a tetrahydro compound **5**, corresponding to saturation of the furan ring. In neither case was further hydrogen consumed nor was there any acidic material produced, thus ruling out a partial structure D of the type found in columbin.[8]

Infrared evidence indicated that nepetaefolin and nepetaefuran each contained two carbonyl groups and, in experiments designed to probe the nature of these functions, the basic hydrolysis of **1** and **2** was examined. Treatment of **1** with ethanolic potassium hydroxide, followed by an acidic work-up, afforded a product $C_{20}H_{26}O_6$ (**6**) which, from the disappearance of carbonyl absorption at 1735 cm^{-1} and methyl singlet at 2.02 ppm, was clearly derived by saponification of an acetate.

(1) Address correspondence to Oregon State University.

(2) J. M. Watt and M. G. Breyer-Branwijk, "Medicinal and Poisonous Plants of Southern and Eastern Africa," E. and S. Livingstone, London, 1962, p 520.

(3) We are indebted to Mr. M. Hasmathullah, Warrenville, Trinidad, for the collection of plant materials and to Dr. K. Jewers, Tropical Products Institute, London, for botanical identification.

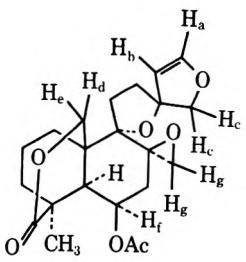
(4) Preliminary communication: J. D. White and P. S. Manchand, *J. Amer. Chem. Soc.*, **92**, 5527 (1970).

(5) A previous investigation of *L. Nepetaefolia* was confined to the seed oil, from which only fatty acids were reported: C. F. Asenjo, J. A. Goyco, and Z. Martinez-Pico, *ibid.*, **67**, 1936 (1945).

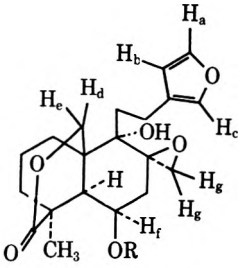
(6) W. G. Dauben and V. F. German, *Tetrahedron*, **22**, 679 (1966).

(7) C. R. Enzell and R. Ryhage, *Ark. Kemi*, **23**, 367 (1965).

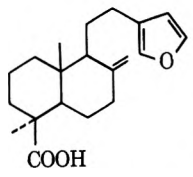
(8) D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 2090 (1956).



1



2, R = $COCH_3$
6, R = H



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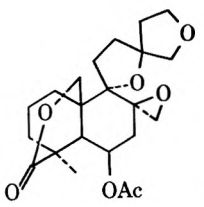
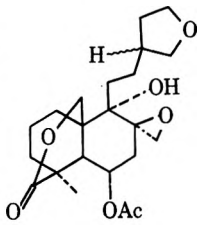


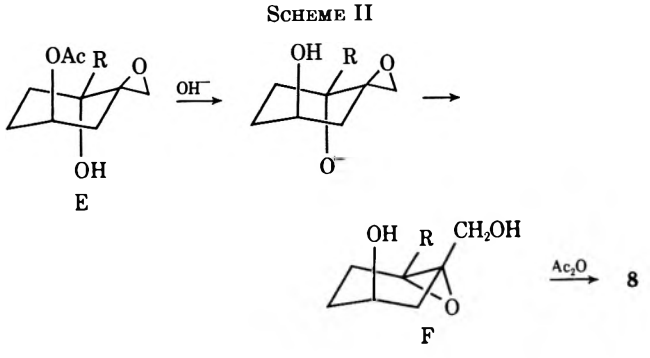
4



5

As expected, hydrolysis had been accompanied by the spirodihydrofuran–furan rearrangement, and it was also apparent that a carbonyl group (1721 cm^{-1}) had been retained in this process. Deuterium exchange established that **6** was a diol, and, when it was allowed to react with acetic anhydride, nepetaefuran (**2**) was formed in moderate yield. The presence of a one-proton signal at 4.22 ppm in **6**, which shifted downfield to 5.18 ppm in **2**, proved that the acetate group in nepetaefuran was secondary. Unexpectedly, analogous saponification of **2** gave not **6**, but an isomeric product **7**. Apart from loss of the elements of acetic acid, the major change occurring in this process involved the generation of a primary alcohol function (AB quartet at 3.48 and 3.62 ppm); the diminution of signals in the 2.6–3.0-ppm region suggested that this was at the expense of a terminal epoxide. Acetylation of **7** with acetic anhydride in pyridine yielded a primary monoacetate **8** (AB auartet at 4.06 and 4.18 ppm), containing an intact secondary hydroxyl group (ir absorption at 3550 cm^{-1} and a one-proton signal at 4.05 ppm). Although a small amount of a diacetate, showing no hydroxyl absorption, accompanies **8**, it is evident that the secondary hydroxyl group of **7** is appreciably more hindered than that of **6**. The transformation of **2** to its hydrolysis product **7** is well accommodated by a partial structure E in which formation of an alkoxide promotes internal displacement on a terminal epoxide. This is accompanied by straightforward saponification to give F (Scheme II). The

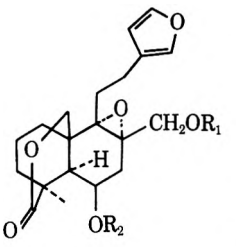
SCHEME II



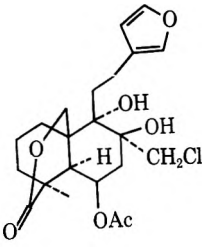
genesis of a new oxirane is feasible only if the participating oxygen functions are arranged trans and diaxially, and this would assure the developing hydroxymethyl group of a pseudoaxial orientation, which could thus provide the source of steric impedance toward acetylation of a neighboring axial hydroxyl function. The failure to observe an analogous epoxide rearrangement in the hydrolysis of **1** implies that the spirodihydrofuran moiety remains intact until acidic work-up, and the 9α alkoxide intermediate is thereby circumvented.

Chemical evidence for the terminal epoxide in nepetaefolin and nepetaefuran was forthcoming from two sources. First, the reaction of either **1** or **2** with phosphorus oxychloride gave a product **9** containing a chloromethyl group (AB quartet at 3.82 and 3.98 ppm). The infrared spectrum of this product revealed that both acetate (1740 cm^{-1}) and lactone (1720 cm^{-1}) functions were preserved, and nmr evidence as well as polarity according to thin layer chromatography was consistent with a diol. Thus, instead of dehydration, this reaction accomplished formal addition of HCl to the terminal epoxide in the anti-Markovnikov sense. A likely explanation for this unusual process involves participation of the ester G derived from **2** (Scheme III) with intramolecular delivery of the chlorine *via* a SNi′ mechanism.

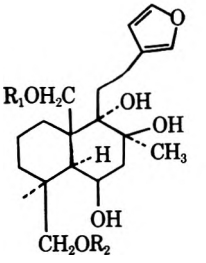
Conclusive proof for the presence of the oxirane in **1** and **2** was obtained when each was reduced with lithium aluminum hydride in tetrahydrofuran. The same pentahydroxy compound **10** was formed from both nepetaefolin and nepetaefuran, and its nmr spectrum clearly displayed a new methyl group with a chemical shift (1.24 ppm) indicative of its placement on a carbon bearing an oxygen function. Lithium aluminum hydride simultaneously accomplished reduction of the acetoxy and δ-lactone functions, thus affording the first



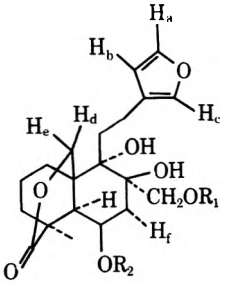
7, $R_1 = R_2 = H$
8, $R_1 = COCH_3$; $R_2 = H$
21, $R_1 = H$; $R_2 = COCH_3$
32, $R_1 = R_2 = COCH_3$



9

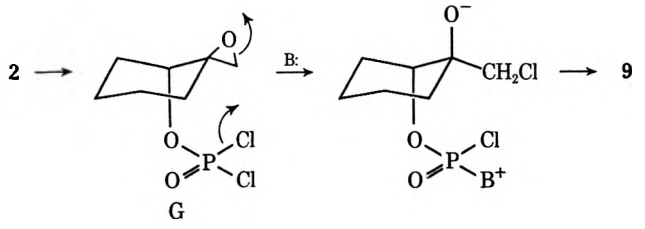


10, $R_1 = R_2 = H$
23, $R_1 = H$; $R_2 = Ts$
24, $R_1 = Ts$; $R_2 = H$

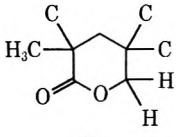


11, $R_1 = H$; $R_2 = COCH_3$
12, $R_1 = R_2 = COCH_3$
13, $R_1 = R_2 = H$
14, $R_1 = COCH_3$; $R_2 = H$
22, $R_1 = Ts$; $R_2 = COCH_3$

SCHEME III



direct chemical evidence for the latter. In hydrolysis studies of **1** and **2** a carboxylate had been isolated but acidification invariably induced immediate relactonization. Moreover, attempts to bring about esterification of the carboxylate were uniformly unsuccessful and suggested that the carboxyl moiety in this system was sterically encumbered. The reduction product **10** showed a new pair of AB quartets (3.26 and 4.19, 3.85 and 4.30 ppm), which therefore requires that the δ-lactone bear a substitution pattern as in H. The presence of a methyl group in nepetaefolin and nepetaefuran was apparent from the three-proton singlet at 1.15 and 1.12 ppm, respectively, with the chemical shift indicative of a placement α to carbonyl.

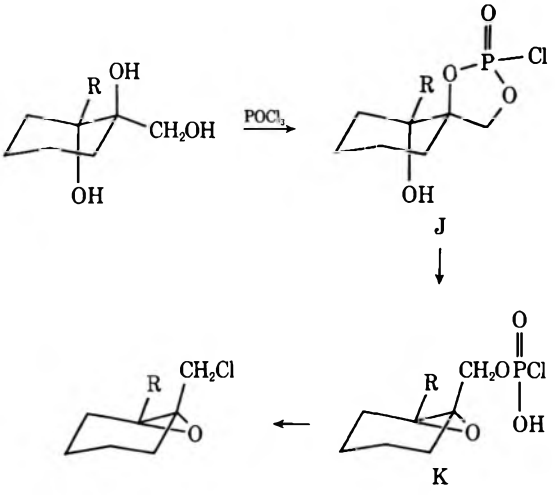


H

Nepetaefuranol.—Further clarification of the structures of nepetaefolin and nepetaefuran became possible with the isolation of a third member of this series, nepetaefuranol (**11**), $C_{22}H_{30}O_8$, differing in composition from **1** and **2** by formal addition of water. Spectral properties as well as the formation of a tetrahydro derivative again pointed to the presence of a β-substituted furan. Deuterium exchange indicated that **11** was a triol, and an AB quartet (3.27 and 3.78 ppm) suggested the presence of a primary alcohol. This was confirmed by formation of a primary acetate **12** (2 H singlet at 4.25 ppm) upon acetylation. Hydrolysis of **11** gave a tetraol **13** derived, as in the case of **2**, by saponification of a secondary acetate; reacetylation gave a primary monoacetate **14**, isomeric with nepetaefuranol. As noted with hydrolysis studies on **2**, the secondary hydroxyl group of **14** is sufficiently hindered to resist acetylation. The second carbonyl functionality due to the δ-lactone had again remained intact throughout these transformations.

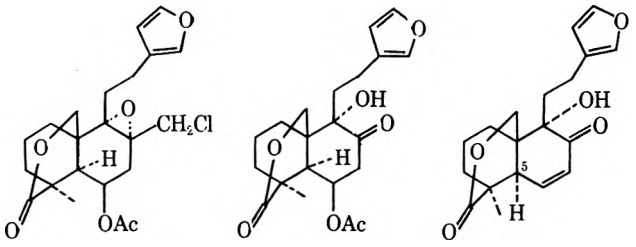
The nature of the hydroxyl substituents in nepetaefuranol was more fully revealed through the action of phosphorus oxychloride, which accomplished chlorinative dehydration to **15**. That this product was a primary halide was clear from the appearance of a new AB quartet at 3.25 and 3.60 ppm, and, since **15** contained neither a hydroxyl group nor unsaturation in the form of an olefinic linkage, an oxirane must have been formed in the dehydration process. On the assumption that a 1,2,3-triol is present in nepetaefuranol, a satisfactory explanation for the phosphorus oxychloride reaction can be found in the formation of the cyclic ester J, which suffers intramolecular displacement to produce the phosphonate ester K. A straightforward SNi transfer of chlorine then gives **15** (Scheme IV). As noted in

SCHEME IV

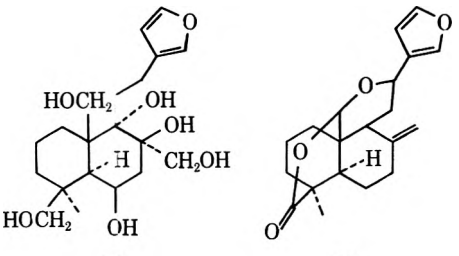


connection with the transformation of **2** to **7** (Scheme II), this mechanism requires a trans-diaxial orientation of tertiary hydroxyl groups, and inversion at the spiro carbon of the cyclic phosponate J converts an initially equatorial primary alcohol to an axial chloromethyl group (*cf.* **9** where the chloromethyl group remains equatorial).

Confirmation of a glycol functionality in **11** was acquired from its reaction with sodium metaperiodate, which gave cleanly a nor ketone **16**. Upon chromatography over alumina, **16** underwent elimination of acetic acid to yield quantitatively a pair of α,β-unsaturated ketones (1670 cm^{-1}) in the ratio 5:1. The major isomer **17** displayed olefinic proton signals at 6.41 and 6.81 ppm corresponding to α and β protons of the enone, respectively, with a cisoid olefinic coupling of 10 Hz. The minor isomer is believed to be epimeric with **17** at C-5, but this material was not fully characterized. The facile elimination of acetic acid from **16** is anticipated from a structure which contains an axial acetoxyl group β to a carbonyl group,[9] and this result serves to complete the placement of functionality in one carbocyclic ring of nepetaefuranol.



15 **16** **17**



18 **19**

(9) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 227.

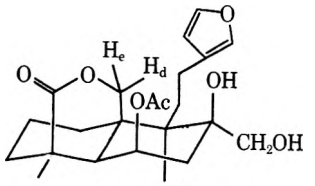
TABLE I

CHEMICAL SHIFTS (δ, PPM) AND PROTON COUPLING CONSTANTS (J, Hz)[a] FOR NEPETAEFOLIN, NEPETAEFURAN, NEPETAEFURANOL, AND LEONOTIN

Compd	Solvent	H_a	H_b	H_c	H_d	H_e	H_f	H_g	CH_3CO	CH_3
1	$CDCl_3$	6.52 (d, J = 3)	5.04 (d, J = 3)	3.97 4.24 (d, J = 10)	5.07 (d, J = 11)	3.96 (d, J = 11)	5.18 (d of t)	2.35 2.58 (d of d, J = 4, 14)	2.02 (s)	1.15 (s)
2	DMSO-d_6–$CDCl_3$ (10:1)	7.38 (t, J = 1)	6.27 (m)	7.27 (s)	5.02 (d, J = 12)	4.05 (d, J = 12)	5.18 (d of t)	2.32 2.70 (d of d, J = 4, 13)	1.96 (s)	1.12 (s)
11	DMSO-d_6–$CDCl_3$ (10:1)	7.38 (t, J = 1)	6.34 (m)	7.28 (s)	5.90 (d, J = 12)	4.04 (d, J = 12)	5.22 (m)	3.27[b] 3.78 (d of d, J = 4, 11)	1.96 (s)	1.10 (s)
20	DMSO-d_6–$CDCl_3$	7.35 (t, J = 1)	6.32 (m)	7.25 (s)			4.75 (d of t, J = 6, 8)			1.02 (s) 1.22 (s) 1.30 (s)

[a] Coupling assignments were checked by double resonance (except for H_f). [b] Collapses to a doublet (J = 11) upon addition of D_2O.

Reduction of nepetaefuranol with lithium aluminum hydride yielded an amorphous hexahydroxy compound **18**, and evidence similar to that cited for the case of nepetaefuran supports a δ-lactone corresponding to part structure H for **11** also. Placement of this lactone within the framework of the three diterpenes is dictated by the fact that its reduction generates two primary alcohol groups and the recognition that all but one of the isoprenoid *C*-methyl groups have been oxidized. Thus, assuming a skeleton of the normal labdane type,[10] a lactone bridge spanning the C-5 and C-10 positions similar to that in sciadin (**19**)[11] provides a full account of the experimental evidence and explains serendipitously the widely divergent chemical shifts of protons H_d and H_e in these diterpenes and several derivatives (Table I). A three-dimensional representation L of **11**



L

shows that H_d is subject to the deshielding influence of both the axial hydroxyl at C-8 and the axial acetoxy group at C-6, whereas in nepetaefolin and nepetaefuran, both containing the spiro epoxide at C-8, the effect is less pronounced. When nmr spectra of **2** and **11** were measured in pyridine-d_5 solution, a further downfield shift of H_d and H_e was observed (Table II). The relatively large shift (0.39 ppm) observed for H_d in **11** accords with the explanation proposed by Demarco, *et al.*, for this phenomenon, involving anisotropic effects arising from coordination of pyridine with a neighboring, axially situated hydroxyl group.[12] As expected, the effect on the more remote proton H_e is smaller. A similar deshielding due to solvent pyridine was noted in the case of the angular methyl group of leonotin (**20**).[13]

TABLE II

PYRIDINE-d_5 CHEMICAL SHIFTS (δ, PPM) OF NEPETAEFURAN AND NEPETAEFURANOL

Compd	H_d	$\Delta\delta$[a]	H_e	$\Delta\delta$[a]	H_g	$\Delta\delta$[a]
2	5.31	0.29	4.20	0.15	2.30	−0.02
					2.93	0.23
11	6.29	0.39	4.22	0.18	3.70	0.43
					4.22	0.44

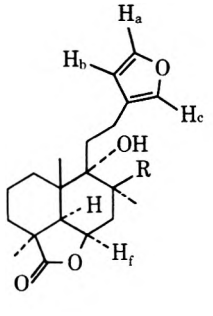
[a] Chemical-shift differences are calculated with reference to the solvent system of Table I.

The structural and stereochemical relationship between nepetaefuran (**2**) and nepetaefuranol (**11**) was confirmed by means of direct interconversion of these two substances. First, the hydrolysis of **2** with aqueous perchloric acid in tetrahydrofuran was found to yield **11**, in addition to products derived from cleavage of the acetate. This result is anticipated, assuming participation of the hydroxyl at C-9 in the opening of the spiro epoxide (*cf.* Scheme II), so that hydrolytic opening of epoxy alcohol **21**, an isolable intermediate in this reaction, assures overall retention (*via* double inversion) at C-8. Furthermore, a product formed in the prolonged treatment of nepetaefuran with phosphorus oxychloride and pyridine or upon similar treatment of **9** was found to be identical with the dehydration product **15** from nepetaefuranol. This quite clearly is the result of a subsequent dehydration of the trans-diaxial glycol **9** with elimination of the oxygen function at C-8. Finally, the reverse correlation of nepetaefuranol with a derivative of **2** was accomplished by conversion of **11** to an unstable, primary tosylate **22** with *p*-toluenesulfonyl chloride in pyridine, followed by treatment with potassium hydroxide. Among other products, a substance identical with the hydrolysis product **7** of nepetaefuran was formed.

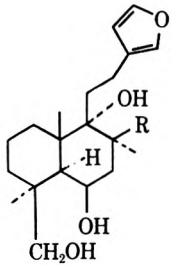
Correlation with Leonotin (20).—The structural hypotheses put forward for nepetaefolin, nepetaefuran,

(10) R. McCrindle and K. H. Overton, *Advan. Org. Chem.*, **5**, 47 (1965).
(11) M. Sumimoto, *Tetrahedron*, **19**, 643 (1963).
(12) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968).
(13) J. D. White, P. S. Manchand, and W. B. Whalley, *Chem. Commun.*, 1315 (1969).

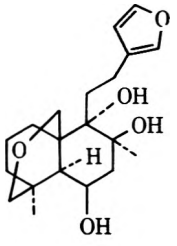
and nepetaefuranol were placed on a firm foundation by a direct interrelation with leonotin (**20**), of established structure and stereochemistry.[13] The reduction product **10** from nepetaefuran (or nepetaefolin), upon treatment with *p*-toluenesulfonyl chloride in pyridine, yielded a crystalline mixture consisting of two primary monotosylates, **23** and **24**. Without purification, this mixture was subjected to hydrogenolysis with lithium aluminum hydride in tetrahydrofuran to give leonotol (**25**), previously prepared by reduction of leonotin (**20**) with lithium aluminum hydride. A relatively fast-moving component in the reduction mixture is believed to be the cyclic ether **26**,[14] since, upon prolonged treatment with lithium aluminum hydride, this material also gave leonotol. Leonotin (8β-hydroxymarrubiin)[15] has, in turn, been correlated with marrubiin (**29**), of



20, R = OH
29, R = H



25, R = OH
28, R = H



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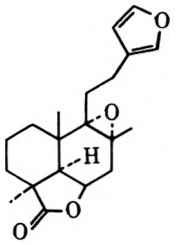
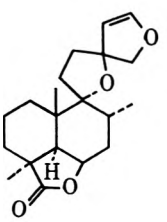


27

established structure and absolute stereochemistry,[16] by dehydration to epoxide **27**, followed by reduction with lithium aluminum hydride to give marrubenol (**28**). The latter has been previously prepared by lithium aluminum hydride reduction of marrubiin,[17] and, when a sample obtained by this method[18] was compared with material acquired from leonotin, they were found to be identical in all respects. Thus, correlation of the nepetaefolin series with a substance of independently ascertained structure is complete; this serves to confirm the stereochemistry at all six chiral centers of nepetaefuran (**2**) and nepetaefuranol (**11**), as well as the corresponding centers in nepetaefolin (**1**). The configuration of the additional spiro carbon in **1** remains undefined.

Identification of the structure of nepetaefolin as **1** places it in a select group of spiro dihydrofuranoid diterpenes comprising, to date, two other members, premarrubiin (**30**)[19] and presolidagenone (**31**).[20] Interestingly, the traditional source of marrubiin (**29**), white horehound (*Marrubium vulgare L.*), was found to produce no trace of **29** when extraction was carried out with cold acetone, and the evidence now clearly points to marrubiin as an artifact arising from **30** *via* a process which has an obvious parallel in the nepetaefolin → nepetaefuran conversion.



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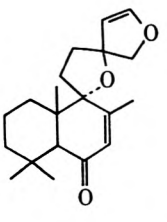

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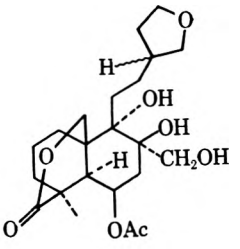

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Experimental Section

General Techniques.—Melting points were determined on a Kofler heating stage or in capillaries on a Büchi melting point apparatus, and are uncorrected. Infrared spectra (ir) were determined as Nujol mulls except where otherwise stated on Perkin-Elmer 237 or 257 spectrometers. Nuclear magnetic resonance spectra (nmr) were recorded on a Varian HA-100 spectrometer with tetramethylsilane as internal standard. Chemical shifts are expressed in δ units (parts per million) and coupling constants (J) in hertz. Mass spectra were determined on an Associated Electronics Industries MS-9 spectrometer, using a direct inlet system with ionization energy of 70 eV; m/e values are given with relative intensities (%) in parentheses. Thin layer chromatograms (tlc) were made from Merck (Darmstadt) silica gel G; spots were made visible by spraying with a 10% solution of ceric sulfate and heating the plates to 110°. Elemental analyses were carried out by Micro-Tech Laboratories, Inc., Skokie, Ill., or by the microanalytical department, Hoffmann-La Roche, Inc., Nutley, N. J.

Isolation of Nepetaefolin (1).—One kilogram of the dried leaves of *Leonotis nepetaefolia R.Br.* was steeped in 10 l. of acetone at room temperature for 3 days and the mixture was decanted through a filter funnel. The filtrate was evaporated *in vacuo* at 40° and the residue was dissolved in 800 ml of ethyl acetate. The mixture was stirred with 50 g of decolorizing charcoal ("Norit A") at 45° for 10 min, cooled, and filtered (this process was repeated until the filtrate was virtually colorless). Evaporation of the filtrate gave 20.3 g of a gum, which was taken up into 150 ml of warm ethanol and allowed to stand at 0° for 3 hr. The crystals of crude nepetaefolin were filtered, washed with 10 ml of cold ethanol, and dried *in vacuo* at 45° to give 1.74 g of colorless needles, mp 250–255°. Repeated crystallizations from acetone–methanol gave analytically pure nepetaefolin: mp 260° dec; $[\alpha]^{25}D$ −14.6° (*c* 0.90, chloroform); ir 1740, 1722, 1612, 1380, 1242, 1140, and 750 cm^{-1}; nmr ($CDCl_3$) δ 1.15 (3 H, s), 2.02 (3 H, s), 2.35 (1 H, d, J = 4 Hz), 2.58 (1 H, d, J = 4 Hz), 3.96 (1 H, d, J = 10 Hz), 3.97 (1 H, d, J = 11 Hz), 4.24 (1 H, d, J = 10 Hz), 5.04 (1 H, d, J = 3 Hz), 5.07 (1 H, d, J = 11 Hz), 5.18 (1 H, d, of t), and 6.52 (1 H, d, J = 3 Hz); mass spectrum m/e (rel intensity) 404 (M^+, 52), 344 (100).

Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.20; H, 6.98.

Isolation of Nepetaefuran (2) and Nepetaefuranol (11).—One kilogram of the dried leaves of *L. nepetaefolia* was steeped in 10 l. of methanol for 10 days. The mixture was decanted through a filter funnel and the filtrate was concentrated to 1 l., diluted with 100 ml of water, and extracted with 1.5 l. of ligroin (bp 60–70°). The extract was dried ($MgSO_4$), concentrated to 750 ml, and treated with decolorizing charcoal as described for the

(14) H. L. Goering and C. Serres, *J. Amer. Chem. Soc.*, **74**, 5908 (1952).
(15) E. R. Kaplan, K. Naidu, and D. E. A. Rivett, *J. Chem. Soc. C*, 1656 (1970).
(16) R. A. Appleton, J. W. B. Fulke, M. S. Henderson, and R. McCrindle, *ibid.*, 1943 (1967); D. M. S. Wheeler, M. M. Wheeler, M. Fetizon, and W. H. Castine, *Tetrahedron*, **23**, 3909 (1967). Total synthesis of marrubiin: L. Mangoni, M. Adinolfi, G. Laonigro, and R. Caputo, *ibid.*, **28**, 611 (1972).
(17) W. Cocker, B. E. Cross, S. R. Duff, J. T. Edward, and T. F. Holley, *J. Chem. Soc.*, 2540 (1953).
(18) Samples of marrubiin were kindly provided by Professor D. M. S. Wheeler, University of Nebraska, and by Dr. D. E. A. Rivett, Rhodes University, Grahamstown, South Africa.
(19) M. S. Henderson and R. McCrindle, *J. Chem. Soc. C*, 2014 (1969).
(20) T. Anthonsen, P. H. McCabe, R. McCrindle, and R. D. H. Murray, *Tetrahedron*, **25**, 2233 (1969).

isolation of 1. Removal of the charcoal and solvent gave 11.0 g of an oil. The aqueous phase from the above partition was diluted with 1 l. of saturated brine and extracted with two 1.5-l. portions of ethyl acetate. The extract was concentrated to *ca.* 750 ml, dried ($MgSO_4$), decolorized with charcoal ("Norit A"), and evaporated to give 12.8 g of a gum. This was chromatographed on 500 g of neutral alumina (Woelm, activity II), with increasing percentages of ethyl acetate in benzene as eluent. Fractions of similar composition (ascertained by tlc, 40% ethyl acetate in benzene) were combined, evaporated, and treated as follows to give the individual diterpenes.

A. Nepetaefuran (2).—A mixture of nepetaefuran and leonotin, eluted with 20–25% ethyl acetate in benzene, was fractionally crystallized from methylene chloride–hexane to give 418 mg of leonotin (20) as plates, mp 175°. The mother liquors from these crystallizations were combined and chromatographed on 150 g of neutral alumina (Woelm, activity II) with 15% ethyl acetate in benzene as eluent. Removal of the solvents and repeated crystallizations of the residue from ethyl acetate–hexane gave nepetaefuran, mp 233–235°. A further crystallization from aqueous ethanol produced large, colorless needles which were dried *in vacuo* at 56° to give 160 mg of nepetaefuran (2): mp 241–242°; $[\alpha]D^{25}$ +32.3° (c 1.35, CH_3OH); ir 3500, 1735, 1730, 1380, 1240, 1145, 1025–1045, and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 10:1) δ 1.12 (3 H, s), 1.2–1.85 (m), 1.96 (3 H, s), 2.2–2.85 (m), 2.32 (1 H, d, J = 4 Hz), 2.70 (1 H, d, J = 4 Hz), 4.05 (1 H, d, J = 12 Hz), 4.87 (1 H, s, disappears on addition of D_2O), 5.02 (1 H, d, J = 12 Hz), 5.18 (1 H, d, of t), 6.27 (1 H, m), 7.27 (1 H, s), 7.38 (1 H, 5, J = 1 Hz); mass spectrum m/e (rel intensity) 404 (M^+, 4) and 81 (100).

Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.30; H, 6.99.

B. Nepetaefolin (1).—A mixture of nepetaefolin and nepetaefuran was eluted with 25–30% ethyl acetate in benzene. The solvents were removed and the residue was dissolved in 5 ml of warm ethanol and allowed to stand at 0° overnight. Filtration gave 103 mg of nepetaefolin, mp 260° (from acetone–methanol). The mother liquor was evaporated and the residue was repeatedly crystallized from ethyl acetate–hexane to give 74 mg of nepetaefuran, mp 235–238°.

C. Nepetaefuranol (11).—Crude nepetaefuranol was eluted with 70–80% ethyl acetate in benzene. Removal of the solvents left a gum which was dissolved in 15 ml of hot methylene chloride, and the mixture was left at 0° overnight. The crystals were filtered, washed with a little cold methylene chloride, and dried *in vacuo* at 56° to give 800 mg of nepetaefuranol (11) as colorless needles: mp 253–255°; $[\alpha]^{25}D$ +17.2° (c 1.053, CH_3OH); ir 3550 (broad), 1735, 1720, and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 10:1) δ 1.10 (3 H, s), 1.6–1.9 (m), 1.96 (3 H, s), 2.1–2.65 (m), 3.27 (1 H, d, J = 11 Hz), 3.78 (1 H, d of d, J = 3 and 11 Hz, becomes d, J = 11 Hz, on addition of D_2O), 4.04 (1 H, d, J = 11 Hz), 4.36 (1 H, disappears on addition of D_2O), 5.20 (1 H, d of t), 5.20 (1 H, s, disappears on addition of D_2O), 5.70 (1 H, t, J = 3 Hz, disappears on addition of D_2O), 5.90 (1 H, d, J = 11 Hz), 6.34 (1 H, m), 7.28 (1 H, s), and 7.38 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 422 (M^+, 5), and 81 (100).

Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.62; H, 7.21.

Conversion of Nepetaefolin (1) into Nepetaefuran (2).—A solution of 40.4 mg (0.10 mmol) of nepetaefolin in 10 ml of chloroform and 10 ml of ethanol was heated under reflux for 5 hr. The solvents were evaporated and the solid residue was crystallized from ethyl acetate–hexane to give 36 mg of 2 as colorless needles, mp 236–238°, $[\alpha]^{25}D$ +31.4° (c 1.120, CH_3OH). This compound was identical in all respects with natural nepetaefuran [mixture melting point, mixed tlc (40% ethyl acetate in benzene), ir, nmr, and mass spectra].

Dihydronepetaefolin (4).—A solution of 40.4 mg (0.10 mmol) of nepetaefolin (1) in 25 ml of ethyl acetate was hydrogenated, at ambient temperature and pressure, over 25 mg of 5% palladium on charcoal until hydrogen absorption ceased; 3.5 ml was absorbed during *ca.* 4 min. The mixture was filtered and the catalyst was washed with 15 ml of ethyl acetate. The filtrate and washings were combined and evaporated to leave 40 mg of a colorless solid, which was crystallized from methylene chloride–hexane to give 33 mg of 4: mp 285–286° dec; $[\alpha]^{25}D$ +34.4° (c 1.236, $CHCl_3$); ir 1740, 1717, 1320, 1247, 1160, and 1030 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 1:1) δ 1.14 (3 H, s), 2.00 (3 H, s), 2.36 (1 H, d, J = 4 Hz), 2.63 (1 H, d, J = 4 Hz), 3.61 (2 H, q, J = 9 Hz), 3.94 (3 H, m), 5.09 (1 H, d, J = 11 Hz), 5.19 (1 H, d of t); mass spectrum m/e (rel intensity) 406 (M^+, 1) and 83 (100).

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.08; H, 7.54.

Tetrahydronepetaefuran (5).—A solution of 80.8 mg (0.20 mmol) of nepetaefuran (2) in 20 ml of 95% ethanol was hydrogenated over 100 mg of 10% palladium on charcoal at atmospheric pressure and room temperature until hydrogen absorption (*ca.* 12 ml) ceased. Removal of the catalyst and solvent yielded 80 mg of a colorless, crystalline solid which was recrystallized from ethanol to give 5 as plates: mp 222°; $[\alpha]^{25}D$ +29.6° (c 1.08, CH_3OH); ir 3400, 1740, and 1725 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 1:1) δ 1.12 (3 H, s), 1.2–1.9 (m), 1.96 (3 H, s), 2.29 (1 H, d, J = 3 Hz), 2.66 (1 H, s, J = 3 Hz), 3.28 (2 H, overlapping t), 3.76 (4 H, m), 4.05 (1 H, d, J = 11 Hz), 4.71 (1 H, s, disappears on addition of D_2O), 5.00 (1 H, d, J = 11 Hz), and 5.17 (1 H, d of t); mass spectrum m/e (rel intensity) 408 (M^+, 2).

Anal. Calcd for $C_{22}H_{32}O_7$: C, 64.44; H, 8.03. Found: C, 64.69; H, 7.90.

Hydrogenation of nepetaefuran in glacial acetic acid with Adams platinum oxide catalyst at room temperature and atmospheric pressure also gave the tetrahydro derivative 5.

Alkaline Hydrolysis of Nepetaefolin (1).—A mixture of 40.4 mg (0.10 mmol) of nepetaefolin and 10 ml of 95% ethanol was stirred at *ca.* 40° for 30 min. The mixture was cooled to room temperature, treated with 5 ml of 10% ethanolic potassium hydroxide, and stirred for a further 1 hr. The solution was diluted with 40 ml of water, acidified with ice-cold 2 *N* hydrochloric acid, and extracted with two 100-ml portions of ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and evaporated to give a gum which was crystallized from methylene chloride–hexane to give 28.1 mg of 6: mp 202–203°; $[\alpha]^{25}D$ + 34° (c 1.01, CH_3OH); ir 3450, 1721, and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 1:1) δ 1.28 (3 H, s), 1.5–2.0 (m), 2.35 (1 H, d, J = 3 Hz), 2.70 (1 H, d, J = 3 Hz), 3.91 (1 H, disappears on addition of D_2O), 3.98 (1 H, d, J = 11 Hz), 4.22 (1 H, broad s), 5.43 (1 H, s, disappears on addition of D_2O), 5.09 (1 H, d, J = 11 Hz), 6.25 (1 H, m), 7.22 (1 H, s), and 7.35 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 362 (M^+, 4) and 81 (100).

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.29; H, 7.11.

Acetylation of 20.2 mg of 6 with 1.0 ml of acetic anhydride and 1 ml of anhydrous pyridine during 16 hr at room temperature gave 12 mg of nepetaefuran (2), identified by melting point, ir, and tlc properties.

Alkaline Hydrolysis of Nepetaefuran.—A solution of 80.0 mg (0.20 mmol) of nepetaefuran (2) in 10 ml of 95% ethanol was stirred with 10 ml of 10% ethanolic potassium hydroxide at room temperature for 1 hr. The solution was diluted with 50-ml of water, acidified with ice-cold 5% hydrochloric acid, and extracted with 150 ml of ethyl acetate. The extract was washed with two 125-ml portions of water, dried ($MgSO_4$), and evaporated to give 75 mg of a crystalline solid. Recrystallization from ethyl acetate–hexane gave 72 mg of 7 as colorless prisms: mp 196–198°; $[\alpha]^{25}D$ +29.6° (c 1.287, CH_3OH); ir 3500, 1715, and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$) δ 1.27 (3 H, s), 3.48 (1 H, d, J = 12 Hz), 3.62 (1 H, d, J = 12 Hz), 5.08 (1 H, m), 5.29 (1 H, d, J = 11 Hz), 5.89 (1 H, J = 11 Hz), 6.30 (1 H, m), 7.29 (1 H, s), 7.38 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 362 (M^+, 3) and 81 (100).

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.30; H, 7.28.

A mixed tlc (55% ethyl acetate in benzene) of this material with a sample of 6 from the preceding experiment did not show a clear separation, but the mixture melting point showed a depression (mmp 170–180°); the ir, nmr, and mass spectra of the two samples were clearly different.

Acetylation of 7.—To a mixture of 50 mg (0.12 mmol) of hydrolyzed nepetaefuran (7) and 2 ml of anhydrous acetic anhydride (warming was necessary to obtain a solution) was added 1 drop of anhydrous pyridine. The mixture was allowed to stand at 0° for 16 hr. The solution was added to 100 ml of ice-cold water and extracted with 150 ml of ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated to give a colorless solid. Tlc (40% ethyl acetate in benzene) and mass spectral data (M^+ at 404 and 446) indicated that the major product was the monoacetate 8, with 10–15% of the diacetate also present. Crystallization of the solid from ethyl acetate–hexane furnished 34 mg of 8 as colorless needles: mp 165–166°;

$[\alpha]^{25}D$ +23° (c 1.319, $CHCl_3$); ir 3550, 1740–1720 (broad), 1380, 1210–1240, 1165, 1045 and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 1:5) δ 1.23 (3 H, s), 1.5–2.0 (m), 2.12 (3 H, s), 2.50 (2 H, t, J = 7 Hz), 4.05 (1 H, d of t), 4.06 (1 H, d, J = 12 Hz), 4.18 (1 H, d, J = 12 Hz), 4.28 (1 H, d, J = 11 Hz), 4.86 (1 H, d, J = 11 Hz), 4.86 (1 H, disappears on addition of D_2O), 6.30 (1 H, m), 7.27 (1 H, s), and 7.37 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 404 (M^+, 5).

Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.11; H, 7.07.

In a mixed tlc (40% ethyl acetate in benzene), **8** (R_f 0.41) was readily separated from nepetaefuran (R_f 0.50). The mother liquor from the above crystallization was evaporated and the residue was dissolved in 2 ml of pyridine, to which was added 2 ml of anhydrous acetic anhydride. The mixture was allowed to stand at room temperature for 24 hr, and then added to 50 ml of ice-cold water and extracted with two 50-ml portions of ethyl acetate. The extract was washed, dried (Na_2SO_4), evaporated, and filtered through 25 g of neutral alumina (Woelm, activity II) with 15% ethyl acetate in benzene as eluent. Removal of the solvents gave 19 mg of **32** as a colorless gum which, although homogeneous by tlc (15% ethyl acetate in benzene), could not be induced to crystallize: $[\alpha]^{25}D$ −4.2° (c 1.120, $CHCl_3$); ir ($CHCl_3$) 1741, 1730, 1380, 1240–1210, 1160, 1050–1035, and 878 cm^{-1}; nmr ($CDCl_3$) δ 1.19 (3 H, s), 1.7–2.7 (m), 2.08 (3 H, s), 2.15 (3 H, s), 4.10 (2 H, s), 4.44 (1 H, d, J = 12 Hz), 4.68 (1 H, d, J = 12 Hz), 5.13 (1 H, m), 6.26 (1 H, m), 7.21 (1 H, s), 7.34 (1 H, s); mass spectrum m/e (rel intensity) 446 (M^+, 4).

Reaction of Nepetaefuran (2) with Phosphorus Oxychloride.—To a solution of 50 mg (0.12 mmol) of nepetaefuran (**2**) in 5 ml of anhydrous pyridine was added 1.5 ml of freshly distilled, anhydrous phosphorus oxychloride. The mixture was stirred at 100° for 4 hr, cooled to *ca.* 10°, and added to crushed ice (200 g). The mixture was extracted with 200 ml of ether, and the extract was washed with three 200-ml portions of water, dried ($MgSO_4$), and evaporated. Crystallization of the residue from ethyl acetate–hexane gave 44 mg of **9** as colorless needles, mp 209–211°. This sample was dried *in vacuo* to give 38 mg of pure **9**: mp 211–212°; $[\alpha]^{25}D$ −1.60° (c 1.14, $CHCl_3$); ir 3650, 3500, 1740, 1720, and 872 cm^{-1}; nmr (DMSO-d_6–acetone-d_6) δ 1.12 (3 H, s), 1.98 (3 H, s), 2.1–2.6 (m), 3.82 (1 H, d, J = 11 Hz), 3.98 (1 H, d, J = 11 Hz), 4.14 (1 H, d, J = 11 Hz), 5.21 (1 H, d of t), 5.94 (1 H, d, J = 11 Hz), 6.37 (1 H, m), 7.31 (1 H, s), and 7.39 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 442 (M^+, 3), 81 (100).

Anal. Calcd for $C_{22}H_{29}O_7Cl$: C, 59.93; H, 6.63; Cl, 8.08. Found: C, 60.00; H, 6.84; Cl, 8.12.

Reaction of Nepetaefolin (1) with Phosphorus Oxychloride.—Nepetaefolin (**1**) was treated under conditions identical with respect to quantities, reaction time, and work-up with those previously described for nepetaefuran. Crystallization of the product from ethyl acetate–hexane gave colorless needles, mp 210–211°. This product was identical in all respects with the product obtained from nepetaefuran [mmp 210–211°; mixed tlc (40% ethyl acetate in benzene), ir, nmr, and mass spectra].

Lithium Aluminum Hydride Reduction of Nepetaefuran.—A solution of 40.4 mg (0.10 mmol) of nepetaefuran (**2**) in 1 ml of anhydrous tetrahydrofuran was added to a stirred suspension of 200 mg of lithium aluminum hydride in 5 ml of anhydrous tetrahydrofuran. The mixture was heated under reflux with stirring for 3.5 hr, cooled to 0–5°, and treated with ethyl acetate to destroy excess hydride reagent. The slurry was added to 100 ml of ice-cold 5% sulfuric acid and extracted with two 100-ml portions of ethyl acetate. The extract was washed with saturated brine until it was neutral, dried ($MgSO_4$), and evaporated. Crystallization of the residue from methylene chloride gave 34 mg of colorless prisms, mp 124–127°. Further crystallizations from ethyl acetate–hexane and acetone–hexane gave an analytical sample of **10**: mp 137–138°; $[\alpha]^{25}D$ +21.4° (c 0.761, CH_3OH); ir 3425, 3340, 3160, and 875 cm^{-1}; nmr (DMSO-d_6–acetone-d_6) δ 1.09 (3 H, s), 1.24 (3 H, s), 3.26 (1 H, d, J = 12 Hz), 3.85 (1 H, d, J = 13 Hz), 4.19 (1 H, d, J = 12 Hz), 4.30 (1 H, d, J = 13 Hz), 6.42 (1 H, m), 7.39 (1 H), and 7.49 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 368 (M^+, 1) and 81 (100).

Anal. Calcd for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75. Found: C, 65.00; H, 8.61.

Lithium Aluminum Hydride Reduction of Nepetaefolin.—Nepetaefolin (**1**) was reduced under the conditions described for nepetaefuran. Acid work-up of the reaction mixture gave a product which was identical in all respects with the product obtained from the hydride reduction of nepetaefuran [mixture melting points, mixed tlc (80% ethyl acetate in benzene), ir, nmr, and mass spectra].

Acetylation of Nepetaefuranol (11).—A mixture of 65 mg (0.13 mmol) of nepetaefuranol (**11**) in 4.0 ml of anhydrous acetic anhydride was warmed to obtain a solution and, after cooling to room temperature, the solution was treated with 2 drops of anhydrous pyridine. The solution was allowed to stand at room temperature for 17 hr, added to 50 ml of ice-cold water, allowed to stand for 1.5 hr, and extracted with two 100-ml portions of ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated with addition of benzene to effect azeotropic removal of traces of acetic acid. Crystallization of the residue from ethyl acetate–hexane gave 60 mg of **12** as colorless crystals: mp 185–186°; ir ($CHCl_3$), 3500, 1735, 1715, and 872 cm^{-1}; nmr ($CDCl_3$) δ 1.15 (3 H, s), 1.6–1.95 (m), 2.03 (3 H, s), 2.12 (3 H, s), 2.55 (1 H, disappears on addition of D_2O), 2.86 (1 H, disappears on addition of D_2O), 4.14 (1 H, d, J = 11 Hz), 4.25 (2 H, s), 5.25 (1 H, d of t), 5.78 (1 H, d, J = 11 Hz), 6.32 (1 H, m), 7.28 (1 H, s), and 7.38 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 464 (M^+, 10), 344 (100), and 81 (95).

Anal. Calcd for $C_{24}H_{32}O_8$: C, 62.06; H, 6.94. Found: C, 61.91; H, 7.02.

Alkaline Hydrolysis of Nepetaefuranol (11).—To a solution of 84.4 mg (0.20 mmol) of nepetaefuranol (**11**) in 20 ml of 95% ethanol was added 5.0 ml of a 10% solution of ethanolic potassium hydroxide. The solution was allowed to stand at room temperature for 1.0 hr, diluted with 50 ml of water, slowly acidified with ice-cold dilute sulfuric acid, and extracted with two 100-ml portions of ethyl acetate. The extract was washed with saturated brine, dried (Na_2SO_4), and evaporated to give colorless crystals. Recrystallization from ethyl acetate–hexane gave 68 of large, colorless prisms: mp 196–197°; $[\alpha]^{25}D$ +22.5° (c 1.080, CH_3OH); ir 3650, 3460, 1735, and 874 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 10:1) δ 1.23 (3 H, s), 1.5–2.0 (m), 2.4–2.7 (m), 3.30 (1 H, d of d, J = 11 and 3 Hz; collapses to d on addition of D_2O, J = 11 Hz), 3.76 (1 H, d of d, J = 3, 11 Hz; collapses to d on addition of D_2O, J = 11 Hz), 4.03 (1 H, d, J = 11 Hz), 4.30 (1 H, broad s), 5.10 (1 H, disappears on addition of D_2O), 5.18 (1 H, disappears on addition of D_2O), 5.28 (1 H, d, J = 5 Hz, disappears on addition of D_2O), 5.40 (1 H, d, J = 11 Hz), 5.68 (1 H, broad t, J = 4 Hz, disappears on addition of D_2O), 6.32 (1 H, m), 7.30 (1 H, s), and 7.39 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 380 (M^+, 4) and 81 (100).

Anal. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C, 63.15; H, 7.31.

Acetylation of Hydrolyzed Nepetaefuranol (13).—A mixture of 38.0 mg (0.10 mmol) of the tetraol **13** in 1.0 ml of acetic anhydride was warmed (to dissolve), cooled to room temperature, and treated with 1 drop of anhydrous pyridine. The mixture was allowed to stand at room temperature for 16 hr, added to 100 ml of ice-cold water, allowed to stand at room temperature for 1.5 hr, and extracted with two 100-ml portions of ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and evaporated to give 37 mg of a gum: ir ($CHCl_3$) 3600, 1740, 1725, and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 1:1) δ 1.16 (3 H, s), 2.13 (3 H, s), 4.14 (1 H, d, J = 11 Hz), 4.20 (2 H, s), 4.35 (1 H, broad s), 5.40 (1 H, d, J = 11 Hz), 6.33 (1 H, m), 7.30 (1 H, s), and 7.35 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 422 (M^+, 5) and 81 (100). This compound (R_f 0.39) was readily separated from nepetaefuranol (**11**, R_f 0.52) in a mixed tlc (50% ethyl acetate in benzene).

Hydrogenation of Nepetaefuranol (11).—A solution of 84.4 mg (0.20 mmol) of nepetaefuranol (**11**) in 15 ml of 95% ethanol was hydrogenated over 90 mg of prereduced 10% palladium on charcoal at atmospheric pressure and room temperature until absorption ceased; 12 ml of hydrogen was absorbed during 10 min. Removal of the catalyst and solvent gave a solid which was crystallized from acetone–hexane and then from ethyl acetate–hexane to give 53 mg of **32** as colorless plates, mp 234–236°, mass spectrum m/e (rel intensity) 426 (M^+, 1) and 348 (60).

Reaction of Nepetaefuranol with Phosphorus Oxychloride.—To a solution of 84.4 mg (0.20 mmol) of **11** in 10 ml of anhydrous pyridine was added 1.0 ml of redistilled, anhydrous phosphorus oxychloride. The mixture was then stirred at 100° for 4 hr, cooled to *ca.* 10°, poured into 100 g of crushed ice, and extracted with 150 ml of ether. The extract was washed with two 125-ml portions of water, dried (Na_2SO_4), and evaporated.

The residue was further dried at 40° *in vacuo* (0.10 mm) to yield 43 mg of a gum which was crystallized from methylene chloride–hexane (at 0°) to give **15** as needles: mp 65–68°; ir ($CHCl_3$) 1740, 1725, 1340, and 875 cm^{-1}; nmr ($CDCl_3$) δ 1.16 (3 H), 2.04 (3 H, s), 3.25 (1 H, d, J = 10 Hz), 3.60 (1 H, d, J = 10 Hz), 4.30 (1 H, d, J = 11 Hz), 4.67 (1 H, d, J = 11 Hz), 5.11 (1 H, d of t), 6.26 (1 H, m), 7.26 (1 H, s), and 7.40 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 424 (M^+, 12) and 81 (100). This unstable compound gave a persistent green color in the Beilstein test.

Reduction of Nepetaefuranol with Lithium Aluminum Hydride.—A solution of 84.4 mg (0.20 mmol) of **11** in 5 ml of anhydrous tetrahydrofuran was added to a stirred suspension of 400 mg of lithium aluminum hydride in 10 ml of anhydrous tetrahydrofuran. The mixture was heated under reflux with stirring for 3 hr, cooled with an ice bath, and treated with ethyl acetate to destroy excess reagent. The cold mixture was added to 10 ml of ice-cold, 5% sulfuric acid, and extracted with two 50-ml portions of ethyl acetate. The extract was washed with saturated brine, dried ($MgSO_4$), and evaporated to give a gum which, on addition of hexane, gave 72 mg of **18** as an amorphous solid: mp 108–113°; ir 3600 and 3500 cm^{-1}, with no carbonyl absorptions; nmr (DMSO-d_6–$CDCl_3$, 3:1) δ 1.03 (3 H, s), 3.30 (1, H, d, J = 11 Hz), 3.35 (1 H, d, J = 11 Hz), 3.74 (2 H, m), 4.07 (2 H, m), 4.30 (1 H, m), 6.35 (1 H, m), 7.33 (1 H, s), and 7.42 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 384 (M^+, 4) and 81 (100).

Reaction of Nepetaefuranol (11) with Sodium Periodate (Norketone 16).—To a stirred solution of 42.2 mg (0.10 mmol) of **11** in 8 ml of ethanol and 8 ml of water was added a solution of 120 mg of sodium acetate in 1.0 ml of water, followed by 110 mg of sodium metaperiodate in 2 ml of water during 5 min. The mixture was stirred at room temperature for a further 1 hr, diluted with 25 ml of water, and extracted with 100 ml of ethyl acetate. The extract was washed with 100 ml of saturated brine followed by 100 ml of water, dried ($MgSO_4$), and evaporated to give a gum. Crystallization of this material from methylene chloride–hexane gave 33 mg of nor ketone **16** as colorless needles: mp 188–189°; ir 3450, 1740–1720 (broad), and 875 cm^{-1}; nmr (DMSO-d_6–$CDCl_3$, 1:5) δ 1.16 (3 H, s), 1.5–1.9 (m), 1.98 (3 H, s), 2.3–2.6 (m), 3.58 (2 H, d of d, J = 13 and 4 Hz), 4.07 (2 H, d, J = 12 Hz), 4.27 (2 H, d, J = 12 Hz), 5.20 (1 H, s, disappears on addition of D_2O), 5.50 (1 H, d of t), 6.30 (1 H, m), 7.24 (1 H, s), and 7.36 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 390 (M^+, 13), 236 (100), and 81 (95).

Anal. Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.83; H, 6.72.

Elimination of Acetic Acid from 16 (α,β-Unsaturated Ketone 17).—A solution of 30 mg (0.077 mmol) of **16** in ethyl acetate–benzene (1:10) was chromatographed on 100 g of neutral alumina (Woelm, activity I) with 15% ethyl acetate in benzene as eluent. The main fraction was collected (as shown by tlc, 20% ethyl acetate in benzene), and the solvents were removed, leaving 24 mg of a gum. Preparative scale tlc (1 mm thick plates, 10% ethyl acetate in benzene) separated this material into two components and the major component (**17**, 17 mg) solidified: mp 175–177°; ir ($CHCl_3$) 3450, 1720, 1670, 1630, and 870 cm^{-1}; nmr ($CDCl_3$) δ 1.12 (3 H, s), 3.92 (1 H, d, J = 9 Hz), 4.54 (1 H, d, J = 9 Hz), 6.25 (1 H, m), 6.41 (1 H, d, J = 9) Hz), 6.81 (1 H, d, J = 9 Hz), 7.16 (1 H, s), and 7.35 (1 H, s); mass spectrum m/e (rel intensity) 330 (M^+, 50) and 81 (100). The minor component (5 mg) had a mass spectrum virtually identical with that of **17**.

Reaction of Nepetaefuran (2) with Perchloric Acid.—To a solution of 40.4 mg of nepetaefuran in 4 ml of tetrahydrofuran was added to 0.4 ml of perchloric acid, and the mixture was allowed to stand at room temperature for 15 hr. The mixture was diluted with 50 ml of saturated brine and extracted with 50 ml of ethyl acetate. The extract was washed with 50 ml of 1% $NaHCO_3$ solution followed by two 50-ml portions of saturated brine, dried (Na_2SO_4), and evaporated to leave a gum. Tlc (40% ethyl acetate in benzene) showed the product to be a complex mixture containing compounds **7**, **11**, **13**, and **21**. Chromatography of the mixture on neutral alumina (Woelm, activity II) with 75–80% ethyl acetate in benzene gave 11 mg of nepetaefuranol (**11**) (identified by melting point, mixed tlc, and ir spectrum). Reaction of nepetaefolin (**1**) under the above conditions gave an identical result.

Conversion of Nepetaefuranol (11) into 7.—A solution of 42.2 mg (0.10 mmol) of **11** in 5 ml of anhydrous pyridine containing 20 mg of *p*-toluenesulfonyl chloride was allowed to stand at 0° overnight. The solution was diluted with 75 ml of saturated brine and extracted with 75 ml of ethyl acetate. The extract was washed with saturated brine, dried (Na_2SO_4), and evaporated at 30° to give a gum which was dried *in vacuo* (0.02 mm) for 3 hr. This material was dissolved in 5 ml of 90% ethanol, treated with 5 ml of 10% potassium hydroxide, and allowed to stand at room temperature for 2 hr. After dilution with 50 ml of saturated brine, the mixture was extracted with 100 ml of ethyl acetate, and the extract was dried (Na_2SO_4) and evaporated, leaving 32 mg of a gum, which was chromatographed over 25 g of neutral alumina (Woelm, grade II) with 80% ethyl acetate in benzene to give 14 mg of **7** (identified by mixture melting point, mixed glc, and ir spectrum).

Reaction of 10 with *p*-Toluenesulfonyl Chloride (Tosylates 23 and 24).—A solution of 28 mg (0.076 mmol) of **10** in 1.5 ml of anhydrous pyridine containing 35 mg of *p*-toluenesulfonyl chloride was allowed to stand at room temperature for 14 hr. The mixture was diluted with 5 ml of water and extracted with two 10-ml portions of ethyl acetate. The extract was washed twice with a saturated solution of $CuSO_4$ and once with saturated $NaHCO_3$ solution, and dried (Na_2SO_4). Evaporation of the solvent gave 33 mg of a residue which crystallized, and which was shown by tlc (3% methanol in benzene) to consist of two closely related compounds (**23** and **24**); mass spectrum m/e 522 (M^+).

Reduction of Tosylates 23 and 24 with Lithium Aluminum Hydride. Leonotol (25).—To a solution of 33 mg (0.063 mmol) of **23** and **24** in 10 ml of anhydrous tetrahydrofuran was added 15 mg of lithium aluminum hydride and the mixture was heated under reflux for 4 hr. The mixture was treated cautiously with water to decompose excess reagent and extracted with ether. The extract was dried (Na_2SO_4) and the solvent was evaporated to leave a gum which, according to tlc, contained leonotol (**25**) in admixture with several other components. Preparative layer chromatography (2% methanol in benzene) with methanol as eluent, followed by crystallization from chloroform–hexane, afforded 8 mg of **25**, mp 139–140°, identified with leonotol by mixture melting point, ir spectrum, mixed tlc, and mass spectrum.

Epoxy Alcohol (21).—To a stirred solution of 40.4 mg (0.10 mmol) of nepetaefolin (**1**) in a 4 ml of tetrahydrofuran was added 0.4 ml of 60% perchloric acid. A slightly exothermic reaction ensued, after which the mixture was stirred at room temperature for 2.25 hr and then added to 40 ml of saturated brine and extracted with 50 ml of ethyl acetate. The extract was washed with 40 ml of 1% sodium bicarbonate solution and with two 40-ml portions of saturated brine, and dried (Na_2SO_4). Evaporation of the solvent left 38 mg of a gum, which was chromatographed on 20 g of neutral alumina (Woelm, activity II) with 40% ethyl acetate in benzene as eluent. The major fraction gave, after evaporation of the solvents, a colorless gum which solidified *in vacuo* during 4 hr to give 27 mg of **21** in a semicrystalline state: mp 146–149°; $[\alpha]^{25}D$ −4.4° (*c* 1.45, $CHCl_3$); ir 3330, 1740, 1700, 1380, 1240, 1040, and 875 cm^{-1}; nmr ($CDCl_3$) δ 1.08 (3 H, s), 1.96 (3 H, s), 3.52 (1 H, d, J = 11 Hz), 3.66 (1 H, d, J = 11 Hz), 4.36 (1 H, d J = 11 Hz), 4.70 (1 H, d, J = 11 Hz), 5.07 (1 H, d of t), 6.24 (1 H, m), 7.19 (1 H, s), and 7.31 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 404 (M^+, 4) and 81 (100).

Anal. Calcd for $C_{22}H_{28}O_7$; C, 65.33; H, 6.98. Found: C, 64.97; H, 7.01.

Treatment of nepetaefuran (**2**) under the above conditions also gave **21**. Acetylation of **21** as described for **7** gave diacetate **32**, identical with material obtained previously.

Reduction of Leonotin. Leonontol (25).—A solution of 34.8 mg (0.01 mmol) of leonotin (**20**) in 1.0 ml of anhydrous tetrahydrofuran was added to a stirred suspension of 50 mg of lithium aluminum hydride in 3.0 ml of tetrahydrofuran. The mixture was heated under reflux with stirring for 4 hr, cooled (ice bath), and treated slowly with 10 ml of ethyl acetate. The resulting slurry was added to 50 ml of ice-cold, 5% sulfuric acid and the mixture was extracted with two 50-ml portions of ethyl acetate. The extract was washed with saturated brine until it was neutral, dried (Na_2SO_4), and evaporated to give 32 mg of a gum. Crystallization from ethyl acetate–hexane (1:5) gave **25** as colorless prisms: mp 136–138°; $[\alpha]^{25}D$ +32.0° (*c* 1.07, $CHCl_3$); ir ($CHCl_3$) 3600, 3300, 1021, and 873 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (3 H, s), 1.25 (3 H, s), 1.42 (3 H, s), 3.18 (1 H, d, J = 11 Hz), 4.12 (1 H, d of t), 4.22 (1 H, d, J = 11 Hz), 5.0–5.6 (broad, disappears on addition of D_2O), 6.35 (1 H, m), 7.27 (1 H, s), 7.36 (1 H, t, J = 1 Hz); mass spectrum m/e (rel intensity) 352 (M^+, 2).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.44; H, 9.32.

Registry No.—**1**, 29606-32-4; **2**, 29461-24-3; **4**, 37705-47-8; **5**, 37759-46-9; **6**, 29606-33-5; **7**, 37759-48-1; **8**, 37759-49-2; **9**, 37705-50-3; **10**, 29461-38-9; **11**, 29722-58-5; **12**, 37759-52-7; **13**, 37759-53-8; **15**, 37759-54-9; **16**, 37759-55-0; **17**, 37759-56-1; **18**, 37705-51-4; **20**, 26549-00-8; **21**, 37759-57-2; **23**, 37759-58-3; **24**, 37759-59-4; **25**, 29389-54-6; **32**, 37759-61-8.

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Biogenetically Patterned Total Syntheses of (+)-Occidentalol and 7-Epi-(−)-occidentalol[1,2]

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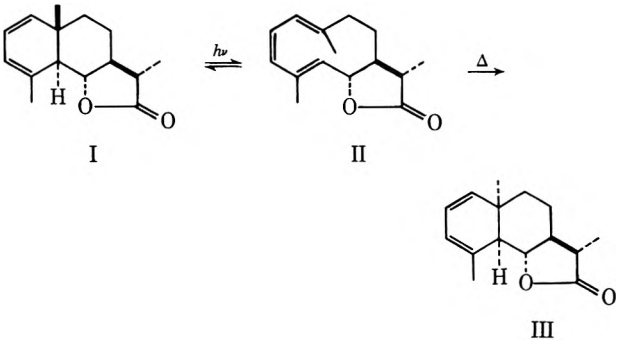
Diene (−)-**9** was prepared from (−)-**3** by standard procedures. Irradiation of **9** at −78° led to a probable photoequilibrium between **9** and an unstable intermediate believed to be **10**. Cyclodecatriene **10** underwent thermally induced cyclization at > −30° to yield cis-fused dienes (−)-**11** and (+)-**12** in a 2:1 ratio. The stereostructures assigned to the cis-fused dienes were based on conformational analysis, nmr, ORD, and CD data, and the finding that (−)-**11** is converted to (−)-**12** by base-catalyzed epimerization at C-7. Treatment of (+)-**12** with CH_3Li afforded (+)-occidentalol [(+)-**2**], thereby establishing the absolute stereostructure of this natural product. Similarly, (−)-**12** gave (−)-occidentalol [(−)-**2**] and (−)-**11** gave 7-epi-(−)-occidentalol [(+)-**1**]. A hypothetical biosynthetic scheme is outlined for the formation of (+)-occidentalol and some other known cis-fused eudesmanes by disrotatory cyclization of *trans,cis,trans*-cyclodecatrienes derivable from farnesol. A biogenetic-type synthesis of (+)-**2** and (+)-**1** *via* thermally induced cyclization of **15**, presumed to be generated during irradiation of (−)-**14**, is also described.

(+)-Occidentalol, a eudesmane-type sesquiterpene alcohol isolated from the wood of *Thuja occidentalis* L.[3,4] and *T. koraiensis* Nakai,[5] has been shown to have stereostructure (+)-**2**.[6] The coincident presence of a rarely occurring cis ring junction and a 1,3-diene system in occidentalol suggests that a unique biosynthetic pathway[7] involving disrotatory thermal cyclization[8] of a *trans,cis,trans*-cyclodecatriene intermediate derivable from farnesol may be operative in the formation of (+)-**2** and related cis-fused eudesmanes. We report here two total syntheses of (+)-**2** and (+)-**1** by routes (see Scheme I) which parallel the presumed biogenesis[7] and would seem to be generally applicable to the synthesis of other polyfunctionally substituted cis-fused decalins. A preparation of (−)-**2** from a common intermediate is also described.[9-11]

Total Synthesis and Stereochemistry of (+)-Occidentalol, (−)-Occidentalol, and 7-Epi-(−)-occidentalol



[(+)-**2**, (−)-**2**, and (+)-**1**].—The observation that thermally induced cyclization of cyclodecatriene II (generated by photolysis of I) affords cis-fused diene III[12] provided and experimental basis for the hypothetical biosynthetic scheme for (+)-**2** already outlined[7] as well as the biogenetically patterned syntheses of (+)-**2** shown in Scheme I.

Thus, keto ester (−)-**3**, prepared from (+)-carvone,[13] was brominated to yield the 2α-bromo derivative **4**. Dehydrobromination of crude **4** with LiBr and $LiCO_3$ in DMF at 120° gave the olefinic keto ester **5**, which could be purified by recrystallization of the corresponding acid, **6**, followed by remethylation of **6** with CH_2N_2 in ether. Reduction of either **5** or **6** with aluminum isopropoxide gave a mixture of olefinic hydroxy esters, **7** and **8**, *via* hydrolysis of the intermediate isopropyl ester analogs. Dehydration of the oily mixture of epimeric alcohols **7** and **8** by heating at 220° in the presence of alumina containing 2% pyridine[12] afforded the trans-fused diene **9** in ~25% yield. The diene **9** analyzed correctly for $C_{14}H_{20}O_2$ but contained 8–10%

(1) We thank the National Institutes of Health for financial support of this research (Grant GM13441).

(2) Reported in part at the 4th Midwest Regional Meeting of the American Chemical Society, Manhattan, Kans., Nov 1, 1968.

(3) (a) T. Nakatsuka and Y. Hirose, *Bull. Agr. Chem. Soc. Jap.*, **20**, 215 (1956); (b) *ibid.*, **23**, 140 (1959).

(4) E. von Rudloff and H. Erdtman, *Tetrahedron*, **18**, 1315 (1962).

(5) B. Tomita, Y. Hirose, and T. Nakatsuka, *J. Jap. Wood Res. Soc. (Mokuzai Gakkaishi)*, **15**, 76 (1969).

(6) A. G. Hortmann and J. B. DeRoos, *J. Org. Chem.*, **34**, 736 (1969), and references cited therein.

(7) A. G. Hortmann, *Tetrahedron Lett.*, 5785 (1968).

(8) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, Weinheim, Germany, 1970, pp. 38–64.

(9) Subsequent to our preliminary report of this work (ref 2) we were informed by Professor T. Asao (July 28, 1970) that his group has also prepared (+)-**1** and (−)-**2**: M. Ando, K. Nanaumi, T. Nakagawa, T. Asao, and K. Takase, *Tetrahedron Lett.*, 3891 (1970). Two unambiguous total syntheses of (+)-**2** have also been published recently; see ref 10 and 11. See also D. S. Watt and E. J. Corey, *Tetrahedron Lett.*, 4651 (1972), for a synthesis of (±)-**2**.

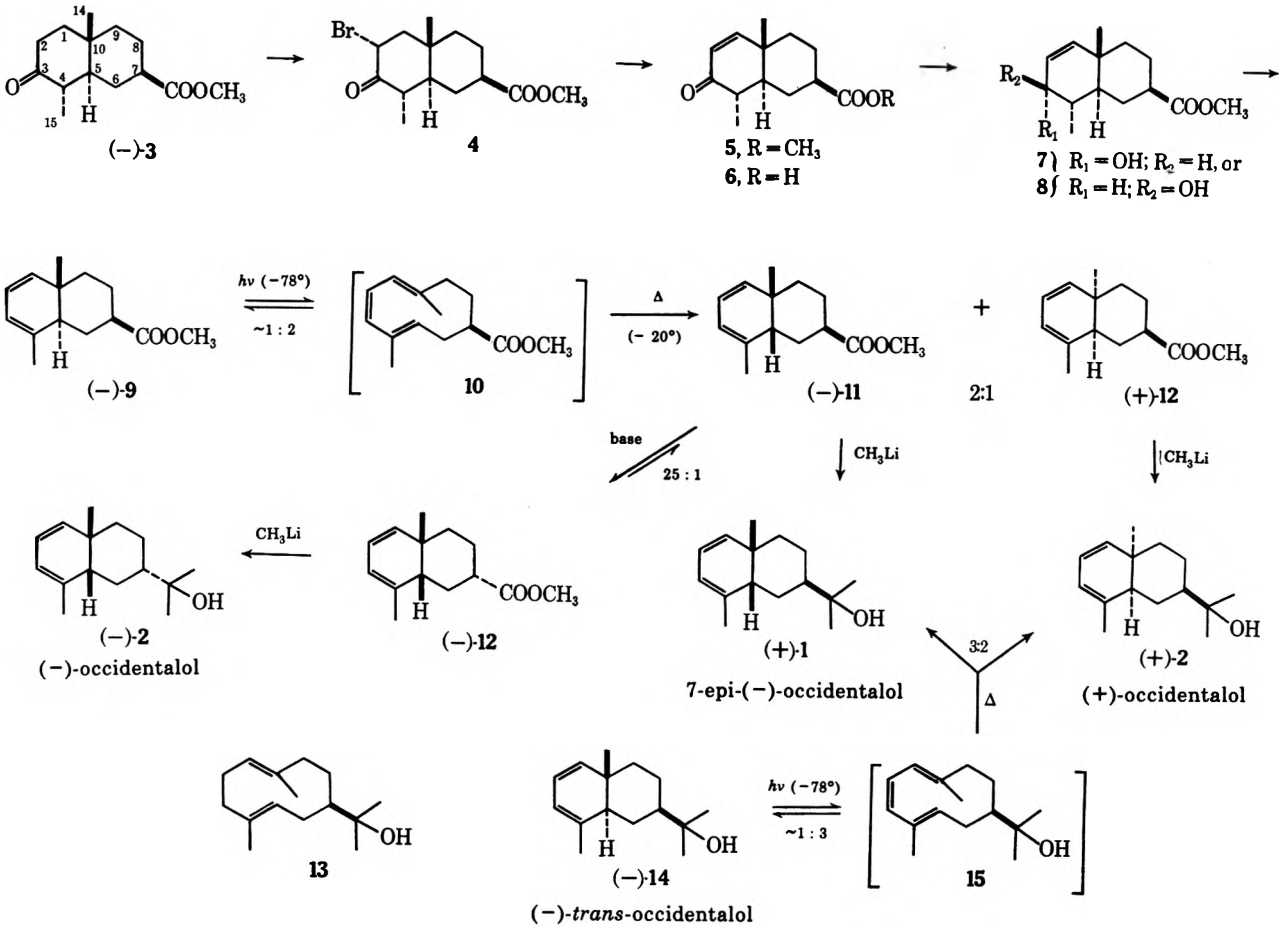
(10) M. Sergent, M. Mongrain, and P. Deslongchamps, *Can. J. Chem.*, **50**, 336 (1972).

(11) Y. Amano and C. H. Heathcock, *ibid.*, **50**, 340 (1972).

(12) E. J. Corey and A. G. Hortmann, *J. Amer. Chem. Soc.*, **85**, 4033 (1963); **87**, 5736 (1965).

(13) A. G. Hortmann, J. E. Martinelli, and Y. Wang, *J. Org. Chem.*, **34**, 732 (1969).

Scheme I



of a major impurity (detectable by nmr analysis) which could not be removed by vpc, adsorption chromatography, or recrystallization of the acid corresponding to **9**. Subsequent attempts to prepare **9** in higher purity by heating pure **7**[14] at lower temperature (190°) in the presence of alumina containing 2% of quinoline afforded a similar yield of **9** which still contained 3–6% of the impurity mentioned above.[15]

The trans-fused diene **9** was irradiated in ether solution at −78° under an argon atmosphere using a small low-pressure mercury–argon discharge tube (Orien Optics Type C-13-61, 90% of output emitted at 2537 Å). Vpc analysis of aliquots withdrawn at 90–120-min intervals and warmed to 25° indicated the gradual appearance of two new peaks due to substances having greater mobility than **9** and shown by subsequent conversions (see below) to be cis-fused dienes **11** and **12** in a ratio of 2:1. A photostationary state was eventually reached at −78°, as evidenced by attainment of an approximately constant ratio (4:2:3) of **11**:**12**:**9** at 25°. On the basis of existing analogy,[12] *ca.* 33% of diene **9** remained in the steady-state mixture which resulted at −78°; similarly, the other component of the mixture at low temperature is considered to be triene **10**. Experiments in which the irradiation was monitored by uv spectroscopy at −70° provided support for the latter assumption. An increase in absorption at 222 and *ca.* 300 nm was found to occur as the absorption due to **9** at 266 nm steadily decreased during irradiation; warming aliquots of the irradiated solution prior to attainment of (or nearly at) the photostationary state, followed by recooling and redetermination of the spectrum, showed nearly complete restoration of the original absorption at 266 nm due to formation of **11** and **12** from **10**.[16,17] Observation of the rate of change in OD_{266} of the photolysis solution upon warming indicated that **10** had an approximate half-life of 15–30 min at −20°.

Continued irradiation at the photostationary state led to the gradual formation of at least three new substances (not further investigated) as evidenced by in-

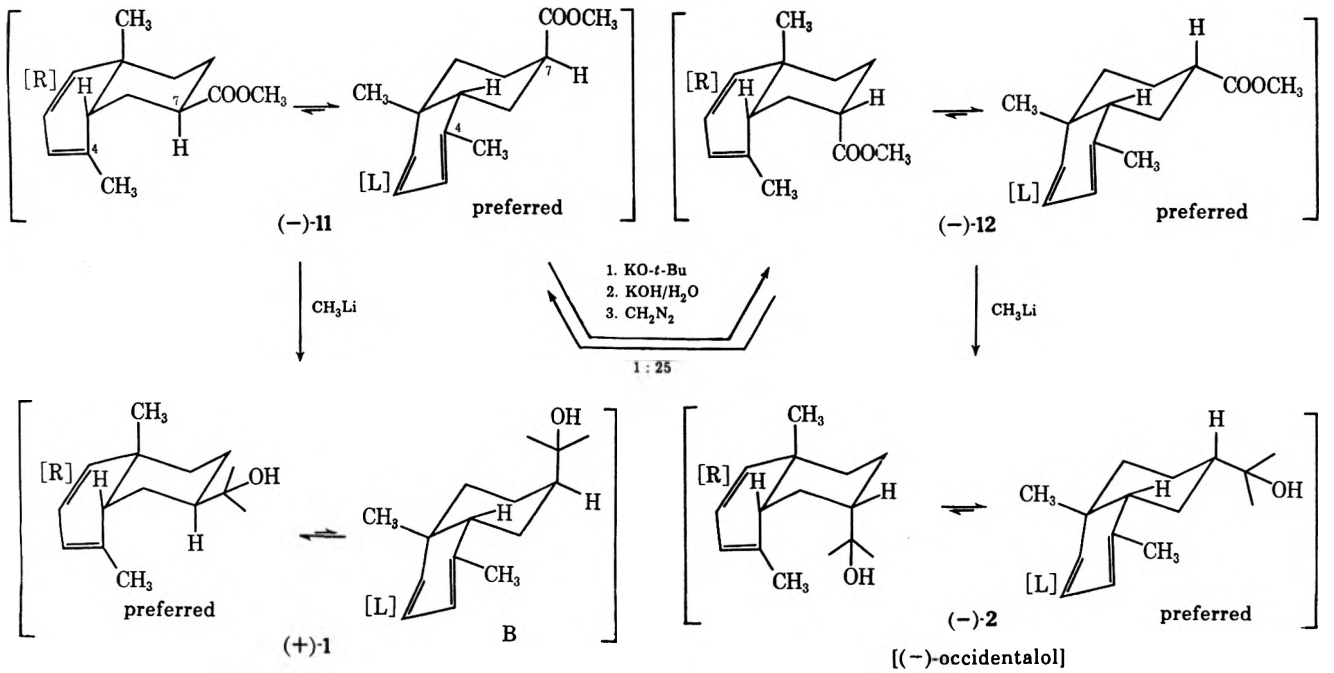
(14) The major isomer of the mixture of **7** and **8** could be crystallized in pure form and was arbitrarily designated as **7**. The configuration of **7** at C-3 was indeterminable.

(15) A possible structure for the impurity could be the $\Delta^{2,4}$ isomer of **9** which may be formed from **9** at elevated temperature by an allowed suprafacial 1,5 hydrogen shift. See R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 2511 (1965); **88**, 2078 (1966); S. W. Staley and T. J. Henry, *ibid.*, **93**, 1292 (1971); H. C. Barrett and G. Büchi, *ibid.*, **89**, 5665 (1967). Attempts to prepare **9** at lower temperature (<150°) by pyrolysis of the 3,5-dinitrobenzoate of **7** [*cf.* A. W. Burgstahler and R. E. Sticker, *Tetrahedron*, **24**, 2435 (1968)], and by heating **7** with (carboxysulfamoyl)triethylammonium hydroxide inner salt methyl ester [*cf.* E. M. Burgess, H. R. Penton, Jr., and E. A. Taylor, *J. Amer. Chem. Soc.*, **90**, 4744 (1968) and references cited therein] gave less satisfactory results (see Experimental Section).

(16) However, upon warm up to 25° the absorption at 222 nm, which increased markedly during the irradiation, only receded to the extent of about 50% (see lines a, b, and b′ of Figure 1). Such behavior might be attributable to the presence of the $\Delta^{2,4}$ isomer of **9** (see ref 15). Photolysis of the $\Delta^{2,4}$ isomer of **9** would yield a ring-opened triene which would not recyclize at 25° and would be expected to have high end absorption and a somewhat more intense uv max than the $\Delta^{2,4}$ compound at *ca.* 260 nm; the latter absorption at 260 nm combined with a low-intensity maximum for **10** at *ca.* 280 nm[17] (note behavior at 300 nm, lines a, b, and b′ in Figure 1) would account for the observation that, whereas only 33% of **9** remains at the photostationary state (by vpc analysis of warmed solutions), OD_{266} is still 60% of the original value due to **9**.

(17) In addition to the uv max (MeOH) 211 nm (ϵ ~16,800) already reported[12] for II, a low-intensity uv max possibly arising from II at ~285 nm (ϵ < 2000) was also observed for solutions of I and II near the photostationary state (A. G. Hortmann, Ph.D. Thesis, Harvard University, 1964, p 40).

SCHEME II[a]



[a] Chirality of 1,3-diene system denoted by [R] or [L].

complete restoration of absorption at 266 nm upon warming to 25°, and by vpc analysis of the products obtained in earlier preparative experiments. In later preparative experiments, irradiation was halted prior to attainment of the photostationary state in order to simplify the vpc purification of **11** and **12** by minimizing the amounts of overirradiation products present.

A facile determination of the stereostructures of the two new dienes (**11**, $[\alpha]D$ −213°; **12**, $[\alpha]D$ +336°) obtained in the photolysis–recyclization sequence was effected by a study of their relative stabilities toward base-catalyzed epimerization at C-7. Treatment of the major diene [(−)-**11**] with potassium *tert*-butoxide, followed by hydrolysis of the resulting mixture of *tert*-butyl esters and methylation with CH_2N_2, afforded a mixture of methyl esters in a 25:1 ratio (nmr and vpc analysis). The minor component had the vpc mobility of the starting ester [(−)-**11**]; the major component had vpc retention time and ir and nmr spectra identical with those of **12**. Thus, **11** and **12** can only be cis-fused dienes, since epimerization of the only possible remaining diastereomer, the 7 epimer of the enantiomer of **9** (derivable by conrotatory photocyclization[8] of **10**) would have yielded the enantiomer of **9** under the epimerization conditions; similarly, (−)-**11** could be converted (*via* epimerization at C-7) only to the *enantiomer* of the minor diene (+)-**12** obtained in the photolysis–recyclization sequence.[18] Consequently, the ester (−)-**11** was assigned the stereostructure shown in Schemes I and II (two equatorial and two axial substituents on the B ring in chair form) on the basis of its observed epimerization to afford the more stable cis-fused structure [*i.e.*, (−)-**12**; three equatorial and one axial substituents on B ring].

Treatment of (−)-**11** with methyllithium afforded (+)-**1**, the structure which had been generally accepted[19] for (+)-occidentalol at the time that this work was in progress. Comparison of the ir and nmr spectra of synthetic (+)-**1** with spectra run on authentic (+)-occidentalol kindly supplied by Dr. E. von Rudloff clearly indicated that the two compounds were dissimilar. When, however, (+)-**12** was treated with CH_3Li, the synthetic (+)-**2** obtained was essentially identical in all respects with authentic (+)-occidentalol; similarly, treatment of (−)-**12** with CH_3Li afforded (−)-**2**, the enantiomer of natural occidentalol.[20]

These results led to a revision of the structure [(+)-**1**] previously accepted[19] for occidentalol to (+)-**2**, and were subsequently confirmed by a careful analysis of the 100-MHz nmr spectrum of (+)-**2**.[6]

Since this chemically based structural revision relied completely on the correctness of the structural assignments for cis-fused dienes **11** and **12**, several aspects of the nmr, CD, and ORD data for the esters and derived alcohols which vitiate any arguments for reversal of our original assignment of stereostructures to **11** and **12** deserve comment. In the vinyl H region of the nmr spectra (60 MHz) of **2**, **12**, and **11**, remarkably similar AMX patterns for H-1,2,3 are observed, whereas for **1** a complex ABC system is observed. In both alcohol **2** and ester **12** the nonsteroid conformations having their

(18) The conclusions rely on the reasonable assumption that epimerization at C-7 does not occur during photolysis of **9** or the recyclization of **10**.

(19) H. Ziffer, T. J. Batterham, U. Weiss, and E. von Rudloff, *Tetrahedron*, **20**, 67 (1964).

(20) The structural work described in this paper was originally undertaken on the assumption, based on optical data [K. Mislow and A. Moscowitz, *Tetrahedron Lett.*, 699 (1963)] and the reservations cited previously (see footnote 17 in ref 6), that (+)-**1** and (+)-**2** were *both* likely structures for (+)-occidentalol. Structure (−)-**1** was also considered as possible on the assumption that appreciable (yet minor) amounts of B′, the enantiomer of conformer B shown for (+)-**1** in Scheme II, in equilibrium with A′ might still give rise to a net positive Cotton effect. Although subsequent consideration of the absolute magnitude of the Cotton effect due to (+)-occidentalol seemed to weaken this argument (see discussion in ref 22), it is interesting to note, in retrospect, the contrast between $[\phi]_{286}$ +13,300 (extremum) for (+)-**1** and $[\phi]_{284}$ +43,000[19] for (+)-**2**.

10-CH_3 group and C-7 substituents equatorially oriented relative to ring B would be expected to be highly preferred;[6] thus, the nmr data suggest that **11** also prefers to exist in a nonsteroid conformation (see Scheme II). Support for this suggestion comes from the width at half-weight ($W_{1/2}$) of ~12 Hz observed for the resonance peak at δ 2.48 due to H-7 in **11** which is consistent with an equatorial orientation for H-7,[21] and from the ORD and CD curves of (−)-**11**, which show a strong negative Cotton effect consistent with a skewing of the cisoid butadiene in (−)-**11** in the sense of a left-handed helix.[22-24] Conversion of the 7-$COOCH_3$ group in (−)-**11** (axially oriented) to a more bulky 7-$CH(CH_3)_2$-OH group in (+)-**1** results, as would be expected, in an alteration of the nonsteroid conformation of **11** to that of the steroid type in **1** having its 10-CH_3 axially oriented and 7-$CH(CH_3)_2OH$ equatorially oriented;[23] conclusive support for this change in conformational preference in going from (−)-**11** to (+)-**1** comes from the ORD and CD curves of (+)-**1**, which exhibit a positive Cotton effect, indicating that the skew sense of the cisoid butadiene in (+)-**1** is that of a right-handed helix.[25] The strong conformational preferences assumed above for **12** and **2** and indicated in Scheme II were established by the observation of strong positive Cotton effects in the ORD and CD curves of (+)-**2** and (+)-**12**.[26]

The photolysis–recyclization sequence described above would appear to be specifically applicable to the synthesis of other known cis-fused eudesmanoid compounds incorporating either a 1,3-diene[24] or a Δ^1-3-ketone system;[27,28] more generally, it opens a route to polyfunctionally substituted cis decalins which originate from more readily available and predictably substituted trans decalins. Of additional interest is the finding that the *less stable* of the two possible cis-fused products is the predominant isomer formed in the thermally induced cyclization of **10**.

Of relevance to the photochemical studies described above are other recent studies of photoequilibria between 1,3-cyclohexadienes and 1,3,5-hexatrienes[29] and investigations of dihydronaphthalene–cyclodecapentene valence bond isomer systems.[30]

Biogenetic-Type Synthesis of (+)-1 and (+)-2.—Having established its absolute stereostructure, we turned our attention to a biogenetic-type synthesis[31] of (+)-occidentalol (**2**) modeled on its presumed biogenesis.[7] Generation of the required cyclodecatriene alcohol **15**, which in nature may be derived from "hedycaryol" (**13**),[32] was accomplished by photofission of diene (−)-**14** at −78° in a manner similar to that described for **9** → **10**. Irradiation was stopped when the system had reached the photostationary state. Warming the photolysis solution to 25° afforded a mixture of (+)-**2**, (+)-**1**, and **14** in a ratio of 6:9:5, respectively, thus providing direct experimental support for the plausibility of the postulated role of **15** in the biosynthesis of (+)-**2**.

The value of 1.5 found for [(+)-**1**/(+)-**2**] in the thermally induced cyclization of **15** is of particular interest in that it is very close to that found for [(+)-occidol (**20**)[33]/(+)-occidentalol (**2**)] in *T. occidentalis* (1.3)[34] and *T. koraienis* (1.7).[5] Since (+)-occidol (**20**) is a major constituent of the wood oil in both species (46% in the former, 12% in the latter), and since (+)-**1** is apparently not present in significant amount (if at all) in the oil of either, it is tempting to suggest that (+)-**20** arises in *Thuja* by an efficient conversion of any (+)-**1** formed *in vivo* by nonenzymatically controlled cyclization of **15**, whereas (+)-**2** formed *in vivo* from **15** remains unaltered.

An elaboration of the biogenetic scheme outlined previously[7] for the formation of cis-fused eudesmane-type sesquiterpenes, including the dehydrochamaecynenes (**18**)[24] and chamaecynones (**19**),[27] appears in Scheme III.[35] Also depicted is a novel suggestion due to Tomita and Hirose[36] for the formation (*via* **15** and **17**) of the unusual dihydrooxepin, (+)-occidenol (**21**),[5,36] which coexists with (+)-**2** and (+)-**20** in both *Thuja* species mentioned above.

Experimental Section[37]

3-Oxo-5,7αH,4βH-12,13-bisnoreudesm-1-en-11-oic Acid (6).—Keto ester (−)-**3**[13] (7.14 g, 0.030 mol) in 175 ml of $CHCl_3$ at 5° was treated with 4.92 g (0.031 mol) of Br_2 in 10 ml of CCl_4. The solution was stirred at room temperature until the orange

(21) See M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(22) U. Weiss, H. Ziffer, and E. Charney, *Tetrahedron*, **21**, 3105 (1965).

(23) See ref 6 (footnote 11 and references cited therein) for a discussion of conformational preferences in other known examples of cis-fused eudesmanoid compounds, especially with regard to the orientation of C-7 substituents; see also ref 24.

(24) T. Asao, S. Ibe, K. Takase, Y. S. Cheng, and T. Nozoe, *Tetrahedron Lett.*, 3639 (1968).

(25) That such a conformational change had occurred was also suggested by a marked reversal noted in the vpc mobilities of **1** and **2** when compared with **11** and **12**, by the magnitude of $\Delta[\alpha]_D$ (*cf.* Mislow and Moscowitz in ref 20) noted in going from (−)-**11** to (+)-**1**, and by the differences in the vinyl H region of the nmr spectra of **1** *vs.* **2**, **11**, and **12** already mentioned.

(26) For (+)-**1** to correspond to (+)-occidentalol, as previously supposed (ref 19), would require that the photolysis–recyclization product having $[\alpha]_D$ +336° correspond in structure to that assigned in this work to (−)-**11**, and that this structure exist (to account for the large positive $[\alpha]_D$ and the strong positive Cotton effects observed in its ORD and CD curves) in a preferred conformation differing from that shown in Scheme II (which by itself seems plausible, although it makes nmr data cited for H-7 more difficult to rationalize). However, it then follows that the photolysis–recyclization product which has $[\alpha]_D$ − 213° must have the structure assigned in this work to (+)-**12**, and that this structure would have to exist in the clearly unfavorable conformation having one equatorial and three axial substituents on ring B in a chair form.

(27) T. Nozoe, Y. S. Cheng, and T. Toda, *Tetrahedron Lett.*, 3663 (1966); see also T. Nozoe, T. Asao, M. Ando, and K. Takase, *ibid.*, 2821 (1967).

(28) *Cf.* M. Miyashita, H. Uda, and A. Yoshikoshi, *Chem. Commun.*, 1396 (1969).

(29) W. G. Dauben, J. Rabinowitz, N. D. Vietmeyer, and P. H. Wendschuh, *J. Amer. Chem. Soc.*, **94**, 4285 (1972); W. G. Dauben and M. S. Kellogg, *ibid.*, **93**, 3805 (1971).

(30) S. Masamune and R. T. Seidner, *Chem. Commun.*, 542 (1969); S. Masamune, R. T. Seidner, H. Zenda, M. Wiesel, N. Nakatsuka, and G. Bigam, *J. Amer. Chem. Soc.*, **90**, 5286 (1968); E. E. van Tamelen, T. L. Burkoth, and R. H. Greeley, *ibid.*, **93**, 6120 (1971).

(31) E. E. van Tamelen, *Fortschr. Chem. Org. Naturst.*, **19**, 245 (1961).

(32) Isolation and synthesis of this biogenetically important sequiterpene have been reported: R. V. H. Jones and M. D. Sutherland, *Chem. Commun.*, 1229 (1968); 892 (1970); P. S. Wharton, C. E. Sundin, D. W. Johnson, and H. C. Kluender, *J. Org. Chem.*, **37**, 34 (1972).

(33) T.-L. Ho, *Can. J. Chem.*, **50**, 1098 (1972), and references cited therein.

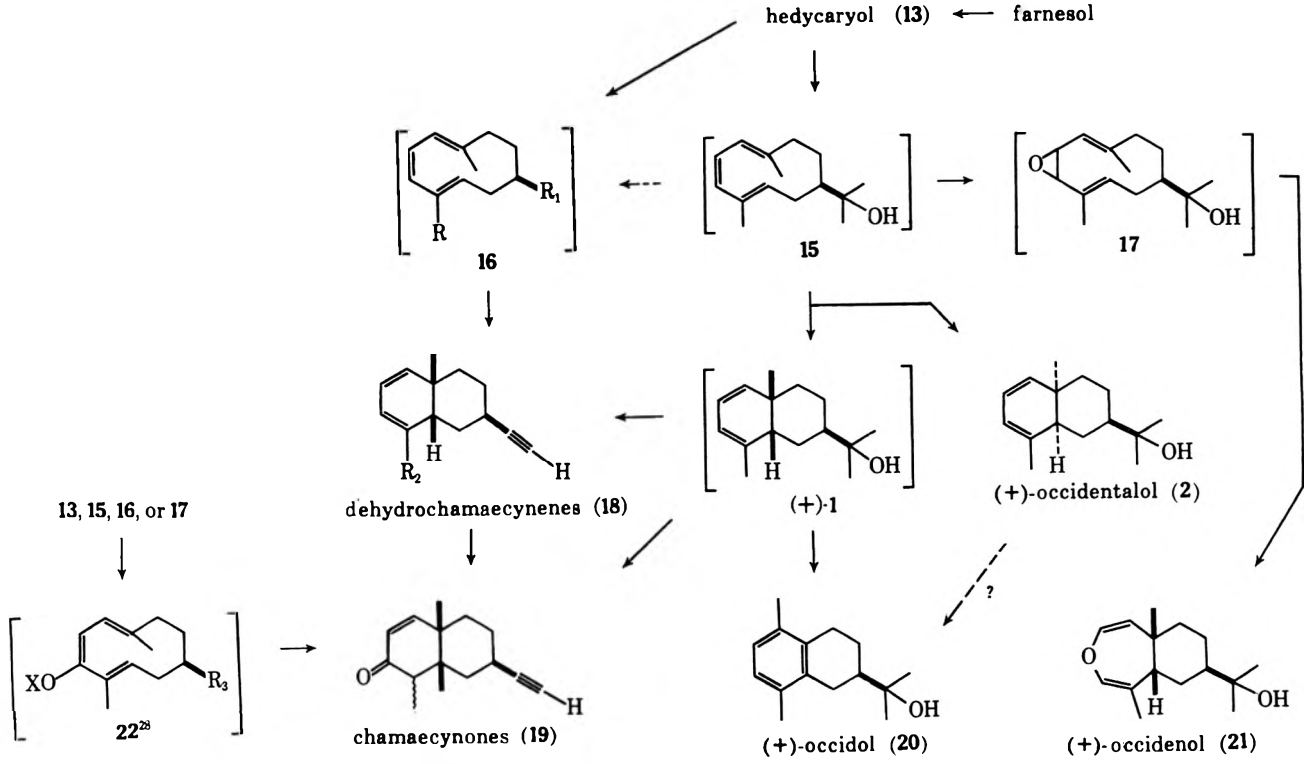
(34) E. von Rudloff and G. V. Nair, *ibid.*, **42**, 421 (1964).

(35) For a discussion of an alternative biosynthetic route to occidentalol (and occidol) see ref 34.

(36) B. Tomita and Y. Hirose, *Tetrahedron Lett.*, 235 (1970).

(37) All boiling points and melting points are uncorrected. Rotations were measured in $CHCl_3$. Infrared spectra were recorded in CCl_4 on a Perkin-Elmer Model 457 grating spectrophotometer. Mass spectra were determined using a Varian M-66 instrument; precise mass determinations have a precision of ±0.03 amu. Uv spectra were recorded in MeOH on Cary 11 and Cary 14 recording spectrophotometers. ORD and CD curves were measured in MeOH using a Durrum-Jasco Model J-20 spectropolarimeter; concentrations are stated in g/100 ml; only extreme values of ϕ and θ and locations of extrema are indicated. Nmr spectra were obtained for solutions in CCl_4 (unless stated otherwise) on a Varian A-60A spectrometer; peak positions are recorded in parts per million (δ) downfield from tetramethylsilane as an internal standard. Microanalyses were performed by Mikroanalytisches Laboratorium, Vienna, Austria.

SCHEME III



color disappeared (0.3 hr). After an additional 0.4 hr, the reaction mixture was poured into a separatory funnel and was washed successively with H_2O, 5% $NaHCO_3$ solution, and brine, dried ($MgSO_4$), and concentrated *in vacuo* at 25–35° to afford a yellow oil containing *ca.* 80 mol %[38] of **4**, the 2α-bromo derivative of **3**. The oil was dissolved in anhydrous DMF (75 ml) containing $LiCO_3$ (6 g) and LiBr (4.5 g). The suspension, in a round-bottom flask and under an atmosphere of N_2, was plunged into an oil bath at 135° and stirred rapidly for 1 hr while the temperature of the reaction mixture was maintained at 120–125°. The hot solution was poured into ice water containing ~3% HCl. The resulting mixture was extracted thoroughly with $CHCl_3$ (5 × 40 ml). A normal work-up procedure afforded an orange oil which was chromatographed on alumina (200 g, Woelm, neutral, activity grade ~I) packed in petroleum ether (bp 63–69°)–benzene (3:1). Elution with 2200 ml of the same solvent pair (2:3) afforded 5.08 g of pale yellow oil containing *ca.* 80% of methyl ester **5** by nmr assay. A solution of the oil in 75 ml of CH_3OH–H_2O (4:1) containing 5% KOH was stirred at room temperature for 20 hr, acidified with dilute HCl, and extracted with $CHCl_3$. The extracts were washed with brine, dried ($MgSO_4$), and concentrated to yield 3.78 g of crude **6** in several crops (mp 125–139°) on crystallization from CH_2Cl_2–petroleum ether. Recrystallization afforded 3.03 g (46%) of pure **6**, mp 138–140°. An analytical sample of **6** exhibited mp 141.5–142.5°; ir ($CHCl_3$) 3550–2450 (s, br), 1700, 1670, and 690 cm^{-1}; uv max 227 nm (ε 8610); nmr ($CDCl_3$) δ 1.13 (s, 3, H-14), 1.15 (d, 3, J = 6.7 Hz, H-15), 5.89 (d, 1, J = 10 Hz, H-2), 6.74 (d, 1, J = 10 Hz, H-1), and 11.90 (br s, 1, COOH).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.32; H, 8.27.

The corresponding ester, methyl **3-oxo-5,7αH,4βH-12,13-bisnoreudesm-1-en-11-oate (5)**, was obtained pure (nmr assay) and in quantitative yield on treatment of **6** with CH_2N_2 in Et_2O: mp 34–36°; nmr δ 1.06 (d, 3, $J \cong 7$ Hz, H-15), 1.12 (s, 3, H-14), 3.60 (s, $-OCH_3$), 5.68 (d, 1, J = 9.8 Hz, H-2), and 6.62 (d, 1, J = 9.8 Hz, H-1).

Methyl 3-Hydroxy-5,7αH,4βH-12,13-bisnoreudesm-1-en-11-oate (7) and Its C-3 Epimer (8).—A mixture of 1.033 g (0.0044 mol) of keto ester **5**, 3.04 g of freshly distilled aluminum isopropoxide, and 20 ml of anhydrous 2-propanol was heated at reflux for 4.3 hr; acetone, as it was formed, was slowly distilled through a Vigreux column and detected by formation of its 2,4-DNP derivative. The cooled mixture was poured into dilute HCl and extracted with ether. The ether extracts were washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to yield 1.25 g of the isopropyl ester analogs of **7** and **8** [nmr δ 1.20 (d, 6, J = 6.5 Hz) and 4.90 (septet, 1, J = 6.5 Hz)] as an oil. The oil was dissolved in CH_3OH–H_2O (4:1) containing 0.7% NaOH and the solution was refluxed for 3 hr under N_2, cooled, diluted with HCl, and extracted with Et_2O. A normal work-up followed by treatment of the acidic product with CH_2N_2 gave 0.95 g (91%) of a 3:1 mixture of isomeric hydroxy methyl esters **7** and **8** which crystallized partially to yield 0.30 g (29%) of the major isomer, **7** (pure by vpc),[39] as white needles: mp 90–91.5°; ir 3610, 3440 (s, br), and 1720 cm^{-1}; nmr ($CDCl_3$) δ 0.98 (s, 3, H-14), 1.03 (d, 3, $J \cong 7$ Hz, H-15), 1.78 (s, 1, -OH), 3.69 (s, 3, $-OCH_3$), ~3.69 (m, 1, H-3), and 5.53 (s, 2, H-1 and H-2). The mother liquor contained 0.60 g of **7** and **8** in a ratio of 3:2 as indicated by the relative peak areas for vinyl signals at δ 5.53 (s) and 5.69 (m, $W_{1/2}$ ~5 Hz).

Treatment of 0.33 g of the major isomer (**7**, mp 90–91.5°) with 3,5-dinitrobenzoyl chloride (4.11 g) in pyridine (25 ml) at 13° for 38 hr afforded, after several recrystallizations, 0.53 g (88%) of the 3,5-dinitrobenzoate of **7**: mp 185–187°; nmr ($CDCl_3$) δ 1.02 (d, 3, J = 6.5 Hz, H-15), 1.10 (s, 3, H-14), 3.69 (s, 3, $-OCH_3$), 5.25–5.90 (m, 3, ABC system, H-1,2,3), and 9.02 (m, 3, ArH).

(−)-Methyl 5,7αH-12,13-Bisnoreudesma-1,3-dien-11-oate (9). Method A.—Hydroxy ester **7** (mp 91–92.5°, 0.900 g, 0.0038 mol) was mixed with 5.4 g of alumina (Woelm, neutral activity grade ~I) that had been freshly treated with quinoline (2% by weight). The mixture was placed in a glass "boat" which was inserted into a preheated section of Pyrex tubing at 191° under an atmosphere of N_2 (flow rate ~160 ml/min).[12] The product slowly distilled from the alumina and condensed at the cool end of the tube as an oil (0.56 g) which was chromatographed on Florisil (14 g) to yield 0.25 g of crude diene **9** and 0.15 g of starting alcohol **7**. Two distillations of the diene in an evaporative still afforded 0.19 g (23%) of **9** as an oil: bp 34–39° (0.08 mm); uv max 264 nm (ε 4770); $[\alpha]^{25}D$ −55° (c 0.11); ir 1730 cm^{-1}; nmr δ 0.82 (s, 3, H-14), 1.77 (m, 3, $W_{1/2} \cong 3.5$ Hz, H-15), 3.62 (s, 3, $-OCH_3$), and 5.30–5.88 (m, 3, H-1,2,3). Diene **9** obtained in this manner contained 5–6% (nmr assay) of an impurity having a *C*-methyl (?) singlet at δ 0.93. The combined product ob-

(38) Determined by comparison of the area under the signal at δ 4.87 (dd, 1, $J_{2\beta,1\alpha}$ = 13.2 Hz, $J_{2\beta,1\beta}$ = 6.5 Hz, H-2β) with the total area under peaks due to $-OCH_3$.

(39) A 5 ft × 0.25 in. aluminum column containing 5% SE-52 on Anakrom ABS (60/70) was used for the analysis.

tained in 25% yield from two other identical runs contained 3–4% of the same impurity.

Method B.—Direct reduction of keto acid 6 (2.93 g) with aluminum isopropoxide in the manner described above for keto ester 5 afforded 2.00 g of hydroxy methyl esters 7 and 8 as a yellow oil after hydrolysis of the intermediate isopropyl esters and methylation of the crude hydroxy acids with CH_2N_2. The allylic alcohols were mixed with neutral alumina (12 g, pretreated with 2% pyridine) and pyrolyzed at 220° exactly as described previously[12] to afford 0.99 g of pale yellow oil. Chromatography on Florisil gave 0.77 g of colorless oil consisting of *ca.* 85% of diene 9, 8–10% of a major impurity having a CCH_3 peak at δ 0.93 (see A), and several minor impurities (<2% of each by vpc analysis). Evaporative distillation afforded 0.687 g of 9 which was devoid of most minor impurities; a portion of the distilled material was sent for analysis.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.08; H, 9.36.

Extensive attempts to separate the diene 9 from the remaining major impurity (CCH_3 at δ 0.93) by glc, and tlc and column chromatography (including $AgNO_3/Al_2O_3$ and $AgNO_3/SiO_2$) failed.

Method C.—A mixture of 465 mg of the 3,5-dinitrobenzoate of 7 and 2.04 g of neutral alumina (Woelm, pretreated with 2% quinoline) was pyrolyzed at 174° as described in A. Florisil chromatography and evaporative distillation of the product gave 74 mg of an oil consisting of *ca.* 30% of diene 9 and at least four other unidentified methyl esters as determined by nmr analysis of the $-OCH_3$ region.

Method D.—A mixture of 147 mg of the 3,5-dinitrobenzoate of 7 and 2.9 g of base-washed sand was heated slowly to 150° (0.04 mm) in a short-path distillation apparatus. An oily solid (21 mg) having a complex nmr spectrum and containing no more (if any) than 5 mg of 9 condensed on the thermometer bulb. Washing the sand with $CHCl_3$ afforded 100 mg of a mixture of starting dinitrobenzoate and 3,5-dinitrobenzoic acid by nmr assay.

Method E.—(Carboxysulfamoyl)triethylammonium hydroxide inner salt methyl ester was prepared according to the procedure of Atkins and Burgess.[40] The inner salt (340 mg) was added to a solution of 130 mg (0.55 mmol) of allylic alcohol 7 in 15 ml of anhydrous benzene. The mixture was heated at 55° for 1 hr, cooled, diluted with Et_2O, washed with brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to leave 163 mg of oil. Chromatography on alumina followed by evaporative distillation afforded 30 mg (25%) of crude diene 9 contaminated with at least three other compounds [signals at δ 0.93 (~5%), 0.98 (~10%), and 1.07 (~5%)].

Photolysis of (−)-Methyl 5,7αH-12,13-Bisnoreudesma-1,3-dien-11-oate (9). Formation of (−)-11 and (+)-12.—The photolysis apparatus consisted of a Pyrex jacket (i.d. 59 mm) with side arm and fitted with a gas inlet tube at the bottom. A quartz Hanovia immersion well (o.d. 50.5 mm) was inserted into the Pyrex vessel. Irradiation was effected with an unshielded quartz low-pressure Hg–Argon discharge tube (Oriel Optics Type C-13-61; length 2.125 in., o.d. 6.5 mm; dissipated wattage *ca.* 4.6; 90% of output concentrated at 2537 Å)[41] powered by a 17-mA transformer (Oriel Optics Model C-73-16).

Run A.—A solution of 279 mg of diene 9 (prepared by method A) in 220 ml of anhydrous Et_2O was purged with ultrahigh-purity argon for 45 min, cooled to −78° in a Dry Ice–Et_2O bath, and purged for 20 min longer. After a short warm-up period the Hg–Argon lamp was suspended in the immersion well. Argon gas was continuously bubbled through the photolysis solution to provide agitation. The course of the reaction was followed by removing 2-ml aliquots with a syringe at 90-min intervals. The aliquots were warmed to room temperature, concentrated *in vacuo*, and assayed by vpc (5% SE-52; column 147°; head 185°).[39] As the ratio of peaks due to 11, 12, and 9 approached an approximately steady value previously determined to be about 4:2:3, the irradiation was stopped (420 min). The entire solution was warmed, concentrated *in vacuo*, and assayed by vpc, which indicated the presence of the same major components along with three very minor products, N, TT, and T (order of vpc mobility: 11, N, 12, TT, 9, and T). The major components were separated by preparative vpc (10% XE-60; column 190°, head 210°)[42] to yield 96 mg of 11 (95% purity; contained N), 76 mg of 12 (60% purity; contained some 11 and N, and about 35% TT and 9), and 71 mg of 9 (contained some TT and T). Rechromatography (vpc) of the first fraction (96 mg) afforded 50 mg (18%) of pure (−)-**methyl 7αH,5βH-12,13-bisnoreudesma-1,3-dien-11-oate** [(−)-11] as an oil: $[\alpha]^{25}D$ −213° (*c* 0.31); ir 1730, 1640, 1585, 1440, 1190, and 721 cm^{-1}; uv max 263 nm (ϵ 4900); ORD (*c* 0.00396) $[\phi]_{277}$ −28,200°, $[\phi]_{258}$ 0°, and $[\phi]_{230}$ +40,500°; CD (*c* 0.00396) $[\theta]_{258}$ −51,600° [lit.[9] CD (CH_3OH) $[\theta]_{259}$ −33,800°]; nmr δ 0.86 (s, 3, H-14), 1.80 (br s, 3, H-15), 2.48 (m, 1, $W_{1/2} \cong$ 12 Hz, H-7), 3.64 (s, 3, $-OCH_3$), 5.22 (br d, 1, J = 9.5 Hz, H-1), 5.52 (br m, 1, H-3), and 5.79 (dd, 1, J = 9.5, 5.5 Hz, H-2); mass spectrum molecular ion theoretical 220.146, found 219.981.

Rechromatography (vpc) of the second fraction (76 mg) gave 45 mg (16%) of (+)-**methyl 5,7αH,10α-methyl-12,13-bisnoreudesma-1,3-dien-11-oate** [(+)-12] containing about 15% TT. Two additional passes afforded (+)-12 of 95% purity (vpc) as an oil: $[\alpha]^{25}D$ +336° (*c* 0.43); ir 1733, 1645, 1587, 1445, and 722 cm^{-1}; uv max 264 nm (ϵ 4800); ORD (*c* 0.0035) $[\phi]_{281}$ +37,200°, $[\phi]_{262}$ 0°, and $[\phi]_{232}$ −62,000°; CD (*c* 0.0035) $[\theta]_{258}$ +75,300° (lit.[9] CD for (−)-12, $[\theta]_{262}$ −49,200°); nmr δ 0.87 (s, 3, H-14), 1.81 (br s, 3, H-15), 3.58 (s, 3, $-OCH_3$), 5.29 (br d, 1, J = 9.5 Hz, H-1), 5.57 (br d, 1, J = 5 Hz, H-3), and 5.84 (dd, 1, J = 9.5, 5 Hz, H-2); mass spectrum molecular ion theoretical 220.146, found 220.150.

Run B.—Diene 9 (400 mg, prepared by method B) was irradiated in two equal portions essentially as described above (run A) to yield, after the photolysis solutions were warmed, a mixture of 11, 12, and 9 in a ratio of ~2:1:1 along with N, TT, and T, totaling about 10–15% of the crude photolysis product. Separation by preparative vpc (10% XE-60)[42] afforded 85 mg of 11 (90–95% pure by vpc assay; contained N), 59 mg of a mixture of 12 (~50%), 11 (~20%), 9 (~10%), and smaller amounts of N and TT (determined by vpc assay and estimation of the areas of peaks due to $-OCH_3$ in 11, 12, and 9 at δ 3.64, 3.56, and 3.61, respectively), and 57 mg of a mixture of 9, TT, and T.

Run C.—Diene 9 (606 mg in 580 ml of Et_2O; prepared by method B) was irradiated at −75° for 20 hr under argon using a larger Pyrex jacket (67-mm i.d.). Vpc analysis of the product obtained after the solution was allowed to warm to room temperature under argon showed the presence of 11, 12, and 9 in a ratio of 7:4:5. Repeated combination and repurification of fractions obtained by preparative vpc (10% XE-60)[42] afforded 110 mg of (−)-11 (~98% purity) and 230 mg of a mixture of (−)-11, (+)-12, and 9 (~85%) of total material in a ratio of *ca.* 3:8:7.

Detection of Possible Photostationary State for 9 ⇌ 10 at −70°.—A solution of 16 mg of 9 (prepared by method B) in 210 ml of Et_2O was purged with argon and irradiated at −72 to −77° in the apparatus described above. Using a syringe which had been precooled in powdered Dry Ice, 8-ml aliquots were withdrawn at 0, 1.2, and 3.0 hr. The aliquots were transferred immediately to a precooled 1-cm quartz uv cell which was centered at the base of a small unsilvered quartz dewar and surrounded by Et_2O. The Et_2O in the dewar was maintained at −70 to −75° by addition of small chips of Dry Ice. The dewar (which was fitted near its base with two pairs of flat quartz windows at 180° to each other, and had a 2.2-cm path length between the inner faces of the inner windows) was secured by a custom-built cradle and placed in a Cary 11 uv spectrophotometer with its windows, and those of the enclosed uv cell, in the path of the sample beam. A base-line spectrum was previously run with pure Et_2O at −70 to −75° in the dewar and 1-cm cell, using two 1-cm cells filled with Et_2O at room temperature in the reference beam. The sample at t = 0 gave a spectrum of 9 at −70 to −75° having uv max 266 nm (ϵ 3000); the same sample of 9 in Et_2O at 25° exhibited uv max 265 nm (ϵ 4300). The sample withdrawn at 1.2-hr irradiation time showed uv max 268 nm (ϵ 1800), appearance of strong end absorption at 222 nm (ϵ 3440), and additional absorption at longer wavelength out to 340 nm (line b, Figure 1); warming the t = 1.2 hr aliquot to room temperature and recooling to −70 to −75° gave a spectrum (line b′) due to 11, 12, and 9, having absorption intensity at ~265 nm, similar to that of starting diene 9. The aliquot withdrawn at t = 3.0 hr showed a spectrum (line c) similar to that obtained after 1.2 hr, but with somewhat reduced end absorption at 222

(40) G. M. Atkins, Jr., and E. M. Burgess, *J. Amer. Chem. Soc.*, **90**, 4744 (1968).

(41) Oriel Optics Corp., Stamford, Conn. 06901.

(42) A 12 ft × 0.375 in. aluminum column containing 10% XE-60 on Anakrom ABS (60/70) was used.

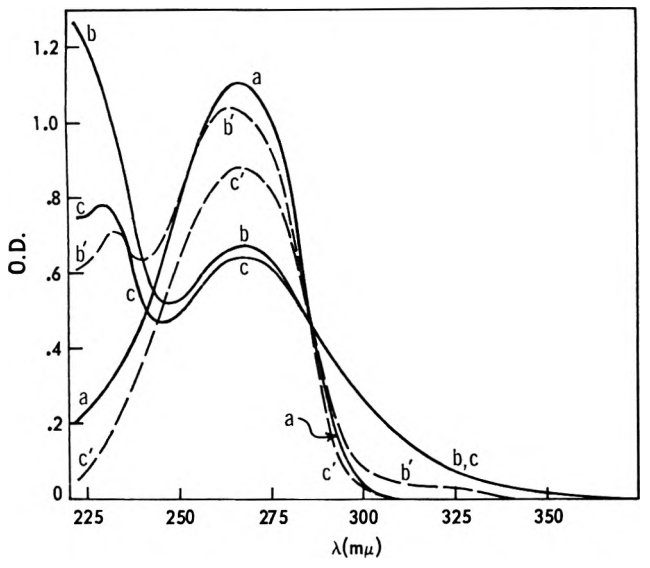


Figure 1.—Irradiation of 9 at −72 to −77°. All spectra were measured at −70 to −75°: (a) solution of 9 at t = 0; (b) irradiated solution of 9 at t = 1.2 hr (photostationary state for 9 ⇌ 10 approximately attained; (b′) solution b after warming to 25° and recooling; (c) irradiated solution of 9 at t = 3.0 hr; (c′) solution c after warming to 25° and recooling.

nm; warming and recooling led to regeneration of 80% of the approximate absorption expected at 265 nm if the final solution was composed solely of eudesma-1,3-dienes (*i.e.*, 11, 12, and 9).[42] Triene 10 at −70° could be estimated to have uv max at ~215 nm (ε ~500) and ~280 (~2200) by consideration of the differences in the b and b′ lines of Figure 1 and the assumption that 9 and 10 are present in a ratio of ~1:2 after 1.2-hr irradiation time (based on the ratio of 9 to 11 + 12 observed after warming solutions near the photostationary state in large-scale irradiations). Vpc analysis of the oil obtained after warming and concentrating the bulk of the photolysis solution after 3.0 hr irradiation time showed the presence of 11, 12, and 9 in a ratio of ~2:1:1 along with appreciable amounts of impurities (*e.g.*, N, T, and TT) typically formed when irradiation is continued at the photostationary state.

Estimation of the Half-Life of 10 at −20°.—The transparent quartz dewar used in the above uv determinations was fitted with a head to which was attached a tube which extended two-thirds of the way to the base of the dewar (*i.e.*, above the windows) and protruded from the top of the head. A side arm used as a nitrogen inlet was located near the top of the tube; a nitrogen outlet tube was located in the head. A 1-cm quartz uv cell having a long tube attached at its mouth was positioned with its windows facing the inside windows of the dewar; the tube attached to the uv cell traversed the inside of the tube attached to the head with enough clearance for two thermocouple wires which were fitted between the two tubes and attached at their termini to one side-wall of the uv cell (one at the top of the cell and one at the bottom). The same Hg–Ar lamp used in the irradiations of 9 described above was attached to the outside of the quartz dewar opposite the remaining side wall of the cell. The cell tube and thermocouple wires were fixed with a gas-tight seal to the top of the head tube. The open end of the cell tube was fitted with an ampoule cap and a long syringe needle which served as an argon inlet for both purging and agitating a solution contained in the cell; a short syringe needle served as an argon outlet. The entire unit was secured in the sample beam of a Cary 11 spectrophotometer by a custom-built cradle and the nitrogen inlet was attached to a tube leading to a 10-l. storage dewar containing liquid N_2 and fitted with a gas-tight head; a small heating element controlled by a rheostat was suspended in the N_2 from the head and allowed the boiling rate of the N_2 to be varied.

A solution of 9 (11.8 mg/100 ml) was injected into the uv cell and purged with argon. Agitation with argon was continued as the solution was cooled to −40 to −60° by circulation of cold N_2 gas which was forced through the system by increasing the boiling rate of the liquid N_2 in the reservoir. The solution was irradiated for 7-min intervals (3 ×) until the original OD at 260–270 nm was reduced by about one-third; the OD was measured after shutting off the lamp and withdrawing the argon inlet needle from the solution. No significant change in OD_{265} occurred as the solution was held at temperatures up to −30°; upon warming the solution above −30°, the OD_{265} increased at a rate consistent with a half-life for 10 of approximately 15–30 min at −20°.

Base-Catalyzed Isomerization of (−)-11 to (−)-12.—A solution of 95 mg of (−)-11 (84 mg from photolysis run B and 11 mg from earlier runs; contained ~5% of N) in 17 ml of anhydrous *tert*-butyl alcohol containing 0.68 g of potassium *tert*-butoxide was heated at reflux for 2.2 hr under N_2. Water (4 ml) was added and refluxing was continued for 3.8 hr longer. The cooled solution was diluted with cold HCl (10%) and extracted thoroughly with $CHCl_3$. The extracts were washed with brine, dried ($MgSO_4$), filtered, concentrated *in vacuo* at room temperature, treated with CH_2N_2 in Et_2O, and evaporated to dryness *in vacuo* to yield 88 mg of oil which consisted of (−)-12 and (−)-11 in a ratio of 25:1 by vpc analysis (10% XE-60; column 173°, head 184°; retention times 12, 14.7 min; 11, 10.2 min);[42] an impurity (5–6%) having the retention time of N (11.1 min) was also present. Pure (−)-12 (37 mg) was obtained as an oil by preparative vpc (10% XE-60):[42] uv max 263 nm (ε 4530); ir and nmr spectra identical with those of (+)-12 obtained by photolysis of 9.

(−)-11-Hydroxy-5,7β*H*,10β-methyleudesma-1,3-diene [(−)-2] [(−)-Occidentalol].—A solution of 35 mg of (−)-12 from the base-catalyzed isomerization of (−)-11 described above was treated with CH_3Li in Et_2O to yield 38 mg of semicrystalline material. Sublimation at 0.1 mm gave a pale yellow glass ($[\alpha]^{25}D$ −219°) containing 70–80% of 2 by nmr and vpc assay. Preparative vpc (10% XE-60)[42] afforded 10.2 mg of >90% pure (−)-2; mp 83–86°; $[\alpha]^{27}D$ −329° (*c* 0.33); uv max 263.5 nm (ε 5520); ir essentially identical with that of authentic (+)-occidentalol; vpc assay indicated 5–10% of a minor impurity having slightly longer retention time than (−)-2; no nmr was run. Repurification of 5.1 mg of the product by vpc on a 12 ft × 0.25 in. 10% XE-60 analytical column gave (−)-occidentalol: mp 93.8–94.8°; $[\alpha]^{27}D$ −356° (*c* 0.15); uv max 263.5 nm (ε 3960).

(+)-11-Hydroxy-5,7α*H*,10α-methyleudesma-1,3-diene [(+)-2] [(+)-Occidentalol]. **A.**—A solution of (+)-12 (35 mg in 1 ml Et_2O) from photolysis run A was treated with methyllithium (2 ml, 2.3 *M* in Et_2O) under N_2 at 0°. A normal work-up procedure gave 30 mg (86%) of an oil having an nmr spectrum essentially identical with that of authentic (+)-occidentalol.[6] Vpc assay (5% SE-52)[39] indicated the presence of 89% (+)-occidentalol (2) and 11% of three additional minor components in the oil. Purification by preparative vpc (XE-60, column 169°, head 204°)[42] gave 10.8 mg of crystalline material which was repurified by vpc to yield 5 mg of (+)-occidentalol (2) as fine needles: mp 92.5–94° (lit.[3a,4,10] mp 95°, 97.5–98°, 95°); $[\alpha]^{25}D$ +334° (*c* 0.16) [lit.[3a,4,10] $[\alpha]^{24}D$ +361° (*c* 2.4, $CHCl_3$), $[\alpha]^{25}D$ +363.2° (*c* 1.6, $CHCl_3$), $[\alpha]_{578}$ +369° ($CHCl_3$)]; uv max 264 nm (ε 4720) [lit.[3a] uv max 266 nm (ε 3980)]; ORD (*c* 0.0032) $[\phi]_{282}$ +38,700°, $[\phi]_{262}$ 0°, $[\phi]_{237}$ −54,500° [lit.[44] ORD (*c* 0.026, MeOH) $[\phi]_{284}$ +43,000°, $[\phi]_{240}$ −85,000°)]; CD (*c* 0.0032) $[\theta]_{260}$ +74,000° [lit.[44] CD (*c* 0.0026, EtOH) $[\theta]_{263}$ +66,260°].

B.—An ethereal solution of 59 mg of the vpc fraction containing 12, 11, and 9 obtained from photolysis run B was treated with excess CH_3Li. Work-up afforded 65 mg of a semicrystalline gum which contained *ca.* 50% (+)-occidentalol (2) and 15–25% of 1 by vpc analysis. [The order of mobility of the esters (−)-11 and (+)-12 was reversed in the corresponding alcohols 1 and 2, thus facilitating the purification of (+)-occidentalol (2) prepared in this manner from impure (+)-12; the ester (+)-12 can be purified only with considerable difficulty and losses of material.] Preparative vpc (10% XE-60)[42] afforded 21.2 mg of (+)-occidentalol (2): mp 79–85°; $[\alpha]^{25}D$ +301° (*c* 0.34, $CHCl_3$); uv max 262.5 nm (ε 5900). Two further purifications of 17.6

(43) Since the solutions could be run only after the last trace of Dry Ice in the Et_2O coolant was consumed (*i.e.*, after CO_2 bubbling ceased), the solutions tended to warm up slowly (to −55 to −65°) while the spectrum was recorded. Consequently, the solutions were recooled and the spectra were recorded several times for each aliquot to assure that any variation on OD values due to temperature changes were within reasonable limits; OD values near 265 nm were within ±0.05 of those shown in Figure 1 for each rerun. It should also be noted that the attenuation of OD noted for 9 in going from 25° to −70° may vary for the other species in solution, thus rendering any quantitation of results of dubious value.

(44) E. von Rudloff, cited in ref 22.

mg of the product by vpc gave 7.4 mg of partially crystalline material having mp 93.5–95.5° (softens at 91°). Sublimation gave (+)-occidentalol (2) having mp 94.2–95.0°; uv max 263.5 nm (ε 4300, 3940); $[\alpha]^{26}D$ +364°, +360° (*c* 0.36, $CHCl_3$). The nmr (microcavity tube) and ir spectra of synthetic (+)-occidentalol were essentially identical with spectra determined on a sample of authentic (+)-occidentalol (kindly supplied by Dr. E. von Rudloff) which exhibited mp 94–95.5°; $[\alpha]^{26}D$ +341° (*c* 0.53); uv max 263.5 nm (ε 4450).

C.—Treatment of the mixture (230 mg) containing (+)-**12** (*ca.* 86 mg) from photolysis run C with CH_3Li in Et_2O followed by preparative vpc afforded 35 mg of (+)-occidentalol (**2**), $[\alpha]^{27}D$ +290° (*c* 2.92); vpc showed ≥85% purity. Further purification of 29.2 mg of (+)-**2** by vpc gave 14.7 mg of a partly crystalline glass, $[\alpha]^{25}D$ +352° (*c* 0.19, $CHCl_3$). Sublimation of the glassy material gave (+)-occidentalol (**2**) as needles, mp 91.0–92.5°, uv max 264 nm (ε 3905).

(+)-11-Hydroxy-5β,7αH-eudesma-1,3-diene [(+)-1] [7-Epi-(−)-occidentalol].—A solution of (−)-**11** (40 mg from run A in 2 ml of Et_2O at 0°) was treated with methyllithium (1 ml of 2.3 *M* solution in Et_2O) under N_2. A normal work-up gave an oil which was purified by glpc (XE-60, column 190°, head 216°)[42] to yield 28 mg (70%) of (+)-**1** as a viscous liquid: $[\alpha]^{25}D$ +60.7° (*c* 0.15); uv max 266 nm (ε 4900) and 273 (shoulder); ORD (*c* 0.0029) $[\phi]_{286}$ +13,300°, $[\phi]_{266}$ 0°, $[\phi]_{234}$ −28,300°; CD (*c* 0.0029) $[\theta]_{281}$ +27,600°, $[\theta]_{270}$ +24,500° (shoulder), and inflections at 255 and 285 nm; nmr δ 1.10 (s, 3, H-14), 1.14 (s, 6, H-12 and H-13), 1.81 (br s, 3, H-15), and 5.1–5.8 (m, 3, H-1,2,3); mass spectrum molecular ion theoretical 220.182, found 220.170.

(−)-11-Hydroxy-5,7αH-eudesma-1,3-diene [(−)-14] [(−)-*trans*-Occidentalol].—A solution of 191 mg (0.87 mmol) of diene **9** (prepared by method A) in 10 ml of Et_2O was treated with 5 ml of 2.3 *M* methyllithium in Et_2O. The mixture was poured into ice water and worked up in the normal manner to yield 187 mg (98%) of solid. Recrystallization from hexane afforded 81 mg (42%) of (−)-*trans*-occidentalol (**14**) as white needles: mp 94–95.5°; $[\alpha]^{25}D$ −47° (*c* 0.32); ir ($CHCl_3$) 3620, 3480, 1645, and 1590 cm^{-1}; uv max 264 nm (ε 4700); ORD (*c* 0.0043) $[\phi]_{272}$ −8100°, $[\phi]_{255}$ 0°, $[\phi]_{225}$ +25,000°; CD (*c* 0.0043) $[\theta]_{250}$ −21,400°, $[\theta]_{210}$ +7200°; nmr ($CDCl_3$) δ 0.79 (s, 3, H-14), 1.22 (s, 6, H-12 and H-13), 1.38 (s, 1, OH), 1.80 (d, 3, *J* = 1.4 Hz, H-15), and 5.39–5.98 (m, 3, H-1,2,3).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98; mol wt, 220.183. Found: C, 81.85; H, 10.86; mol wt, 220.203 (mass spectrum).

Photolysis of (−)-*trans*-Occidentalol [(−)-14].—A solution of trans-fused alcohol (−)-**14** (110 mg) in 270 ml of deoxygenated Et_2O at −78° was irradiated (4.1 hr)[45] as described above for the diene **9** (run A). Warm up (25°) and concentration of the solution afforded 115 mg of oil which consisted of (+)-occidentalol (**2**) (30%), 7-epi-(−)-occidentalol [(+)-**1**] (44%), (−)-*trans*-occidentalol (**14**) (24%), and a minor impurity (2%) as determined by vpc analysis on 10% XE-60[42] (column 190°, head 220°; retention times—**2**, 15.9 min; **1**, 20.9 min; **14**, 23.6 min; impurity, 28.0 min).

Registry No.—(+)-**1**, 29484-47-7; (−)-**2**, 29484-46-6; (+)-**2**, 473-17-6; (−)-**3**, 18508-76-4; **4**, 37573-94-7; **5**, 37573-95-8; **6**, 37573-96-9; **7**, 37573-97-0; **7** (3,5-DNB), 37573-98-1; **8**, 37573-99-2; **9**, 37574-00-8; (−)-**11**, 29484-53-5; (+)-**12**, 37574-02-0; (−)-**14**, 37574-03-1.

Acknowledgment.—We thank Professor S. I. Weissman for a loan of equipment for the low-temperature uv experiments.

(45) Preliminary experiments (see footnote 9 in ref 7) indicated that the photostationary state was probably achieved after about 3.7 hr.

Conformational Isomerism in Dihydropregeijerene and Hedycaryol[1,2]

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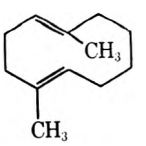
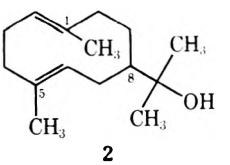
Conformations available to the 1,5-dimethyl-*trans,trans*-1,5-cyclodecadiene sesquiterpenes dihydropregeijerene (**1**) and hedycaryol (**2**) are discussed in terms of the cubic array of Chart I. Conformers have either a crossed or parallel relation of the double bonds in association with arrangements of the C-7,8,9,10 methylene segment which are described as chair, twist-boat, and twists. They are interconverted by three processes: rotation of each of the double bonds through the ring and inversion of the C-8,9 unit. Variable-temperature nmr spectra of **1** and **2**, particularly of samples deuterated at C-2, were helpful in assessing conformer populations and interconversions. All interconversions rates are rapid at 90°; all are slow at −30°. The conformational compositions of both **1** and **2** consist of a mixture of crossed chair and approximately equal amounts of parallel twists *T′* and *T″* with a temperature-dependent composition favoring the parallel set at higher temperatures. However, the relative amounts of the crossed and parallel sets differ for the two molecules: for **1** the parallel set increases from 15% at −70° to 35% at 0°; for **2** the parallel set already predominates to the extent of 75% at −30°. The demonstration of the existence of specific conformers of hedycaryol provides an experimental basis for biogenetic speculations which have invoked stereospecific, conformationally controlled reactions.

Since 1959 many sesquiterpene *trans,trans*-1,5-cyclodecadienes (members of the germacrane class) have been isolated. Following the establishment of constitution and configuration, data have started to accumulate on conformations and their relation to reactivity, an area of considerable biogenetic importance.[3] This article provides data pertinent to the conformations in solution of two of the simplest sesquiterpene *trans,trans*-1,5-cyclodecadienes, dihydropregeijerene (**1**) and hedycaryol (**2**).



1



2

Hedycaryol is the simplest known representative of sesquiterpene *trans,trans*-1,5-cyclodecadienes which contain one or more chiral centers (in hedycaryol at C-8) in addition to the potential chirality of the ring system itself. Dihydropregeijerene is an even simpler molecule, lacking any chiral center and indeed any substitu-

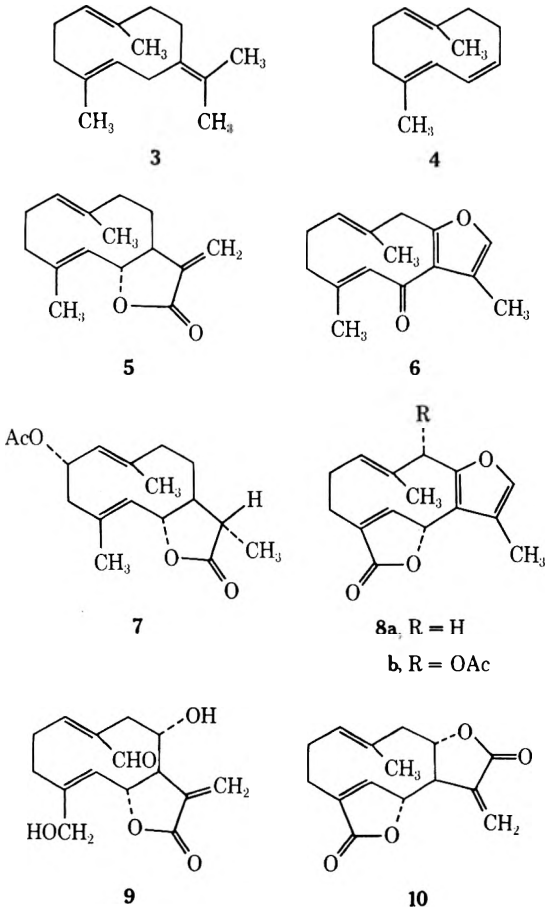
(1) The investigation was supported by Public Health Service Research Grant GM 16338 from the Division of General Medical Sciences, U. S. Public Health Service.

(2) The article is abstracted from the Ph.D. theses of Y. C. P. and H. C. K., Wesleyan University, 1971.

(3) For a review see W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev., Chem. Soc.*, **21**, 321 (1967). The earliest significant speculation is that of J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959).

tion on saturated carbon. However, the characteristic methyls present on the two double bonds are attached unsymmetrically to C-1 and C-5, thereby making nonequivalent the otherwise equivalent double bonds.

It has been recognized that sesquiterpene *trans,trans*-1,5-cyclodecadienes may adopt conformations in which the two double bonds face each other across the ring in either a crossed or parallel relation. X-Ray analyses have shown that crystalline silver nitrate complexes of germacrene B (**3**) and pregeijerene (**4**) consist of racemic mixtures of crossed conformations.[4,5] (At the same time interesting distortions of the double bonds have been revealed.) Costunolide (**5**) has similarly been shown to exist in a crossed conformation.[6] In solution, application of the nuclear Overhauser effect has led to the assignment of crossed conformations to furanodienone (**6**)[7], dihydrotamaulipin A acetate (**7**),[8] and linderalactone (**8a**).[9] In a few instances interconvertible conformations have been demonstrated. Urospermal (**9**) extraordinarily exists in two isolable, crystalline forms, each stabilized in a crossed conformation by hydrogen bonding.[10] The two forms equilibrate in solution and the equilibrium constant is solvent dependent. Isabelin (**10**) and litsealactone (**8b**) have been observed by nmr spectroscopy at room temperature to consist of pairs of nonisolable conformers in ratios of ~60:40 and 85:15, respectively.[9,11] The major isomers have been assigned crossed conformations. The minor forms of **10** (interestingly, probably the only conformer present in the crystalline state) and **8b** appear to be parallel conformers. In this work the structurally simple molecules of dihydropregeijerene (**1**) and hedycaryol (**2**) are shown to consist of mobile equilibria in solution of crossed and parallel conformers.



Dihydropregeijerene (1). Conformational Analysis—Although conformational analysis of cyclodecane[12] is complex, the introduction of double bonds imposes geometric restrictions which make it progressively simpler for *trans*-cyclodecene[13] and *trans,trans*-1,5-cyclodecadiene. The analysis carried out in the present work was based on mechanical models from which conformers were generated and their interrelationships noted. The models consisted of normal, *i.e.*, undistorted, bond angles even though considerable deviations are known to occur in medium rings.[5,12] The experimental data did not demand more precise geometry and no specific distortions were considered to be justified.

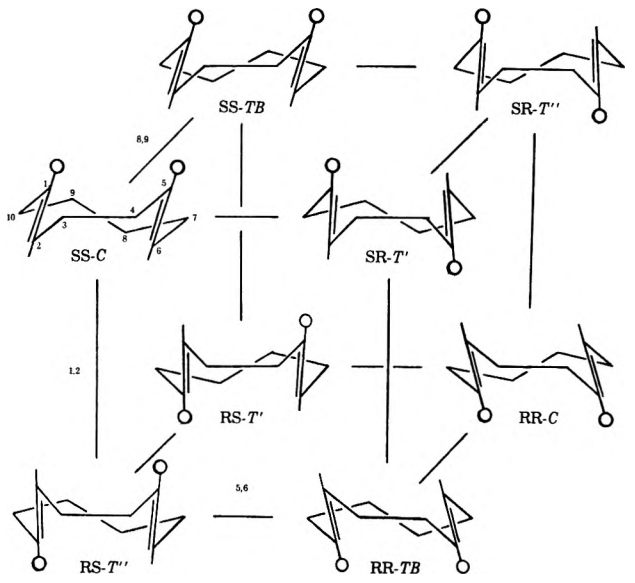
It is useful to start by describing the interconversion operations rather than the conformers themselves. There are three: rotation of the C-1,2 double bond through the ring; rotation of the C-5,6 double bond through the ring; and a change of the C-7,8,9,10 methylene chain which is described as C-8,9 inversion. The conformers so interrelated are not immediately and precisely defined by mechanical models which exhibit considerable flexibility. However, a good chemical and representational assumption is that C-3,4,7,10 lie approximately in a plane. The X-ray data published for costunolide[6] are in accord with this assumption, which corresponds to maximizing separation of the two sides of the ring (as defined by the planes of the two double bonds C-4,5,6,7 and C-10,1,2,3). There are eight low-energy conformers, each capable of conformational change *via* any one of the three interconverting operations. They are represented in Chart I as a cubic array in which each of the three sets of parallel edges of the cube corresponds to an interconverting operation.

So-called crossed conformers have identical planar chirality for the two double bonds, which can therefore be designated R-1, R-5 and S-1, S-5 or, more briefly, RR and SS. Independently, the C-7,8,9,10 methylene segment may resemble a cyclohexane chair (*C*) or twist-boat (*TB*), the two being related *via* C-8,9 inversion. (In some ways the *trans,trans*-1,5-cyclodecadiene system resembles a cyclohexane which has been stretched by insertion of two double bonds.) The total number of crossed possibilities is thus RR-*C* and its enantiomer SS-*C*; and RR-*TB* and its enantiomer SS-*TB*. It is interesting and probably important that the chair is associated with almost ideal staggering of the methylene segments C-3,4 and C-7,8,9,10 whereas the twist-boat has an unfavorable C-8,9 eclipsing. The angles of inclination of the double bond planes to the basal plane of the ring C-3,4,7,10 are not precisely defined because

(4) F. H. Allen and D. Rogers, *Chem. Commun.*, 588 (1967).
(5) J. McClure, G. A. Sims, P. Coggon, and A. T. McPhail, *ibid.*, 128 (1970).
(6) F. Sorm, M. Suchy, M. Holub, A. Linek, I. Hadinec, and C. Novak, *Tetrahedron Lett.*, 1893 (1970).
(7) H. Hikino, C. Konno, T. Takemoto, K. Tori, M. Ohtsuru, and I. Horibe, *Chem. Commun.*, 662 (1969).
(8) N. S. Bhacca and N. H. Fischer, *ibid.*, 68 (1969).
(9) K. Takeda, K. Tori, I. Horibe, M. Ohtsuru, and H. Minato, *J. Chem. Soc. C*, 2697 (1970).
(10) R. K. Bentley, J. G. St. C. Buchanan, T. G. Halsall, and V. Thaller, *Chem. Commun.*, 435 (1970).
(11) H. Yoshioka, T. J. Mabry, and H. E. Miller, *ibid.*, 1679 (1968).
(12) See J. B. Hendrickson, *J. Amer. Chem. Soc.*, **86**, 4854 (1964).
(13) G. Binsch and J. D. Roberts, *ibid.*, **87**, 5157 (1965).

CHART I

CONFORMATIONS OF 1,5-DIMETHYL-1,5-*trans*,*trans*-CYCLODECADIENES AND THEIR INTERRELATIONSHIPS[a]



[a] O designates the methyl groups; 1,2 and 5,6 denote rotation of the C-1,2 and C-5,6 double bonds through the ring, and 8,9 denotes inversion of the C-7,8,9,10 methylene segment. Conformations: *C*, chair; *T*, twist; *TB*, twist-boat.

of a certain amount of flexibility associated with their pivoting about C-3,10 and C-4,7. However, the C-5,6 double bond must be inclined in the sense of the C-5 methyl pointing away from the center of the ring and the C-6 hydrogen into the center of the ring because rotation of the C-5 methyl to a perpendicular position is resisted by stretching of the C-7,8,9,10 segment. The plane of the C-1,2 double bond is similarly influenced but it is likely to be more nearly perpendicular than the C-5,6 double bond because of methyl–methyl repulsion. Crossed conformers in Chart I are drawn for representational convenience with similarly inclined planes, each conformer thereby possessing a pseudo[14]-C_2 axis of symmetry passing through the midpoints of bonds C-3,4 and C-8,9: the methyl–methyl separation is 3.0 Å compared to 3.5 Å measured by X-ray analysis for the silver nitrate complex of pregeijerene.[5]

Parallel conformers are generated from crossed conformers by C-1,2 or C-5,6 rotation through the ring, with the vinyl hydrogen necessarily passing through the ring in each case because the methyl groups are too bulky. Models suggest that, of the two, C-5,6 rotation may be somewhat more facile.

Parallel conformers have double bonds of opposite chirality and both RS and SR combinations are possible: they are pseudo[14] meso forms. Independently, the C-7,8,9,10 segment can be in one of two enantiomeric twist (*T*) forms[15] yielding a total set of RS-*T'* and RS-*T''* which are pseudo[14]-enantiomeric, and related *via* C-8,9 inversion, and the corresponding pair SR-*T'* and SR-*T''*. They all have eclipsing interactions of the C-3,4 and C-8,9 units but there is no methyl–methyl repulsion. The double bonds are quite flexible with respect to pivoting about C-3,10 and C-4,7 and their inclinations in Chart I are rather arbitrarily drawn.

(14) Pseudosymmetry refers to the symmetry of the ring carbons or, equivalently, the total system in which the methyls have been replaced by hydrogens.

(15) All-eclipsed parallel conformers possessing a pseudo[14]-plane of symmetry bisecting the C-3,4, and C-8,9 bonds were rejected as too high in energy to contribute to the ground-state population. They may resemble the transition states in the C-8,9 operation interconverting *T'* and *T''* conformers.

Results and Discussion

Roberts[13] has shown by nmr that the double bond of *trans*-cyclodecene rotates through the ring with an energy of activation of 10.7 kcal mol^{-1} and furthermore that inversion of the C-6,7 methylene segment opposite the double bond requires a comparable energy of activation. Thus all three operations interconverting conformers of dihydropregeijerene might be expected to contribute to the temperature-dependent nmr spectrum.

At ambient temperature the 60-MHz nmr spectrum of **1** shows distinct absorptions corresponding to two vinyl methyls at δ 1.41 and 1.48 ppm, each appearing as a sharp doublet with J = 1 Hz; eight allylic hydrogens as a fairly sharp envelope centered at δ 2.1 ppm; and two vinyl hydrogens as a broad, structureless band with a width of 45 Hz. Both raising and lowering the temperature from ambient leads to marked changes, clearly indicating the existence of interconverting conformers, but overlap of absorptions of the two vinyl hydrogens does not allow more than this generalization. However, examination of the absorption patterns of the individual vinyl hydrogens was rewarding and was made possible by the synthesis of selectively deuterated compounds.

The spectrum changes shown in the pattern of the C-6 vinyl hydrogen of **1-*2*-*d*** were particularly significant. Cooling in carbon disulfide solution led to the formation of two separate areas of absorption centered at δ 4.3 and 5.0. The high-field area developed continuously as a doublet with J = 10 Hz with widths at half-height of 6 Hz at −70°. The low-field area first developed a structure with three prominent peaks, it then yielded a coalescence envelope, and finally developed more structure at −70°. At −70° the area ratio of high- to low-field absorptions was 85:15 but the ratio changed continuously with increasing temperature, attaining 65:35 at 0°. (It should be noted here that the trend and approximate ratios are definite and significant but no great accuracy is claimed for either the temperatures or ratios.) Heating in carbon tetrachloride yielded a symmetrical triplet (J = 7 Hz) of quartets (J = 1 Hz) which was very well defined at 90°.

By comparison the pattern of the C-2 vinyl hydrogen of **1-*6*-*d*** was uninteresting. Cooling in carbon disulfide led to the development of structure but no separation into two areas of significantly different chemical shift occurred, the maximum of absorption remaining almost invariant at δ 4.8 ppm, and heating in carbon tetrachloride yielded, at 90°, a triplet which was poorly defined with only indications of further structure.

Other parts of the spectrum also showed a temperature variation, and the patterns and behavior of the vinyl methyls are significant, each appearing at ambient temperature as a doublet with J = 1 Hz in undeuterated **1**. In **1-*2*,*6*-d_2** there are two sharp singlets which are resolved by cooling into a major pair absorbing at δ 1.32 and 1.48 and a minor pair at 1.40 and 1.45. The highest field absorption at δ 1.32 appears as a singlet in the spectrum of **1-*2*-*d*** and a doublet in the spectrum of **1-**

6-d and is therefore assigned to the C-1 methyl; the methyl absorption at 1.48 shows the opposite behavior.[16]

The data do not justify calculations of enthalpies and entropies for equilibria or rates and they do not justify exhaustive logical argument. They *are* qualitatively interpretable in terms of the array of Chart I with significant results.

At high temperatures all three interconverting operations are expected to be rapid[17] with the consequent rapid interconversion of conformers diagonally related across the body of the cube of Chart I. Such conformers are enantiomeric and their rapid interconversion makes the methylene hydrogens of C-7 enantiotopic, thereby explaining the symmetrical triplet pattern (J = 7 Hz) of the C-6 vinyl hydrogen at 90°. The triplet is further split into quartets (J = 1 Hz) by the C-5 methyl hydrogens. The pattern of absorption for the C-2 vinyl hydrogen is less well defined because of virtual coupling of the methylene hydrogens of C-3 with those on C-4 (both pairs are allylic).

At low temperatures slow[17] rates are expected for all three interconverting operations. A slowing down of both C-1,2 and C-5,6 rotations is first seen, thereby separating crossed and parallel sets of conformers and then, at somewhat lower temperatures, C-8,9 inversion is observably slowed, thereby allowing observation of the individual *C*, *TB*, *T'* and *T''* conformers which are present.[17,18] Crossed and parallel sets are distinguished by the relatively high field absorption of the C-6 vinyl hydrogen and C-1 methyl hydrogens of the crossed set which is accentuated by the specific inclination of the C-5,6 double bond.[19] By contrast, the C-2 vinyl hydrogen is not selectively shielded in either of the sets and no chemical shift separation is observed. Both *T'* and *T''* conformers of the parallel set are significantly populated. Their rapid interconversion *via* C-8,9 inversion at temperatures around 0° leads to structured absorption for the C-6 vinyl hydrogen which arises from rapid averaging. Coalescence then occurs and is followed by the reappearance of structure which is the superposition of absorptions of *T'* and *T''* conformers which are expected to have similar chemical shifts but appreciably different coupling. By contrast the high-field absorption of the C-6 vinyl hydrogen of the crossed set progressively develops into a sharper and sharper symmetrical doublet (J = 10 Hz) with no intermediate line shape changes. At −70° each half of the doublet has a half-height width of 6 Hz for which coupling with the C-5 methyl hydrogens is largely responsible. The barrier to C-8,9 inversion in the parallel and crossed sets would not appear to be very different and the presence of both *C* and *TB* conformers should have led to a phenomenologically similar, unsymmetrical, temperature-dependent spectrum. The observed pattern is consistent with the presence of only one of them.[20] This must be the chair, which does not possess the unfavorable C-8,9 eclipsing interaction of the twist-boat. Moreover, the model of the chair shows dihedral angles of *ca.* 200 and 80° for the C-7 methylene hydrogens consistent with the observed pattern, with coupling for the 80° relation close to zero. The corresponding dihedral angles for the twist-boat are *ca.* 30 and 150° and are inconsistent with the observed pattern.[21]

The equilibrium constant for the crossed and parallel sets is temperature dependent; the crossed set predominates at low temperatures but the parallel set contributes equally at temperatures not much above room temperature. The crossed set is thus favored by enthalpy, the parallel set by entropy, and a significant contribution to the entropy difference must be the population of two parallel conformers but only one crossed.

Hedycaryol (2).—Hedycaryol isolated from natural sources[22] is the *d* isomer, $[\alpha]_D$ +30.8°; our synthetic material is the *dl* racemate. The hydroxypropyl group attached to C-8 makes that carbon asymmetric and the array of Chart I now refers separately to the individual enantiomers of hedycaryol, with all conformers of a given enantiomer diastereomerically related. Conformers situated on the front and back faces of the cube are distinguished by the pseudoequatorial and pseudoaxial nature of the hydroxypropyl substituent and its bulk effectively removes the pseudoaxial set from the ground-state population, and thereby eliminates C-8,9 inversion as an operator contributing to the temperature-dependent nmr spectrum. The effect of C-1,2 and C-5,6 rotations are still observable with crossed and parallel sets emerging from the ambient temperature coalescent pattern of the C-6 vinyl hydrogen of *2-2-d* as two distinct areas centered at δ 4.4 and 5.0 ppm. The same trend in temperature-dependent population is observed, higher temperatures favoring the parallel set, but it is interesting that the parallel set already predominates to the extent of 75% at −30°. If an explanation for the relative favoring of parallel forms by the hydroxypropyl groups is called for (the energy difference being very small), it is worth noting that the nonbonded interactions of the substituent with the C-7,8,9 segment are relieved somewhat in going from the staggered-staggered arrangement of the crossed chair to the staggered-eclipsed arrangement of the parallel twists. This effect should also make the crossed twist-boat relatively more stable, but the effect is too small to be observable; the pattern for the C-6 vinyl hydrogen of the crossed set develops as a doublet, J = 10 Hz, very similar to that of dihydropregeijerene. The corresponding pattern for the parallel set develops structure, which does not go through a coalescence phase, consistent with population of two twist conformers which can only average *via* a crossed conformer. At 90° the conformational composition consists almost completely of these parallel twists, averaging rapidly *via* C-1,2 and C-5,6 rotations, and the spectrum of the C-6 vinyl hydrogen is a much distorted triplet of quar-

(16) Methyl assignments for germacrane sesquiterpenes have been made by R. N. Sathe, G. H. Kulkarri, and G. R. Kelkar, *Chem. Ind.* (*London*), 448 (1968).

(17) Rapid and slow rates refer to the nmr time scale only.

(18) Although C-8,9 inversion is observable at a lower temperature than double-bond rotation, this does not necessarily imply a faster rate constant for C-8,9 inversion because a smaller $\Delta\nu$ is averaged.

(19) The assumption is made that chemical shift differences are largely caused by differential shielding by the opposed double bonds and not by differential distortion effects of the attached double bonds. Consistent with this assumption are the similar and almost normal chemical shifts of *trans*-cyclooctene and *trans*-cyclodecene (δ 5.4 ppm); *cf.* cyclohexene (5.6). The absorptions of *trans,trans*-1,5-cyclooctadiene (4.9) and *trans,trans*-1,5-cyclodecadiene (4.7) are at significantly higher field.

(20) No useful upper limit can be set on the amount of twist-boat present.

(21) For a summary of the angular dependence of coupling, see N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964.

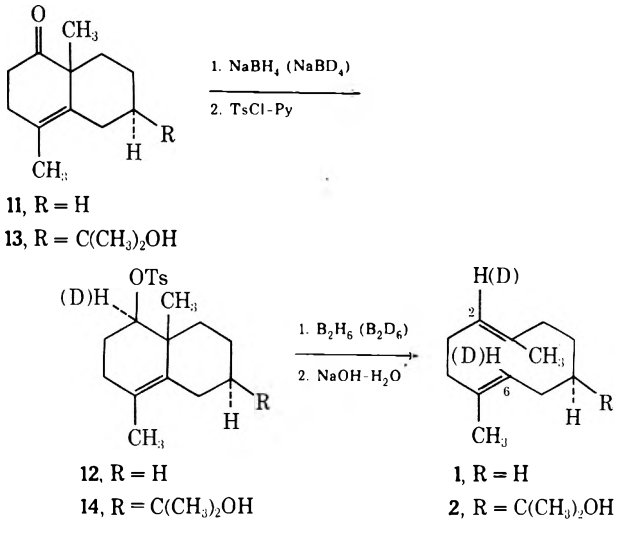
(22) R. V. H. Jones and M. D. Sutherland, *Chem. Commun.*, 1229 (1968).

tets as might be expected from roughly equal amounts of the individual twist conformers with complementary but not equivalent coupling of the C-7 methylene hydrogens.

In conclusion, it can be stated that the use of deuterium substitution proved to be very effective in outlining conformational relationships of dihydropregeijerene and hedycaryol, although they have not been fully dissected. Experimental substance has been provided for biogenetic suggestions which have invoked stereospecific, conformationally dependent reactions and it is now clear that hedycaryol, in particular, can readily adopt three conformations, one crossed chair and two parallel twists.

Synthetic Work—*dl*-Hedycaryol (**2**) was synthesized as previously described[23] and **2**-*2-d* was prepared by using sodium borodeuteride in the conversion **13** → **14** (see Scheme I). Dihydropregeijerene (**1**) was obtained

SCHEME I



for the first time by the same overall procedure. 4-Methyl-$\Delta^{4(10)}$-1-octalone (**11**) was reduced with sodium borohydride in ethanol to a mixture of two alcohols (82:18). It was anticipated that the major isomer would have a cis relationship of the angular methyl and hydroxyl, the methyl sterically favoring trans delivery of hydride. Tosylation of the mixture and subsequent crystallization gave a single tosylate (**12**) in 68% yield, showing an nmr chemical shift for the distinctive methine hydrogen of δ 4.35 ppm, with a width at half-height of 18 Hz. The corresponding chemical shift of the minor tosylate in the mother liquor was δ 4.46 ppm, with a width at half-height of 11 Hz, thus confirming the cis stereochemistry of the major alcohol.[21] Fragmentation of the tosylate was carried out by first treating with excess diborane and then adding aqueous sodium hydroxide;[24] after 6 hr at 70°, work-up, including distillation, afforded a 75% yield of crude product which was purified by silver nitrate extraction and redistillation. The product, isolated in 40% yield, was found to be homogeneous by capillary glpc at 80°; its analysis was consistent with a formula composition of $C_{12}H_{20}$; and spectroscopic data were consistent with its formulation as dihydropregeijerene. Thermally, after 6 hr at 140°, it yielded a Cope-related product, the nmr spectrum of which was found to be in accord with that reported for authentic dihydrogeijerene.[25]

Syntheses of **1**-*2-d*, **1**-*6-d*, and **1**-*2,6-d*$_2$ were accomplished by selective deuteration, a C-2 vinyl deuterium being introduced in the conversion **11** → **12** by using sodium borodeuteride, and a C-6 vinyl deuterium by the use of deuterated diborane in the conversion **12** → **1**.

(23) P. S. Wharton, C. E. Sundin, D. W. Johnson, and H. C. Kluender, *J. Org. Chem.*, **37**, 34 (1972).

(24) J. A. Marshall and G. L. Bundy, *Chem. Commun.*, 854 (1967).

Experimental Section

Physical Data.—Melting points were determined using a Thomas Unimelt capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were obtained using a Perkin-Elmer Model 137 spectrophotometer. Nmr spectra were recorded using a Varian A-60A spectrometer employing tetramethylsilane as an internal reference. Varian unit V-6040 was used for variable-temperature nmr studies. For low-temperature runs both spinner air and coolant nitrogen were predried by passing through Drierite towers and coolant nitrogen was further dried by passing through a liquid nitrogen trap. Temperatures were calibrated by determining the temperature-dependent shift differences in the spectra of methanol and ethylene glycol. Spinning band distillations were performed using a 24-in. Nester-Faust NFT-50 Teflon spinning band column fitted with an automatic reflux ratio control. Gas–liquid phase chromatography (glpc) was performed on Varian Aerograph, Model A-90-P, and Perkin-Elmer, Model F-11, units, using packed and capillary columns, respectively. Peak areas were calculated using a Disc chart integrator. The columns used were (1) 5 ft × 0.25 in. 5% Carbowax M on Chromosorb T (40/60); (2) 1 ft × 0.25 in. SF-96 on Chromosorb P (60/80); (3) 150 ft × 0.01 in. SF-96.

Materials.—Solvents were dried and/or distilled before use with the exception of ether and ethanol. Magnesium sulfate was used as a drying agent.

4,9-Dimethyl-$\Delta^{4(10)}$-1-octalone (**11**) was prepared by modifications of a procedure previously described.[26,27] 1-Acetylcyclohexene was first prepared and then converted to 1-isopropenylcyclohexene by the procedure of Wittig and Schollkopf.[28] Into a 12-l., three-neck flask equipped with mechanical stirrer, condenser, nitrogen inlet, and a solid sample addition device was placed 900 ml (2.02 mol) of a 2.25 *M* solution of *n*-butyllithium in hexane (Alfa) and then 6000 ml of anhydrous ether. A total of 747 g (2.21 mol) of solid methyltriphenylphosphonium bromide (Aldrich, crystallized from ethanol, mp 230–231°) was added slowly with rapid stirring and the resulting orange-red mixture was stirred for 5 hr at room temperature. A total of 175 g (1.41 mol) of 1-acetylcyclohexene,[29] bp 74–77° (10 mm), was added slowly with ice cooling. The resulting suspension was stirred at gentle reflux overnight, and then cooled to room temperature and worked up, eventually yielding a total of 113 g (66%) of 1-isopropenylcyclohexene.[26]

In a 100-ml flask, fitted with condenser and nitrogen inlet, was placed 17.33 g (0.142 mol) of 1-isopropenylcyclohexene, prepared as described above. Ethyl α-acetoxyacrylate[30] (22.45 g, 0.142 mol) and 0.72 g of 3,5-di-*tert*-butylcatechol (Aldrich) were then added. The mixture was thoroughly flushed with nitrogen and then stirred at 160° for 24 hr. Direct distillation at 0.5 mm gave 5.1 g of forerun, bp 46–110°, and then 30.4 g (77%) of cycloadduct: bp 110–112°; nmr (CCl_4) δ 4.15 (q, 2, J = 7 Hz), 1.64 (b, 3), 1.25 (t, 3, J = 7 Hz), and 2.0 ppm (2 sharp s, 3, separated by 2 Hz, in a 75:25 ratio).

Into a 5000-ml flask fitted with condenser, mechanical stirrer, and nitrogen inlet was placed 28.5 g (0.754 mol) of lithium alu-

(25) C. Ganter and B. Keller-Wojtkiewicz, *Helv. Chim. Acta*, **54**, 183 (1971).

(26) P. S. Wharton and C. E. Sundin, *J. Org. Chem.*, **33**, 4255 (1968).

(27) P. S. Wharton and B. T. Aw, *ibid.*, **31**, 3787 (1966).

(28) G. Wittig and U. Schollkopf, *Org. Syn.*, **40**, 66 (1960).

(29) J. H. Saunders, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 22.

(30) The ethyl ester was prepared by the procedure described for the methyl ester by J. Wolinsky, R. Novak, and R. Vasileff, *J. Org. Chem.*, **29**, 3596 (1964).

minum hydride and 1000 ml of anhydrous ether. Cycloadduct, prepared as described above (141.0 g, 0.502 mol), was dissolved in 500 ml of ether and added dropwise at such a rate that gentle reflux was maintained and stirring was continued at room temperature for 2 hr after addition was completed. The reaction mixture was cooled in an ice bath, quenched with water, and stirred for 3 hr. Then 600 ml of 10% hydrochloric acid was added. Further work-up afforded 103.6 g of brown oil which was dissolved in 200 ml of hot acetone. Two crops of pale yellow solids, which rapidly whitened on exposure to air, were obtained, totalling 81.8 g (83%): mp 106–120°; nmr ($CDCl_3$) δ 3.5 (b, 2.0), 1.2–2.8 (m, 17.4 with broad s at 1.66 ppm).

Into a 2000-ml flask fitted with mechanical stirrer, nitrogen inlet, and dropping funnel was placed a solution of 35.0 g (0.178 mol) of the mixture of diols, prepared as described above, in 500 ml of 95% ethanol. A solution of 45.8 g (0.214 mol) of sodium metaperiodate (Baker) in 500 ml of water was added with vigorous stirring. The reaction mixture was stirred at room temperature for an additional 2 hr and was then poured into 2000 ml of brine containing a little sodium thiosulfate. Work-up afforded 26.3 g (90%) of 4-methyl-$\Delta^{4(10)}$-1-octalone:[26] bp 69–72° (0.2 mm); ir (film) 5.82 μ; nmr (CCl_4) δ 2.36 (broad s, 3) and 1.70 (s, 3) superimposed on a broad envelope at 1.0–3.0 ppm.

Into a 2000-ml flask fitted with mechanical stirrer, nitrogen inlet, addition funnel, thermometer, and ice bath was placed 600 ml of dimethoxyethane and then sodium hydride (0.358 mol) obtained by washing with pentane 15.9 g of a 54% dispersion of sodium hydride in mineral oil (Alfa). A solution of 53.5 g (0.326 mol) of octalone prepared as described above and 185 g (1.30 mol) of methyl iodide in 300 ml of dimethoxyethane was then added rapidly with stirring. The reaction mixture became green and eventually gray over a period of 4 hr. The total reaction mixture was treated with 50 ml of ethanol and 100 ml of a 10% solution of sodium hydroxide and then heated on a steam bath for 1 hr. After cooling it was poured into 1500 ml of brine containing a little sodium thiosulfate. Further work-up gave 70 g of yellow oil which was first simply distilled, affording 51.0 g (88%) of a mixture of ketones, bp 63–64° (0.1 mm). The distillate was further subjected to fractional distillation at 0.1 mm, yielding 0.45 g of forerun, bp 42–51°, and a residue of 2.1 g. The 38.0-g fraction of 4,9-dimethyl-$\Delta^{4(10)}$-1-octalone[27] was homogeneous by glpc on column 1 at 180°: ir (film) 5.84 μ; nmr (CCl_4) δ 0.8–2.8 ppm (complex with peaks at 1.68 and 1.18). Later fractions contained considerable quantities of materials with longer glpc retention times.

4,9-Dimethyl-$\Delta^{4(10)}$-1-octalyl *p*-Toluenesulfonate (12).—4,9-Dimethyl-$\Delta^{4(10)}$-1-octalone, prepared as described above (14.0 g, 78.9 mmol), was dissolved in 50 ml of absolute ethanol and placed into a 1000-ml flask fitted with a magnetic stirrer, nitrogen inlet, addition funnel, and ice bath. A solution of 1.50 g (39.4 mmol) of sodium borohydride in 400 ml of absolute ethanol was added with stirring and the resulting mixture was stirred for 2 hr at ice-bath temperatures and then at room temperature overnight. Water (10 ml) and acetic acid (30 ml) were then added and stirring was continued for 2 hr. Further work-up gave 13.5 g (83%) of clear liquid. Glpc analysis on column 1 at 160° showed the presence of three components with retention times of 5.5 (1%), 11 (17%), and 13 min (82%) and the three components were isolated by preparative glpc under the same conditions. The compound with a retention time of 5.5 min was shown to be identical with starting ketone, ir (CCl_4) 5.85 μ. The compound with a retention time of 11 min was characterized by ir (CCl_4) 2.80, 2.92 (OH), 3.45 (CH), 6.95, 9.40 μ; nmr (CCl_4) δ 3.34 (broad, $W_{1/2}$ = 10 Hz), 0.5–2.8 (complex, with a broad spike at 1.59 and sharp spike at 1.05 ppm). The compound with a retention time of 13 min was characterized by ir (CCl_4) 2.80, 2.92 (OH), 3.45 (CH), 6.87, 6.94 μ; nmr (CCl_4) δ 3.35 (complex, $W_{1/2}$ = 15 Hz), 0.5–2.8 (complex, with a broad spike at 1.55 and sharp spike at 0.98 ppm). Distillation of 8.12 g of the mixture of alcohols gave 5.97 g (33.1 mmol) of clear liquid, bp 83.5–84° (0.2 mm), which was dissolved in 12 ml of pyridine. The solution was cooled and then, with rapid stirring, 6.87 g (36 mmol) of *p*-toluenesulfonyl chloride (crystallized from hexane) was added. The resulting mixture was stored at −10° for 3 days, and then treated with a few drops of water. After the mixture became homogeneous, it was poured into 50 ml of water. Further work-up gave 11.0 g of pale yellow solid, crystallization of which from 35 ml of hot hexane gave two crops, 7.56 g, mp 87–89° dec, and 1.19 g, mp 61–78° dec. The first crop was characterized by nmr (CCl_4), δ 4.35 ppm (m, 1, $W_{1/2}$ = 15 Hz). An analytical sample, mp 89–90° dec, was prepared by recrystallizing twice from hot hexane.

Anal. Calcd for $C_{19}H_{26}O_3S$: C, 68.23; H, 7.84; S, 9.59. Found: C, 68.34; H, 7.86; S, 9.68.

In a separate run, the mother liquor remaining, after yielding two crops of the above crystals, was concentrated to an oil, nmr (CCl_4) δ 4.37 ppm (complex, 1, $W_{1/2}$ = 10 Hz).

Dihydropregeijerene (1).—To an ice-cooled solution of 5.00 g (15.0 mmol) of tosylate 12 prepared as described above in 20 ml of tetrahydrofuran was added, under a nitrogen atmosphere, 25 ml of a solution of borane 1.0 *M* in tetrahydrofuran (Alfa). The mixture was stirred for 4 hr. A solution of 9 g of sodium hydroxide in 30 ml of water was then added and the mixture was heated at 70° for 6 hr and then allowed to stand at room temperature overnight. The reaction mixture was heated with 10 ml of 30% hydrogen peroxide solution at 50° (other runs were carried out at room temperature) for 30 min and then poured into 100 ml of water and extracted three times with 25-ml portions of pentane. Most of the pentane was removed by evaporation and the remaining concentrated solution was cooled in Dry Ice–acetone. The clear superficial solution was decanted from insoluble gummy material and dried. Evaporation of solvent and distillation afforded 1.83 g (75%) of a clear liquid, bp 45–50° (0.1 mm). The insoluble gummy material was characterized by nmr (CCl_4) δ 7.30 and 7.75 (q, 4, AB quartet, J_{AB} = 8 Hz), 4.03–4.43 (b, 1, $W_{1/2}$ = 18 Hz), 2.46 (s, 3), and 0.50–2.35 (b, total integration 27.8, with sharp spikes at 0.90, 1.03, 1.04, and 1.07 ppm).

The distilled product, 1.83 g, was added to 200 ml of 20% silver nitrate solution and the solution was agitated with a Vibromixer (Chemapec Inc.). The resulting mixture was extracted once with 25 ml of pentane. The aqueous layer was added to 350 ml of cold concentrated ammonium hydroxide solution and the resulting turbid mixture was extracted with pentane. Further work-up afforded 1.05 g (43%) of clear liquid (distilled in a short path apparatus at 0.1 mm and a bath temperature of 45°) and 0.46 g of residue. Glpc on column 3 at 80° on the distillate indicated that it was 99% one component. The nmr spectrum is discussed elsewhere in this article.[31]

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 87.82; H, 12.16.

Samples of 1-*2-d*, 1-*6-d*, and 1-*2,6-d*$_2$ were obtained by procedures identical with those described above by using lithium aluminum deuteride and/or sodium borodeuteride (Alfa) at the appropriate stage of the synthetic sequence. Their nmr spectra are discussed elsewhere in this article.[31]

Dihydrogeijerene.—Dihydropregeijerene (0.40 g, 2.43 mmol), prepared as described above, was sealed in a glass tube under vacuum and heated in an oil bath at 140° for 6.5 hr. Short-path distillation at 0.1 mm and a bath temperature of 40° of the pyrolysate afforded 0.30 g (75%) of clear liquid and 0.09 g of residue. Preparative glpc on column 2 at 100° yielded a sample with ir (film) 3.30, 3.45, 3.55, 6.11, 11.0, and 11.25 μ; nmr (CCl_4) δ 5.78 (d of d, 1, J_1 = 18, J_2 = 10 Hz), 4.81 (d of d, 1, J_1 = 18, J_2 = 1.5 Hz), 4.80 (d of d, 1, J_1 = 10, J_2 = 1.5 Hz), *ca.* 4.7 (b, 1), 4.53 (b, 1), 1.68 (d, 3, J = 1 Hz), 0.99 (s, 3), with complex absorption from 1.2–2.0 with a maximum at 1.42 ppm. Closely similar data are reported in the literature.[25]

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 88.03; H, 12.18.

dl-Hedycaryol (2) was prepared as previously described: nmr (CS_2) δ 1.17 (s, 6 hydroxypropyl methyls), 1.3 (s, OH), 1.48 (d, C 5 methyl, J = 1 Hz), 1.57 (d, C-1 methyl, J = 1 Hz), 2.15 (eight allylic protons) and 4.9 (center of an envelope 45 Hz broad from C-2 and C-6 vinyl hydrogens). A sample of 2-*2-d* was prepared by the same procedure by substituting sodium borodeuteride at the appropriate stage of the synthetic sequence.[31]

Registry No.—1, 33835-29-9; (±)-2, 32319-39-4; **11**, 17408-20-7; *cis*-12, 33835-31-3; *trans*-12, 33835-32-4; dihydrogeijerene, 37574-08-6.

(31) Nmr spectra of the following will appear following these pages in the microfilm edition of this volume of the journal: 1 and 2 (ambient temperature); vinyl hydrogen region of 1, 1-*2-d*, 1-*6-d*, and 2-*2-d* (variable temperature). Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-73-735. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

Perhydroindan Derivatives. XV. The Synthesis of a Tetracyclic Precursor to Epiallogibberic Acid[1]

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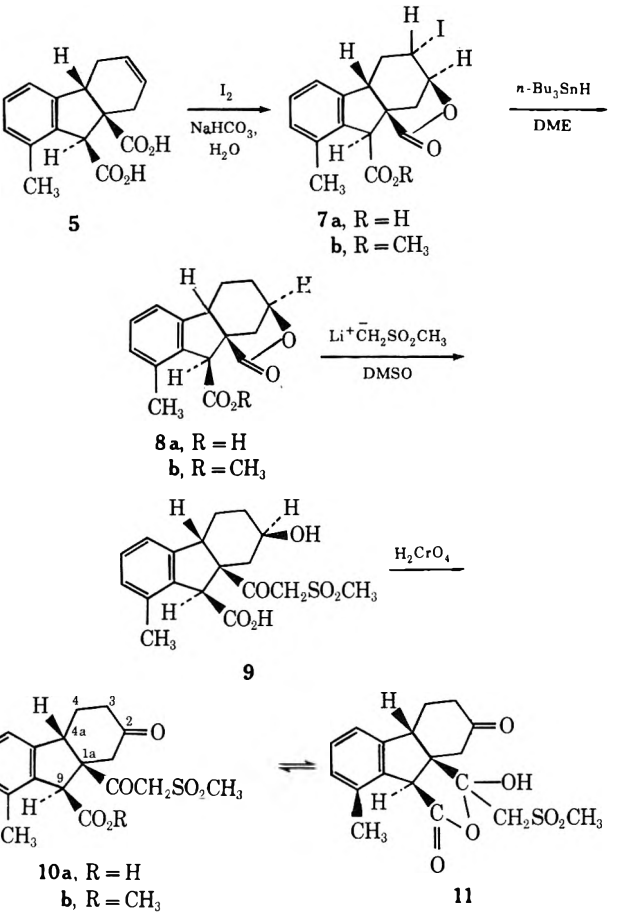
The tetrahydrofluorene derivative **5** has been transformed in a series of steps (Schemes I–IV) into the tetracyclic intermediate **30** that has the appropriate functionality and stereochemistry to serve as a precursor for epiallogibberic acid. A key step in the sequence is the intramolecular aldol condensation **10a** ⇄ **19** that is unfavorable in polar, protic solvents but can be forced to completion by forming a covalent magnesium alkoxide **18** in a nonpolar, aprotic medium.

In our earlier investigation of possible precursors for epiallogibberic acid (**1**), the two tetrahydrofluorene derivatives **2**[3] and **5**[4] were prepared. Since utilization of the precursor **2** and various of its derivatives was severely hampered by lack of reactivity at the C-9 keto function,[3] we concentrated our efforts on the precursor **5** obtained by addition of butadiene to the indene diester **6**. Several improvements (see Experimental Section) in the synthesis of the diester **6** from intermediates **3** and **4** and in the use of **6** as a dienophile provided an adequate supply of the intermediate **5**. The further transformation of intermediate **5** to the diketo sulfone **10**, summarized in Scheme I, is analogous to results obtained in earlier studies with model compounds.[5] The diketo sulfone acid **10a** existed primarily in the form of its lactol tautomer **11**, a result consistent with the assigned cis stereochemistry for substituents at C-9 and C-1a.

Other transformations of the intermediate lactone **8** are summarized in Scheme II. Of particular interest was the selective reaction of the lactone acid **8a** with 2 equiv of methylmagnesium chloride to form, after oxidation, the diketo acid derivatives **15**. However, a variety of attempts to effect an intramolecular aldol condensation with these diketone derivatives **15** to yield the tetracyclic intermediate **24** were not successful. Comparable results had been obtained previously with the model diketone **17**.[5]

An intramolecular aldol condensation to produce tetracyclic intermediates was accomplished by reaction of the diketo sulfone acid **10a** (or **11**) with 2 equiv of *tert*-butylmagnesium chloride in a nonpolar reaction

SCHEME I



(1) This research has been supported by Public Health Service Grant RO1-CA-12634 from the National Cancer Institute.

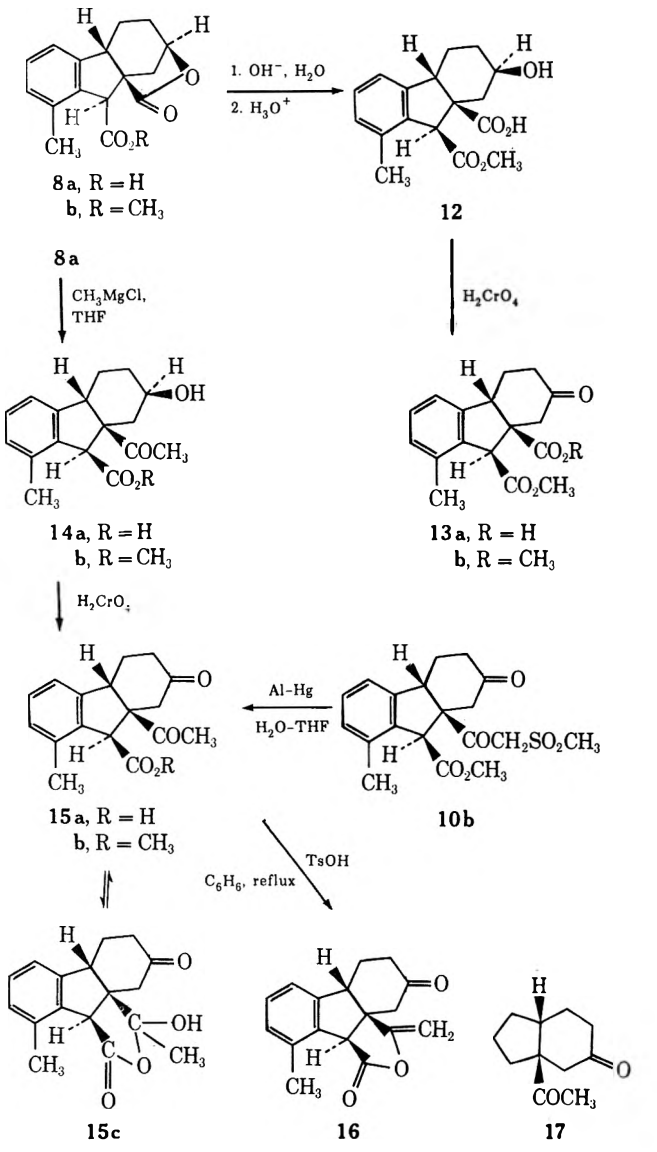
(2) National Science Foundation Predoctoral Fellow, 1965–1969. A portion of this work was taken from the Ph.D. dissertation of Frederick J. Sauter, Massachusetts Institute of Technology, 1969.

(3) H. O. House and R. Darms, *J. Org. Chem.*, **30**, 2528 (1965), and references cited therein.

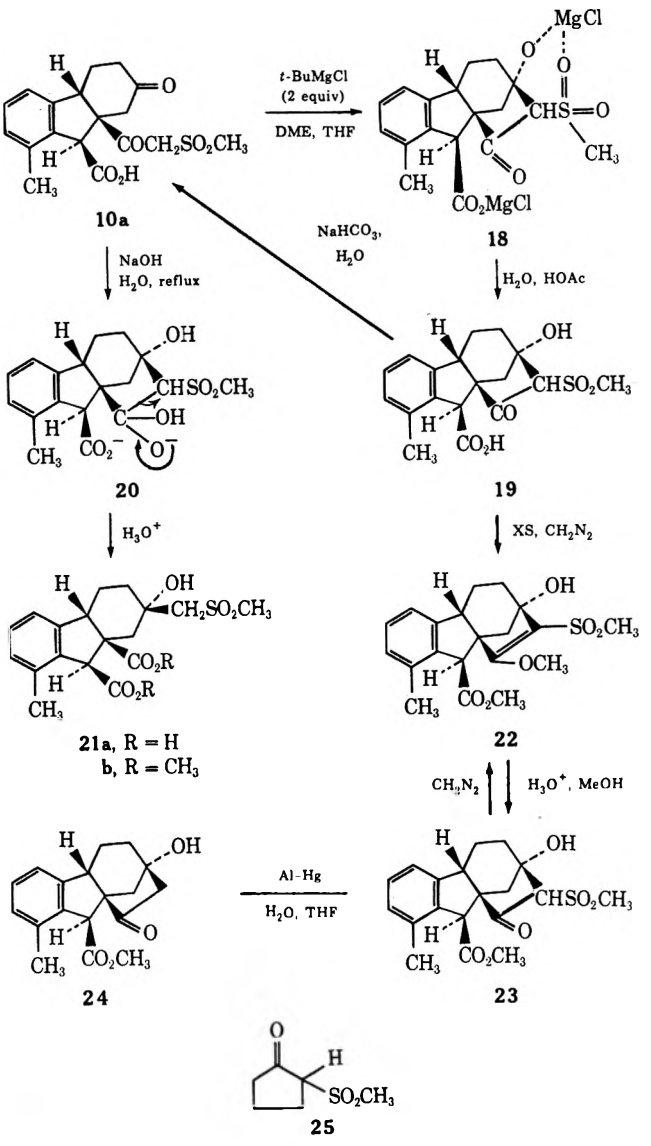
(4) H. O. House, F. J. Sauter, W. G. Kenyon, and J. J. Riehl, *ibid.*, **33**, 957 (1968).

(5) (a) H. O. House, S. G. Boots, and V. K. Jones, *ibid.*, **30**, 2519 (1965); (b) H. O. House and J. K. Larson, *ibid.*, **33**, 61 (1968); (c) L. J. Dolby, S. Esfandiari, C. A. Elliger, and K. S. Marshall, *ibid.*, **36**, 1277 (1971); (d) H. O. House, R. G. Carlson, and H. Babad, *ibid.*, **28**, 3359 (1963), and references cited therein.

SCHEME II



SCHEME III



medium (DME + THF, Scheme III). We attribute the success of this aldol condensation and other examples to be discussed elsewhere[6] to the formation of a covalent metal alkoxide such as the metal chelate **18** that is stable in the absence of polar solvents which could compete as ligands for the metal ion. An indication of the value of this procedure for effecting aldol condensation is provided by the ready reversal of the reaction when the aldol product **19** was treated with even very weak bases such as aqueous sodium bicarbonate. Reaction of the diketone **10a** with refluxing aqueous sodium hydroxide evidently produces a small equilibrium concentration of the aldol product **19** which is cleaved (see structure **20**) on prolonged reaction to form the diacid **21a**.

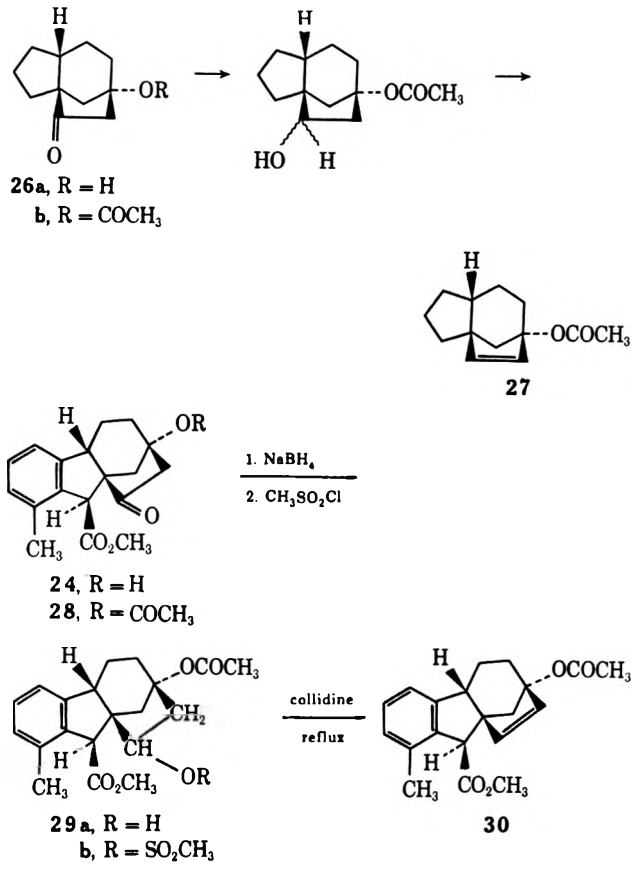
Reaction of the aldol product **19** with diazomethane posed an unexpected difficulty in that the initially formed keto ester **23** reacted relatively rapidly with additional diazomethane to form an enol ether **22**. Since we found no evidence for the presence of a significant quantity of the enol tautomer of the keto ester **23** and the model β-keto sulfone **25** did not react readily with diazomethane, the reason for the ready formation of the enol ether **22** from the ketone **23** remains unclear. It might also be noted that the *O*-acetyl derivative of a structure analogous to acid **19** was converted with diazomethane to a methyl ester without apparent problem from enol ether formation.[5c] This difficulty was best overcome in the synthetic scheme by reaction of the aldol product **19** with excess diazomethane to form the dimethoxy derivative **22**. Subsequent acid-catalyzed hydrolysis afforded the desired keto ester **23**, which was reductively cleaved with aluminum amalgam to form the hydroxy ketone **24**.

Conversion of the hydroxy ketone **24** to the acetoxy olefin **30** (Scheme IV) followed a sequence devised by Nagata and coworkers[7] and explored previously[5b] in the model systems **26** → **27**. The further transformation of the tetracyclic acetoxy olefin **30** to degradation products of gibberellic acid will be described in a subsequent publication.

(6) H. O. House, D. S. Crumrine, H. D. Olmstead, and A. Y. Teranishi, to be published.

(7) W. Nagata, T. Sugasawa, M. Narisada, T. Wakabayashi, and Y. Hayase, *J. Amer. Chem. Soc.*, **89**, 1483 (1967); W. Nagata, M. Narisada, T. Wakabayashi, and T. Sugasawa, *ibid.*, **89**, 1499 (1967).

SCHEME IV



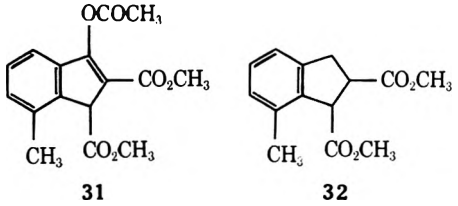
Experimental Section[8]

o-Tolylsuccinic Anhydride (3).—Tetracarboethoxyethylene, mp 52.5–54° (li.[9a] mp 52.5–53.5°), was obtained by previously described methods.[9] A 1.00 *M* solution of *o*-tolylmagnesium chloride was prepared by reaction of 52.39 g (0.41 mol) of *o*-chlorotoluene with 10.75 g (0.46 g-atom) of triply sublimed Mg[10] in 250 ml of tetrahydrofuran. To 326 ml of this cold (0°) solution (containing 326 mmol of the Grignard reagent) was added a solution of 103.3 g (327 mmol) of the tetracarboethoxyethylene. The resulting mixture was stirred for 16 hr at 25° and then partitioned between Et_2O and aqueous NH_4Cl. The organic layer was dried and concentrated to leave 175.4 g of crude 1-(*o*-tolyl)-1,1,2,2-tetracarboethoxyethane as a viscous liquid which partially crystallized on standing. A solution of this crude product in 135 ml of concentrated aqueous HCl and 225 ml of HOAc was refluxed for 68 hr, during which time 300 ml of liquid was allowed to distil from the mixture. After the reaction mixture had been further concentrated and then diluted with toluene, 33.3 g of crude *o*-tolylsuccinic acid separated and was collected. The mother liquors were subjected to the hydrolysis and decarboxylation procedure again to form an additional 30.7 g (total yield 65 g) of crude *o*-tolylsuccinic acid. A solution of the crude acid in 170 g of Ac_2O was refluxed for 1.5 hr and then distilled to separate 44.7 g (72% overall) of the anhydride **3** as a viscous yellow liquid, bp 119–128° (0.13 mm) [lit.[11] bp 174–176° (5 mm)]. Repitition of this same procedure on a larger scale produced the same anhydride **3** in a yield of 76% overall. In accord with previous observations,[4] repetition of this same reaction sequence starting with 120.2 g (380 mmol) of tetracarboethoxyethylene and 380 mmol of *o*-tolylmagnesium chloride prepared from ordinary Grignard-grade magnesium (Eastman Organic Chemicals) produced a series of very impure reaction intermediates. At the end of the sequence distillation separated 32.3 g (45% overall) of the desired anhydride **3**, bp 120–136° (0.2–0.3 mm), accompanied by 7.0 g (26%) of crude succinic anhydride, mp 117–119°, which sublimed during the early part of the distillation. This by-product was identified with an authentic sample by a mixture melting point determination and comparison of ir spectra.

A 1.5-g (72 mmol) sample of *o*-tolylsuccinic acid was esterified with excess ethereal CH_2N_2 to form the dimethyl ester, obtained as 1.5 g (88%) of colorless liquid after distillation in a short-path still (0.2 mm and 140° bath): ir (CCl_4) 1740 cm^{-1} (ester C=O); uv max (95% EtOH) 265 mμ (ε 574) and 272 (597); nmr (CCl_4) δ 6.9–7.1 (4 H, m, aryl CH) with singlets at 3.52 (6 H, OCH_3) and 2.37 (3 H, aryl CH_3) superimposed on a multiplet in the region 2.4–4.4 (3 H, aliphatic CH); mass spectrum *m/e* (rel intensity) 236 (33, M^+), 205 (20), 204 (50), 177 (21), 176 (21), 172 (20), 144 (42), 143 (40), 135 (100), 117 (43), 116 (23), 115 (27), and 91 (27).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.90; H, 6.87.

1,2-Dicarbomethoxy-7-methylindene (6).—The previously described[4] procedures were used to convert the *o*-tolylsuccinic anhydride to the indene diester **6**, mp 79–80.5° (lit.[4] mp 79.9–81°). In exploring various methods to hydrogenate the intermediate enol acetate **31** to the indan triester, a 3.04-g (10 mmol) sample of **31** in 50 ml of HOAc was hydrogenated at 1 atm and 27° over 0.3 g of a 10% Pd/C catalyst. When the H_2 uptake (500 ml or 2 equiv) ceased, the product (a liquid) was chromatographed on silica gel to separate 1.3 g (42%) of one stereoisomer of the indan diester **32**, mp 65–70°, in fractions eluted with



Et_2O–hexane mixtures. Recrystallization from hexane separated one pure stereoisomer of the indan **32** as white prisms: mp 76–77°; ir (CCl_4) 1745 cm^{-1} (ester C=O); uv (95% EtOH) series of weak maxima (ε 244–296) in the region 250–280 mμ; nmr (CCl_4) δ 6.8–7.2 (3 H, m, aryl CH), 2.8–4.4 (3 H, m, aliphatic CH), 3.65 (3 H, s, OCH_3), 3.52 (3 H, s, OCH_3), and 2.30 (3 H, s, aryl CH_3).

Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.47; H, 6.46.

To explore an alternative synthesis of the indene **6**, β-(*o*-tolyl)propionic acid was esterified with MeOH and H_2SO_4 to form methyl β-(*o*-tolyl)propionate (92% yield) as a colorless liquid: bp 70–74.3° (0.2–0.3 mm); $n^{26.8}D$ 1.4998–1.500; ir (CCl_4) 1750 cm^{-1} (ester C=O); uv (95% EtOH) series of weak maxima (ε 200–258) in the region 250–280 mμ; nmr (CCl_4) δ 6.8–7.4 (4 H, m, aryl CH), 3.56 (3 H, s, OCH_3), 2.3–3.1 (4 H, m, aliphatic CH), and 2.28 (3, H, s, aryl CH_3); mass spectrum *m/e* (rel intensity) 178 (32, M^+), 119 (36), 118 (100), and 105 (56).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.86; H, 7.95.

To a refluxing solution of 7.2 g (300 mmol) of NaH and 13.02 g (110 mmol) of $(CO_2CH_3)_2$ in 100 ml of PhH was added, dropwise over 1 hr, a solution of 17.82 g (100 mmol) of methyl β-(*o*-tolyl)propionate in 150 ml of PhH. After the reaction mixture had been refluxed for an additional 1 hr, it was acidified with 26.2 ml of HOAc and then partitioned between PhH and H_2O. The crude keto diester **33** (25.2 g) recovered from the organic layer was added to 20 g (100 mmol) of $Cu(OAc)_2$ in 200 ml of

(8) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated $MgSO_4$ was employed as a drying agent. The ir spectra were determined with a Perkin-Elmer Model 237 or Model 257 infrared recording spectrophotometer fitted with a grating. The uv spectra were determined with a Cary Model 14 or a Perkin-Elmer Model 202 recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Model A-60 or Model T-60 nmr spectrometer. The chemical shifts are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with an Hitachi Perkin-Elmer or a Varian Model M-66 mass spectrometer. All reactions involving strong bases or organometallic intermediates were performed under a nitrogen atmosphere.

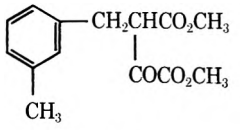
(9) (a) B. B. Corson and W. L. Benson, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 273; (b) C. S. Palmer and P. W. McWherter, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1964, p 245.

(10) This purified magnesium metal was obtained through the kindness of Dr. Francis Johnson of the Dow Chemical Co.

(11) K. Mori, M. Matsui, and Y. Sumiki, *Agr. Biol. Chem.* (*Tokyo*), **27**, 27 (1963).

warm (60°) H_2O. The resulting mixture was extracted with PhH and the organic extract was concentrated. Crystallization of the residue from a PhH–hexane mixture separated 11.16 g (43.5%) of the copper complex of the β-keto ester **33** as green needles: mp 158–163° dec; ir (CCl_4) 1745 (ester C=O) and 1605 cm^{-1} (β-keto ester enolate); uv max (95% EtOH) 284.5 mμ (ε 18,200).

Anal. Calcd for $C_{28}H_{30}CuO_{10}$: C, 56.99; H, 5.12; Cu, 10.77. Found: C, 56.70; H, 4.91; Cu, 10.51.



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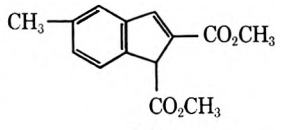

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After 1.00 g of this copper complex had been shaken with 100 ml of aqueous 0.5 *M* H_2SO_4 and 25 ml of Et_2O, the Et_2O layer was separated, washed with H_2O, dried, concentrated, and distilled in a short-path still (0.15 mm, 130–160° bath). The partially enolic keto diester **33** was collected as a colorless liquid: $n^{21.9}D$ 1.5060; ir (CCl_4) 1760, 1740 (ester C=O), 1665 (weak), and 1610 cm^{-1} (weak) (partially enolic keto ester); uv max (95% EtOH) 217 mμ (ε 5000), 260 (1800), and 272.5 (shoulder, 1660); nmr (CCl_4) δ 6.7–7.1 (4 H, m, aryl CH), 2.27 (3 H, s, aryl CH_3), and a multiplet in the region 2.9–4.5 (9 H, OCH_3 singlets and aliphatic CH); mass spectrum *m/e* (rel intensity), 264 (9, M^+), 173 (51), 145 (55), and 105 (100).

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.54; H, 6.15.

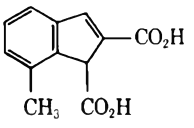
A 4.40-g (16.6 mmol) sample of the keto diester **33** was added dropwise and with stirring over 30 min to 50 g of warm (103–105°) polyphosphoric acid. The resulting mixture was stirred for an additional 30 min and then treated with ice and extracted with Et_2O. The ethereal extract was washed successively with aqueous $NaHCO_3$ and aqueous NaCl, and then dried and concentrated. Successive crystallization of the residual liquid (3.40 g) from Et_2O and from MeOH separated 1.12 g of tan prisms, mp 50–74°, with nmr absorption consistent with the presence of a mixture of comparable amounts of esters **6** and **34** and their double bond isomers. A solution of 670 mg of this material was equilibrated[12] in 15 ml of boiling MeOH containing 20 mg of TsOH. The recovered material was fractionally crystallized from Et_2O–hexane and from hexane to separate 70.5 mg of the indene diester **34** as white prisms: mp 82.5–84°; ir (CCl_4) 1745 (ester C=O) and 1720 cm^{-1} (conjugated ester C=O); uv max (95% EtOH) 232.5 mμ (ε 18,400), 238.5 (19,000), and 292 (14,800); nmr ($CDCl_3$) δ 7.74 (1 H, d, J = 1.8 Hz, vinyl CH), 7.0–7.6 (3 H, m, aryl CH), 4.63 (1 H, m, benzylic CH), 3.84 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), and 2.37 (3 H, s, aryl CH_3); mass spectrum *m/e* (rel intensity) 246 (100, M^+), 214 (36), 187 (52), 157 (78), 156 (42), 143 (61), 129 (33), 128 (78), 127 (36), and 59 (31).

Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.42; H, 5.73.

Since we were unable to find a practical method for separating the indene diesters **6** and **34**, this synthetic scheme was not explored further.

A solution of 2.26 g (9.2 mmol) of the diester **6** in a mixture of 75 ml of aqueous 12 *M* HCl and 75 ml of HOAc was heated to 90° for 2.5 hr and then concentrated under reduced pressure. The residual yellow solid (2.04 g) was triturated with $CHCl_3$ (to remove the soluble monoacids **36a**) to leave 1.65 g (82%) of the insoluble diacid **35** as a white solid, mp 171–180° dec. Samples of this diacid **35**, which were purified by solution in boiling $CHCl_3$ followed by concentration, were obtained as white solids melting with decomposition within the range 183–193°. Samples of **35** which had been decomposed solidified and remelted at 203–207° corresponding to the subsequently described monoacid **36a**; the ir spectra of these samples also indicated them to be the monoacid. The samples of the diacid **35** had ir absorption (KBr pellet) at 1705 and 1665 cm^{-1} (unconjugated and conjugated carboxyl C=O); titration (aqueous NaOH) indicated an equivalent weight of 114 (calcd 109). Esterification of 101 mg of this diacid **35** with excess ethereal CH_2N_2 yielded 118 mg

(12) H. O. House, J. K. Larson, and H. C. Muller, *J. Org. Chem.*, **33**, 961 (1968).



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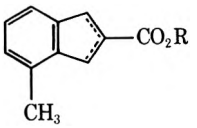
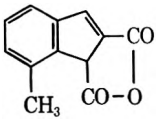


36a, R = H
b, R = CH_3



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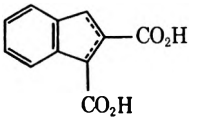

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of the crude diester **6**, mp 70–75°, which was identified with an authentic sample by comparison of nmr spectra.

Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.14; H, 4.78.

A variety of attempts to convert the diacid **35** to the anhydride **37**, including methods which had been successful for the conversion of the diacids **38** to the corresponding anhydrides,[12] resulted either in recovery of the starting diacid or in the formation of other products which appeared to be derived from the monoacid **36a**.

The Diels–Alder Reaction with the Indene 6.—A mixture of 11.61 g (47.2 mmol) of the diester **6**, 955 mg of phenothiazine (a free-radical inhibitor), 50 ml of liquid butadiene, and 70 ml of PhH was heated to 180–192° in an autoclave for 24 hr. The mixture was cooled, 50 ml of liquid butadiene was added, and heating to 170° was continued for an additional 24 hr. Then an additional 30-ml portion of liquid butadiene was added and heating at 170° was continued for an additional 48 hr. The resulting reaction mixture was concentrated and then extracted with four 150-ml portions of boiling MeOH. The combined MeOH extracts were concentrated, diluted with Et_2O, and cooled to separate 973 mg (8.5%) of the starting diester **6**. The mother liquors were concentrated, mixed with 100 ml of aqueous 10% NaOH, and refluxed for 13 hr. After the resulting mixture had been extracted with Et_2O, the aqueous phase was acidified (HCl) and extracted with Et_2O. The acidic Et_2O solution was dried and concentrated slowly. The initial material, which separated as light, fluffy needles, was the crude monoacid **36a**. After this material had been removed, further concentration of the Et_2O solution resulted in the crystallization of 5.98 g (37%) of the ether solvate of the diacid **5** as dense prisms, mp 74° dec (lit.[4] mp 75° dec).

Recrystallization of the crude monoacid **36a** from $CHCl_3$ afforded the pure acids (presumably a mixture of double-bond isomers) as white needles: mp 214° dec; ir (KBr pellet) 3000 (broad, associated OH) and 1660 cm^{-1} (broad, carboxyl C=O); uv max (MeOH) 227 mμ (ε 10,800), 234.5 (9500), and 285 (16,800); nmr (DMSO-d_6) δ 7.6–7.8 (1 H, m, vinyl CH), 7.0–7.5 (3 H, m, aryl CH), 3.4–3.7 (2 H, m, benzylic CH_2), 2.42 and 2.33 (two singlets, total 3 H, aryl CH_3 groups of double bond isomers).

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.60; H, 5.74.

An 851-mg sample of the acids **36a** was esterified with excess ethereal CH_2N_2 to yield 800 mg of the esters **36b** as tan needles: mp 43–45°; ir (CCl_4) 1715 cm^{-1} (conjugated ester C=O); uv max (95% EtOH) 231 mμ (ε 10,100), 237 (9000), and 292 (18,100); nmr (CCl_4) δ 7.5–7.8 (1 H, m, vinyl CH), 6.9–7.4 (3 H, m, aryl CH), 3.77 (3 H, s, OCH_3), 3.4–3.7 (2 H, m, benzylic CH_2), 2.46 and 2.35 (two singlets, total 3 H, aryl CH_3 of double bond isomers); mass spectrum *m/e* (rel intensity) 188 (78, M^+), 157 (25), 129 (100), and 128 (44).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.75; H, 6.54.

The Iodolactones 7.—The ether solvate of the diacid **5** (6.12 g, 17.7 mmol) was dissolved in a mixture of 240 ml of saturated aqueous $NaHCO_3$, 19.2 g (75.5 mmol) of I_2, 42 g (246 mmol) of KI, and 180 ml of H_2O and allowed to stand at 25° for 48 hr. After the reaction mixture had been acidified (HCl), it was extracted with $CHCl_3$ and the organic extract was washed with aqueous $Na_2S_2O_3$ and then dried and concentrated. Recrystallization of the residue (6.04 g) from EtOAc separated 5.37 g (75%) of the iodolactone **7a** as colorless prisms: mp 214° dec; ir ($CHCl_3$) 1790 (γ-lactone C=O) and 1720 cm^{-1} (broad, car-

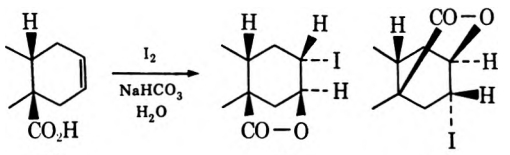
boxyl C=O); uv max (CH_3CN) 262 mμ (ε 877); nmr (pyridine-d_5) δ 11.4 (1 H, broad, OH), 6.8–7.7 (3 H, m, aryl CH), 5.10 (1 H, m, OCH), 4.2–4.6 (1 H, m, CHI), 4.30 (1 H, s, benzylic CHCO), 3.7–4.2 (1 H, m, benzylic CH), 1.8–3.4 (4 H, m, aliphatic CH), and 2.36 (3 H, s, aryl CH_3).

Anal. Calcd for $C_{16}H_{15}IO_4$: C, 48.26; H, 3.79; I, 31.86. Found: C, 48.29; H, 3.91; I, 31.76.

Esterification of 800 mg of the iodolactone acid **7a** with excess ethereal CH_2N_2 yielded 519 mg (63%) of the ester **7b** as colorless prisms from Et_2O–CH_2Cl_2: mp 210 dec; ir ($CHCl_3$) 1790 (γ-lactone C=O) and 1740 cm^{-1} (ester C=O); uv max (95% EtOH) 263 mμ (ε 912) and 270 (shoulder, 715); nmr ($CDCl_3$) δ 7.0–7.5 (3 H, m, aryl CH), 5.0–5.4 (1 H, m, CHO), 4.2–4.7 (1 H, m, CHI), 4.00 (1 H, s, benzylic CHCO), 3.5–4.0 (1 H, m, benzylic CH), 3.69 (3 H, s, OCH_3), 2.1–3.5 (4 H, m, aliphatic CH), and 2.24 (3 H, s, aryl CH_3).

Anal. Calcd for $C_{17}H_{17}IO_4$: C, 49.53; H, 4.16; I, 30.78. Found: C, 49.47; H, 4.36; I, 30.85.

The ir absorption of these iodolactones **7** and the related deiodinated lactones **8** at 1790 cm^{-1} establishes that these products are γ-lactones **39** and not δ-lactones **40**. Comparable iodolactonization studies of an analogous acid **41** in a model



41 39 40

series[6a] as well as earlier studies[6d] have demonstrated that the formation of γ- rather than δ-lactones is the preferred course of this reaction.

The Lactones 8.—To a solution of 2.00 g (5.02 mmol) of the iodolactone acid **7a** in 30 ml of 1,2-dimethoxyethane was added, portionwise and with stirring over 15 min, 4.38 g (15.0 mmol) of (n-Bu)$_3$SnH.[13] The resulting mixture was stirred for 4 hr and then extracted with saturated aqueous $NaHCO_3$. The aqueous solution was acidified to precipitate 1.08 g (79%) of the lactone acid **8a**, mp 268° dec. Recrystallization from EtOAc afforded the pure acid **8a** as white prisms: mp 270° dec; ir (KBr pellet) 3400, 2940 (broad, associated OH), 1790 (γ-lactone C=O), and 1705 cm^{-1} (carboxyl C=O); uv max (CH_3CN) 263 mμ (ε 250) and 272 (187); nmr (pyridine-d_5) δ 11.4 (1 H, OH), 6.8–7.5 (3 H, m, aryl CH), 4.62 (1 H, broad, CHO), 4.16 (1 H, s, benzylic CHCO), 3.4–4.1 (1 H, m, benzylic CH), 2.26 (3 H, s, aryl CH_3), and 1.3–2.3 (6 H, m, aliphatic CH).

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.33; H, 5.78.

In an alternative procedure, after reaction of 4.00 g (10.0 mmol) of the crude iodolactone **7a** with 8.9 g (31 mmol) of (n-Bu)$_3$SnH in 55 ml of 1,2-dimethoxyethane at 25° for 4 hr, the reaction mixture was filtered and the residue was washed with Et_2O. The residual lactone acid **8a** amounted to 2.32 g (85%) of white solid, mp 280–286° dec, which was sufficiently pure for use in further synthetic transformations.

Esterification of the acid **8a** with excess ethereal CH_2N_2 afforded the lactone ester **8b** as colorless prisms from MeOH: mp 187–188°; ir ($CHCl_3$) 1780 (γ-lactone C=O) and 1735 cm^{-1} (ester C=O); uv max (95% EtOH) 260 mμ (shoulder, ε 220), 263.5 (253), and 272 (176); nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH), 4.82 (1 H, m, CHO), 3.94 (1 H, s, benzylic CHCO), 3.72 (3 H, s, OCH_3), 3.4–4.0 (1 H, m, benzylic CH), 2.24 (3 H, s, aryl CH_3), and 1.5–2.6 (6 H, m, aliphatic CH).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.06; H, 6.38.

The Keto Sulfones 10.—To a suspension of the lithio derivative prepared from 3.4 g (36 mmol) of $CH_3SO_2CH_3$ and 33 mmol of CH_3Li in 300 ml of 1,2-dimethoxyethane was added 3.00 g (11 mmol) of the lactone acid **8a**. The resulting solution was refluxed for 15 hr and then cooled, neutralized (4 ml of HOAc), acidified (100 ml of aqueous 1.2 *M* HCl), concentrated, and extracted with $CHCl_3$. The crude alcohol **9** (5.4 g of yellow liquid) obtained from the $CHCl_3$ extract was dissolved in 250 ml of cold (5°) acetone and oxidized with excess aqueous 8 *N* H_2CrO_4 (Jones reagent).[14] After following the usual isolation procedure,[14] the crude product (3.7 g) was recrystallized from CH_2Cl_2–Et_2O to separate 2.35 g (59%) of the keto sulfone **10a** as white prisms, mp 161° dec. This product **10a**, which exists in solution primarily as the tautomeric lactol **11**, was recrystallized to raise the decomposition point to 160–165°: ir ($CHCl_3$) 3420 (broad, OH), 1795 (γ-lactol C=O), 1720 (C=O), 1330, 1320, and 1120 cm^{-1} (sulfone S=O); uv max (CH_3CN) 256 mμ (shoulder, ε 247), 263 (shoulder, 320), 267 (380), 276 (330), and 293 (31); nmr (pyridine-d_5) δ 11.0 (1 H, broad, OH), 7.0–7.7 (3 H, m, aryl CH), 5.22 (1 H, broad, $COCH_2SO_2$), 4.4–4.8 (2 H, m, benzylic CH), 3.35 (3 H, s, SO_2CH_3), 2.0–3.2 (9 H, m, aliphatic CH and aryl CH_3 at δ 2.57).

Anal. Calcd for $C_{18}H_{20}O_6S$: C, 59.33; H, 5.53; S, 8.80. Found: C, 59.06; H, 5.64; S, 8.75.

A 166-mg sample of this lactol **11** (or **10a**) was esterified with excess ethereal CH_2N_2 to yield 97 mg (57%) of the ester **10b** as white prisms from Et_2O–CH_2Cl_2: mp 152–154° (recrystallization raised the melting point to 154.5–156°); ir ($CHCl_3$) 1725 (broad, ester and ketone C=O) and 1320 cm^{-1} (SO_2); uv max (CH_3CN) 266 mμ (ε 318), 271 (shoulder, 264), 275 (228), and 290 (75); nmr ($CDCl_3$) δ 6.8–7.5 (3 H, m, aryl CH), 3.9–4.5 (4 H, m, including singlets at 4.30 and 4.07, $COCH_2SO_2$ and benzylic CH and CHCO), 3.65 (3 H, s, OCH_3), 3.14 (3 H, s, SO_2CH_3), and 2.0–3.4 (9 H, m, including a singlet at δ 2.32, aryl CH_3 and aliphatic CH); mass spectrum m/e (rel intensity) 378 (9, M^+), 299 (60), 239 (50), 198 (27), 197 (100), 169 (40), 155 (37), 141 (27), and 79 (26).

Anal. Calcd for $C_{19}H_{22}O_6S$: C, 60.30; H, 5.86; S, 8.47. Found: C, 60.44; H, 6.28; S, 8.63.

Preparation of the Diketo Ester 15b. A. From the Sulfone 10b.—To a solution of 110 mg (0.29 mmol) of the sulfone **10b** in 10 ml of a 1:10 (v/v) H_2O–tetrahydrofuran mixture was added the Al amalgam prepared[15] from 78 mg (2.9 mg-atoms) of Al foil. The mixture was heated to 65° with stirring for 75 min and then cooled, filtered, concentrated, and partitioned between CH_2Cl_2 and aqueous 2 *M* HCl. Concentration of the organic phase left 89 mg of crude product which was chromatographed on 4.5 g of silica gel. The fractions (47 mg) eluted with Et_2O–hexane mixtures were recrystallized from Et_2O–hexane to separate 42 mg (47%) of the diketone **15b** as white needles: mp 91.5–93°; ir ($CHCl_3$) 1720 cm^{-1} (broad, ester and ketone C=O); uv max (95% EtOH) 265 mμ (ε 301), 269 (shoulder, 260), and 273 (225); nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH), 4.1–4.4 (1 H, m, benzylic CH), 3.94 (1 H, s, benzylic CHCO), 3.56 (3 H, s, OCH_3), and 2.0–2.9 (12 H, m, including singlets at δ 2.21 and 2.33, aliphatic CH, $COCH_3$, and aryl CH_3); mass spectrum m/e (rel intensity) 300 (3, M^+), 105 (30), 86 (38), 84 (56), 77 (26), 55 (25), 49 (100), 43 (32), and 41 (44).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.19; H, 6.57.

B. From the Lactone 8a.—To a cold (0°) suspension of 495 mg (1.82 mmol) of the acid lactone **8a** in 30 ml of tetrahydrofuran was added, dropwise and with stirring, 2.38 ml of an Et_2O solution containing 3.71 mmol of MeMgCl. A solution was obtained after approximately one-half of the MeMgCl had been added. The resulting solution was stirred at 0–25° for 1 hr and then acidified (1 ml of HOAc) and partitioned between EtOAc and aqueous 0.5 *M* HCl. The organic layer was washed with H_2O, dried, and concentrated to leave 515 mg of white solid which was recrystallized from EtOAc. The crude keto acid **14a** separated as 411 mg of white prisms, mp 215–225° dec. A solution of 246 mg of the crude keto acid **14a** in EtOAc was esterified with excess ethereal CH_2N_2. The resulting solution was washed successively with aqueous $NaHCO_3$ and with H_2O and then dried and concentrated. The residual crude keto ester **14b** (243 mg) was recrystallized from a hexane–Et_2O mixture to separate 158 mg (68%) of the ester **14b** as white prisms, mp 145.5–148°. Recrystallization afforded the pure keto ester **14b** as white needles: mp 151–152°; ir ($CHCl_3$) 3620, 3480 (unassociated and associated OH), 1730 (ester C=O), and 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.41; H, 7.25.

A solution of 406 mg (1.41 mmol) of the crude product **14a** in 50 ml of cold 0° acetone was oxided with excess 8 *N* H_2CrO_4[14] for 3 min and then the excess oxidant was destroyed with *i*-

(13) G. J. M. Van der Kerk, J. G. Noltes, and J. G. A. Luijten, *J. Appl. Chem.*, **7**, 366 (1957).

(14) E. J. Eisenbraun, *Org. Syn.*, **45**, 28 (1965).

(15) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

PrOH and the solution was concentrated. The reaction mixture was partitioned between $CHCl_3$ and H_2O and the organic layer was washed with H_2O, dried, and concentrated to leave 420 mg of the diketo acid **15a** as a colorless semisolid. Recrystallization from a hexane–Et_2O mixture afforded 353 mg (88%) of the crude lactol **15c** (from diketo acid **15a**), as white prisms: mp 101–215° dec; ir ($CHCl_3$) 1775 (lactol C=O) and 1715 cm^{-1} (C=O). A 45-mg (0.16 mmol) aliquot of the crude lactol **15c** (from the diketo acid **15a**) was esterified with excess ethereal CH_2N_2 and the crude neutral product (40 mg) was isolated in the usual way. Crystallization from hexane–Et_2O separated 30 mg (63%) of the diketo ester **15b** as white needles, mp 92–93.5°, identified with the previously described sample by a mixture melting point determination.

A solution of 279 mg (0.97 mmol) of the crude diketo acid **15a** and 109 mg (0.57 mmol) of *p*-TsOH·H_2O in 40 ml of PhH was refluxed for 6 hr and then 15 ml of solvent was allowed to distil from the mixture. The residual solution was washed with aqueous $NaHCO_3$ and concentrated. Sublimation (0.04 mm, 61°) of a portion of the residue (223 mg of yellow liquid) separated the enol lactone **16** as a white solid, mp 121.5–123°. Recrystallization from an Et_2O–hexane mixture afforded the pure enol lactone **16** as white prisms: mp 122–123°; ir ($CHCl_3$) 1805 (γ-lactone C=O), 1720 (C=O), and 1670 cm^{-1} (enol C=C); uv max (CH_3CN) 265.5 mμ (ϵ 321) and 274 (255); nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH), 4.75 (1 H, d, J = 2 Hz, vinyl CH), 4.34 (1 H, d, J = 2 Hz, vinyl CH), 3.90 (1 H, s, benzylic CHCO), 3.35 (1 H, m, benzylic CH), 2.80 (1 H, d, J = 15 Hz, CH_2CO), 2.51 (1 H, d, J = 15 Hz, CH_2CO), 2.40 (3 H, s, aryl CH_3), and 1.6–2.4 (4 H, m, aliphatic CH_2); mass spectrum *m/e* (rel intensity) 268 (49, M^+), 198 (90), 170 (20), 156 (100), 155 (20), 142 (35), 141 (43), and 115 (22).

Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.22; H, 5.98.

Preparation of the Diacid Derivatives 12 and 13.—A mixture of 720 mg (2.52 mmol) of the lactone **8b**, 60 ml of MeOH, and 60 ml of aqueous 10% NaOH was stirred at 25° for 2.5 hr and then acidified (HCl), concentrated, and partitioned between EtOAc and aqueous $NaHCO_3$. The aqueous layer was acidfied (HCl) and extracted with EtOAc. After the organic extract had been washed with H_2O, dried, and concentrated, the residual crude product (829 mg, mp 171–174° dec) was recrystallized from EtOAc–hexane to separate 507 mg (66%) of the pure hydroxy acid **12** as white prisms: mp 174–182° dec; ir ($CHCl_3$) 3300 (broad, associated OH) and 1735 cm^{-1} (broad, ester and carboxyl C=O); uv max (95% EtOH) 263 mμ (ϵ 266) and 273 (shoulder, 209); nmr (pyridine-d_5) δ 8.67 (1 H, s, OH), 6.9–7.7 (3 H, m, aryl CH), 3.9–4.9 (3 H, m, CHO and benzylic CH), 3.52 (3 H, s, OCH_3), 1.0–3.2 (6 H, m, aliphatic CH), 2.38 (3 H, s, aryl CH_3), and 1.98 (1 H, s, OH); mass spectrum *m/e* (rel intensity) 304 (1, M^+), 226 (40), 200 (40), 183 (41), 182 (100), 181 (34), 167 (33), 156 (43), 155 (39), 143 (23), 142 (31), 141 (47), 128 (27), and 115 (30). Concentration of the mother liquors separated an additional 162 mg of the crude acid **12**, mp 167.5–175° dec.

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.90; H, 6.67.

A solution of 650 mg (2.14 mmol) of the hydroxy acid **12** in 50 ml of cold (0°) acetone was oxidized with excess aqueous 8 *N* H_2CrO_4[14] for 3 min and then the excess oxidant was destroyed with *i*-PrOH and the reaction mixture was concentrated and partitioned between H_2O and $CHCl_3$. The organic phase was washed with H_2O, dried, and concentrated. Recrystallization of the crude residue (690 mg) from Et_2O–hexane afforded 548 mg (85%) of the crude keto acid **13a** as white prisms, which melted with decomposition over the range 111–125°: ir ($CHCl_3$) 2970 (broad, associated OH) and 1730 cm^{-1} (broad, C=O); uv max (95% EtOH) 264.5 mμ (ϵ 242), 270 (199), and 274 (shoulder, 156); nmr ($CDCl_3$) δ 6.7–7.4 (4 H, m, aryl CH and OH), 4.2–4.5 (1 H, m, benzylic CH), 3.93 (1 H, s, benzylic CHCO), 3.61 (3 H, s, OCH_3), and 2.0–3.3 (9 H, m, including a singlet at δ 2.33, aryl CH_3 and aliphatic CH).

A 201-mg (0.67 mmol) sample of the crude keto acid **13a** was esterified with excess ethereal CH_2N_2 and the crude neutral product (205 mg, mp 102–115°) was isolated in the usual way. Recrystallization from hexane–Et_2O separated 177 mg (88%) of the diester **13b** as white prisms, mp 111.5–113°. After an additional recrystallization the keto diester **13b** melted at 112–113°: ir ($CHCl_3$) 1740 (ester C=O) and 1720 cm^{-1} (shoulder, C=O); uv (95% EtOH) series of weak maxima (ϵ 163–252) in the region 250–275 mμ; nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH), 4.1–4.4 (1 H, m, benzylic CH), 3.93 (1 H, s, benzylic CHCO), 3.75 (3 H, s, OCH_3), 3.64 (3 H, s, OCH_3), and 1.6–2.9 (9 H, m, including a singlet at δ 2.37, aryl CH_3 and aliphatic CH); mass spectrum *m/e* (rel intensity) 316 (8, M^+), 256 (100), 197 (37), 169 (39), 155 (44), and 141 (23).

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.45; H, 6.29.

Reactions of the Diketo Sulfone 10a (or 11). A. With Aqueous NaOH.—When an aqueous solution of the sulfone **10a** and 1.5 equiv of LiOH was stirred at 25° for 4 hr and then acidified and extracted with CH_2Cl_2, the diketo sulfone **10a** was recovered with no evidence (ir spectrum, absorption at 1750 cm^{-1}) for the presence of the aldol product **19**. When an aqueous solution of 364 mg (1.0 mmol) of the sulfone **10a** and 1.46 mmol of NaOH was heated to 95° for 17 hr and then acidified, 155 mg of the crude acid **21a** (mp 130–160° dec) precipitated. Esterification with excess ethereal CH_2N_2 followed by recrystallization from a CH_2Cl_2–Et_2O mixture yielded 100 mg of the diester **21b** as white prisms, mp 172.5–175°. Recrystallization afforded the pure diester **21b**: mp 174–176°; ir ($CHCl_3$) 3490 (broad, associated OH), 1735 (ester C=O), and 1310 cm^{-1} (SO_2); uv (CH_3CN) series of weak maxima (ϵ 148–240) in the region 250–275 mμ; nmr ($CDCl_3$) δ 6.9–7.5 (3 H, m, aryl CH), 4.0–4.3 (1 H, m, benzylic CH), 3.90 (1 H, s, benzylic CHCO), 3.82 (3 H, s, OCH_3), 3.68 (3 H, s, OCH_3), 3.1–3.5 (3 H, m, CH_2SO_2 and OH, 1 H exchanged with D_2O), 2.95 (3 H, s, SO_2-CH_3), and 1.0–2.8 (9 H, m, including a singlet at δ 2.33, aliphatic CH and aryl CH_3); mass spectrum *m/e* (rel intensity) 379 (2, $M^+ - OCH_3$), 253 (37), 193 (20), and 40 (100).

Anal. Calcd for $C_{20}H_{26}O_7S$: C, 58.52; H, 6.38; S, 7.81. Found: C, 58.25; H, 5.37; S, 7.99.

B. With Derivatives of Na, K, and Li.—A series of small-scale reactions were performed in which the sulfone **10a** was treated with NaH, MeLi, *t*-BuOK, $(i\text{-Pr})_2NLi$, or sodium *tert*-amylate in dimethyl sulfoxide, dimethyl sulfoxide–tetrahydrofuran mixtures, or 1,2-dimethoxyethane. The reaction mixtures were acidified (HOAc) and partitioned between aqueous 1 *M* HCl and either CH_2Cl_2 or EtOAc. The organic extracts were washed with H_2O, dried, and concentrated. Examination of the ir spectrum (Nujol mull) of the residue indicated whether or not any aldol product **19** was present by ir absorption at 1750 cm^{-1}. In all of these cases only weak absorption was observed at 1750 cm^{-1} with the most promising results being obtained from reaction with NaH in a 20:1 (v/v) mixture of tetrahydrofuran and dimethyl sulfoxide.

C. With Magnesium Derivatives.—To a cold (0°) solution of 206 mg (0.57 mmol) of the sulfone **10a** in 15 ml of tetrahydrofuran was added, with stirring, 0.39 ml of a tetrahydrofuran solution containing 1.13 mmol of MeMgCl. The resulting suspension was refluxed with stirring for 33 hr and then quenched by adding 0.15 ml of HOAc. The resulting mixture was concentrated and then partitioned between EtOAc and H_2O (pH 4). The organic layer was washed with H_2O (pH 4), dried, and concentrated. Crystallization of the residual yellow liquid (310 mg) from $CHCl_3$ afforded 64 mg (31%) of the keto sulfone acid **19** as a white solid, mp 211–219° dec.

In a second experiment, the mixture from 1.00 g (2.75 mmol) of **10a** in 65 ml of 1,2-dimethoxyethane and 1.93 ml of a tetrahydrofuran solution containing 5.60 mmol of MeMgCl was refluxed for 24 hr and then poured into a solution of 5 ml of HOAc in 50 ml of $CHCl_3$. The resulting mixture was concentrated and then partitioned between $CHCl_3$ and aqueous 0.1 *M* HCl. The organic layer was washed with H_2O, dried, and concentrated and the residue (1.038 g) was crystallized from $CHCl_3$ to separate 450 mg (45%) of the keto sulfone acid **19**, mp 214–220° dec. The same procedure was followed starting with 254 mg (0.70 mmol) of **10a** in 18 ml of dioxane and 1.39 mmol of MeMgCl in 0.48 ml of tetrahydrofuran. The yield of the crude product **19** was 78 mg (31%), mp 213–220° dec. Similarly, a solution of 440 mg (1.21 mmol) of **10a** and 446 mg (2.42 mmol) of $MgBr_2$ in 15 ml of cold (0°) tetrahydrofuran was treated with 15 ml of a tetrahydrofuran solution of $(i\text{-Pr})_2NLi$, prepared from 244 mg (2.42 mmol) of $(i\text{-Pr})_2NH$ and 2.46 mmol of MeLi. The resulting suspension was refluxed for 25 hr and subjected to the same isolation procedure to separate 140 mg (33%) of the product **19**, mp 214–219° dec.

The use of a hindered Grignard reagent to impede competing addition to the carbonyl functions was the most satisfactory procedure. To a cold (0°) solution of 4.73 g (13 mmol) of the

sulfone 10a (as the lactol 11) in 380 ml of 1,2-dimethoxyethane was added, dropwise and with stirring, 20.0 ml of tetrahydrofuran solution containing 29 mmol of *t*-BuMgCl. The resulting white suspension was stirred at 0° for 20 min and at reflux for 51 hr and then partitioned between $CHCl_3$ and aqueous HOAc. The $CHCl_3$ solution was concentrated and the residual yellow oil was partitioned between aqueous 0.5 *M* HCl and EtOAc. The EtOAc solution was dried and concentrated to leave 5.42 g of white solid. Recrystallization from $CHCl_3$ afforded 1.100 g of the hydroxy ketone **19** as a white solid, mp 223–229° dec. The material (4.33 g containing unchanged **10a**) recovered from the mother liquors was again treated with 22 mmol of *t*-BuMgCl in 300 ml of 1,2-dimethoxyethane and 15 ml of tetrahydrofuran. After a reflux period of 46 hr, use of the same isolation procedure separated an additional 3.455 g (total yield 4.555 g or 96%) of the aldol product **19**, mp 224–229° dec.

When a sample of the crude keto sulfone acid **19** was dissolved in aqueous $NaHCO_3$ and the solution was acidified (HCl) after 10 min at 25°, the ir spectrum of the crude recovered solid indicated it to be the lactol **11** from the diketo sulfone acid **10a**. Thus, the product **19** had undergone a reverse aldol condensation under these conditions. The crude keto sulfone acid **19** (presumably a mixture of stereoisomers) was soluble in MeOH and EtOAc and relatively insoluble in CH_2Cl_2 and $CHCl_3$. The material had the following spectral properties: ir (Nujol mull, KBr pellet) 3540, 3420 (associated OH), 1750 (cyclopentanone C=O), 1705 (carboxyl C=O), and 1315 cm^{-1} (SO_2).

A solution of 264 mg (0.72 mmol) of the acid **19** in cold (0°) tetrahydrofuran was esterified with a slight excess of ethereal CH_2N_2. The crude neutral product (283 mg), isolated in the usual manner, was recrystallized from Et_2O–CH_2Cl_2 to separate 159 mg (58%) of one crude epimer of the ester **23** as white needles: mp 148.5–150° (recrystallization raised the melting point to 151–152.5°; however, the sample of the ester **23** was still contaminated with a small amount of the subsequently described enol ether **22**); ir ($CHCl_3$) 1755 (cyclopentanone C=O), 1735 (ester C=O), and 1325 cm^{-1} (SO_2); uv (95% EtOH), intense end absorption (ϵ 21,000 at 201 mμ) with weak absorption (shoulders) at 263 (364) and 271 (268); nmr (CD_3COCD_3) δ 7.0–7.5 (3 H, m, aryl CH), 3.7–4.5 (3 H, m, benzylic CH and $COCHSO_2$), 3.63 (3 H, s, OCH_3), 3.20 (3 H, s, CH_3SO_2), and 1.2–3.0 (9 H, m, aliphatic CH and aryl CH_3); mass spectrum *m/e* (rel intensity) 392 (6, M^+ for **22**), 378 (6, M^+ for **23**), 299 (38), 239 (55), 211 (39), 197 (100), 169 (57), 156 (38), 155 (61), 142 (33), 141 (54), 79 (32), and 55 (35).

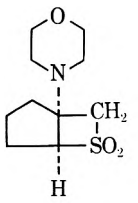
In a subsequent experiment a solution of 4.30 g (11.8 mmol) of the keto acid **19** in tetrahydrofuran was treated with a substantial excess of ethereal CH_2N_2 for 40 min at 0–25°. After concentration, the residue was recrystallized (CH_2Cl_2–Et_2O) to separate 3.506 g (76%) of the enol ether **22** as white plates: mp 174–175.5°; ir ($CHCl_3$) 3650 (associated OH), 1730 (ester C=O), and 1590 cm^{-1} (intense, conjugated C=C); uv (95% EtOH) intense end absorption (ϵ 26,400 at 202 mμ); nmr ($CDCl_3$) δ 6.8–7.3 (3 H, m, aryl CH), 4.16 (3 H, s, OCH_3), 3.4–3.8 (5 H, m, OCH_3 and benzylic CH), 3.24 (1 H, s, OH, exchanged with D_2O), 3.12 (3 H, s, CH_3SO_2), and 1.4–2.4 (9 H, m, aryl CH_3 and aliphatic CH); mass spectrum *m/e* (rel intensity) 392 (50, M^+), 363 (27), 334 (22), 333 (100), 303 (40), 273 (22), 225 (25), 191 (29), 169 (25), 166 (24), 165 (26), 155 (24), 153 (29), 152 (26), 143 (29), 141 (31), 128 (22), and 115 (21).

Anal. Calcd for $C_{20}H_{24}O_6S$: C, 61.20; H, 6.18; S, 8.17. Found: C, 61.21; H, 6.08; S, 8.07.

A 27-mg sample of the previously described crude keto ester **23** in tetrahydrofuran was also treated with excess ethereal CH_2N_2 to yield 21 mg (75%) of the crude enol ether **22**, mp 159–163°. Recrystallization from Et_2O afforded the enol ether **22** as white plates, mp 170–172°, which was identified with the previously described sample by a mixture melting point determination and by comparison of ir spectra.

A solution of 3.45 g (8.8 mmol) of the enol ether **22** and 110 ml of aqueous 2 *M* HCl in 110 ml of MeOH was refluxed for 1.5 hr and then concentrated. The residual white solid was recrystallized from an ether–CH_2Cl_2 mixture to separate 3.29 g (99%) of the crude keto ester **23** as white needles, mp 149–152°. This product was identified with the previously described sample by a mixture melting point determination and comparison of ir spectra. The purified product, mp 151–152.5°, existed as a hemihydrate.

Anal. Calcd for $(C_{19}H_{22}O_6S)_2H_2O$: C, 58.89; H, 5.95; S, 8.27. Found: C, 58.84; H, 6.07; S, 8.28.



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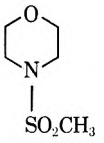

43

To examine the behavior of a simpler model system, 12.07 g (52 mmol) of the previously described[16] cycloadduct **42**, mp 115.5–118° (lit.[16] mp 117–120°), was heated to 135° in a N_2 atmosphere for 20 hr and then cooled and stirred with 40 ml of EtOH and 10 ml aqueous 1 *M* HCl for 1 hr. The solution was concentrated and the residual oil was partitioned between $CHCl_3$ and aqueous 1 *M* HCl. The organic solution was dried and concentrated to leave 7.36 g of residual brown liquid. Distillation separated 4.88 g (58%) of the crude keto sulfone **25** as a pale yellow liquid, bp 112–120° (0.5 mm). Redistillation gave the crude keto sulfone **25** as a colorless liquid: bp 108–110° (0.45 mm); $n^{25}D$ 1.4939 [lit.[17] bp 115–135° (0.6–1.0 mm)]; ir ($CHCl_3$) 1745 (cyclopentanone C=O) and 1315 cm^{-1} (SO_2); uv max (95% EtOH) 210 mμ (ϵ 216) and 271 (136). The nmr spectrum ($CDCl_3$) of this crude keto sulfone exhibits a multiplet in the range δ 1.9–4.0 (aliphatic CH) with a singlet at δ 3.08 (CH_3SO_2) as well as a weak singlet at 2.80 attributable to the methyl group of the sulfonamide **43** present as an impurity. On standing, some of this impurity **43** crystallized from the reaction mixture as white plates, mp 91–93°, and was identified with an authentic sample (mp 92.5–94°[18]) by a mixture melting point determination. Neither this model system **25** nor the keto sulfones **19** and **23** gave a color with $FeCl_3$. Reaction of a sample of the crude keto sulfone **25** with excess ethereal CH_2N_2 for 60 min at 0–25° resulted in recovery of the unchanged starting material **25** (ir analysis).

Reductive Cleavage of the Keto Sulfone 23.—To a solution of 3.288 g (8.7 mmol) of the keto sulfone **23** in 400 ml of 1:9 (v/v) H_2O–tetrahydrofuran was added freshly prepared aluminum amalgam[15] from 2.6 g (96 mg-atoms) of Al foil. The mixture was heated to 65°, with stirring, for 70 min and then concentrated and partitioned between $CHCl_3$ and H_2O. The organic solution was washed with H_2O, dried, and concentrated. The residual semisolid (2.81 g) was recrystallized from hexane–Et_2O to separate 2.029 g (78%) of the hydroxy ketone **24** as white needles, mp 139–141°. Sublimation (0.04 mm and 100°) followed by recrystallization from Et_2O–hexane separated the pure hydroxy ketone **24** as white needles: mp 142–143°; ir ($CHCl_3$) 3610, 3480 (unassociated and associated OH) and 1740 cm^{-1} (broad, ester and cyclopentanone C=O); uv max (95% EtOH) 263 mμ (ϵ 264) and 270 (210); nmr ($CDCl_3$) δ 6.8–7.4 (3 H, m, aryl CH), 3.72 (3 H, s, OCH_3), 3.5–3.7 (1 H, benzylic CH), and 1.6–2.6 (13 H, m, aryl CH_3, OH, and aliphatic CH); mass spectrum *m/e* (rel intensity) 300 (15, M^+), 241 (29), 240 (72), 199 (24), 198 (52), 181 (40), 180 (100), 169 (23), 156 (22), 155 (45), 132 (21), 131 (35), 128 (22), and 115 (22).

Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.99; H, 6.70.

Preparation of the Acetoxy Ketone 28.—A solution of 1.889 g (6.29 mmol) of the hydroxy ketone **24** and 40 ml of Ac_2O in 60 ml of pyridine was stirred at 25° for 41 hr and then partitioned between $CHCl_3$ and aqueous 2 *M* HCl. After the organic solution had been dried and concentrated, recrystallization of the residue (2.2 g of white solid) from Et_2O–hexane afforded 1.981 g (92%) of the acetoxy ketone **28** as white needles: mp 154.5–157° (recrystallization sharpened the melting point of **28** to 155.5–157°); ir ($CHCl_3$) 1740 cm^{-1} (ester and cyclopentanone C=O); uv max (95% EtOH) 262 mμ (ϵ 198) and 270 (156); nmr ($CDCl_3$) δ 7.0–7.5 (3 H, m, aryl CH), 3.3–4.0 [5 H, m, benzylic CH with a singlet at 3.73 (OCH_3)], 1.7–3.1 [14 H, m, including singlets at 2.28 and 2.02 (aryl CH_3 and $COCH_3$)]; mass spectrum *m/e* (rel intensity) 342 (23, M^+), 283 (23), 282 (100), 240 (19), 223 (25), and 180 (21).

Anal. Calcd for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 69.95; H, 6.52.

(16) I. J. Borowitz, *J. Amer. Chem. Soc.*, **86**, 1146 (1964).

(17) W. E. Truce and R. H. Knospe, *ibid.*, **77**, 5063 (1955).

(18) This sulfonamide **43** is reported to melt at 90–91°: A. G. Kostsova, E. I. Kozachenko, O. M. Osina, V. P. Volokhova, and L. D. Maslova, *Zh. Org. Khim.*, **1**, 728 (1965); *Chem. Abstr.*, **63**, 5637 (1965).

Preparation of the Hydroxy Acetate 29a.—A solution of 1.98 g (5.8 mmol) of the ketone **28** and 500 mg (13.2 mmol) of $NaBH_4$ in 75 ml of tetrahydrofuran and 110 ml of MeOH was stirred at 0° for 2.5 hr and at 25° for 1 hr. After 2 ml of HOAc had been added to consume the excess hydride, the solution was concentrated under reduced pressure and the residue was partitioned between $CHCl_3$ and aqueous $NaHCO_3$. The organic phase was washed with H_2O, dried, and concentrated to leave 2.20 g of residual liquid. Crystallization from Et_2O–hexane afforded 1.883 g (95%) of the alcohol **29a** as white prisms: mp 169–171°; ir ($CHCl_3$) 3480 (associated OH) and 1725 cm^{-1} (ester C=O); uv max (95% EtOH) 264 mμ (ϵ 315) and 272 (258); nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH) 4.53 (1 H, d of d, J = 6 and 10 Hz, >CHO), 3.6–4.0 (5 H, m, including a singlet at 3.71, benzylic CH and CH_3O), and 1.5–3.5 [15 H, m including singlets at 2.28 and 1.94 (aryl CH_3 and CH_3CO)]; mass spectrum m/e (rel intensity) 344 (13, M^+), 267 (21), 266 (100), 224 (17), 207 (44), and 43 (19).

Anal. Calcd for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.73; H, 6.93.

Preparation of the Olefin 30.—To a cold (0°) solution of 1.87 g (5.43 mmol) of the alcohol **29a** in 40 ml of pyridine was added, dropwise and with stirring, 4.2 ml of CH_3SO_2Cl. The resulting solution was allowed to stand at 5° for 26 hr and then partitioned between $CHCl_3$ and aqueous 1 *M* HCl. After the organic solution had been washed successively with aqueous HCl, aqueous $NaHCO_3$, and H_2O, it was dried and concentrated to leave 2.33 g of white solid. Recrystallization from Et_2O separated 2.204 g (97%) of the methanesulfonate **29b** as white prisms: mp 148.5–150°; ir ($CHCl_3$) 1730 (ester C=O), 1340, and 1365 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 6.9–7.4 (3 H, m, aryl CH), 5.33 (1 H, d of d, J = 6 and 9 Hz, >CHO), 3.6–4.1 (5 H, m including a singlet at 3.69, CH_3O and benzylic CH), 3.03 (3 H, s, CH_3SO_2), and 1.6–2.9 [14 H, m, including singlets at 2.18 and 1.97 (aryl CH_3 and CH_3CO)].

A solution of 309 mg (0.733 mmol) of the methanesulfonate **29b** in 9.0 ml of γ-collidine was refluxed for 30 hr and then cooled and partitioned between $CHCl_3$ and dilute aqueous HCl. The organic layer was washed successively with aqueous $NaHCO_3$ and aqueous NaCl and then dried and concentrated. The residual semisolid (249 mg) was chromatographed on 11 g of silica gel and the fractions eluted with 16% Et_2O in hexane were recrystallized from hexane to separate 166 mg (70%) of the acetoxy olefin **30** as white needles: mp 100–101°; ir ($CHCl_3$) 1730 cm^{-1} (ester C=O); uv max (95% EtOH) 265 mμ (ϵ 334) with intense end absorption (ϵ 19,800 at 206 mμ); nmr ($CDCl_3$) δ 6.8–7.3 (3 H, m, aryl CH), 6.38 (1 H, d, J = 6 Hz, vinyl CH), 6.08 (1 H, d, J = 6 Hz, vinyl CH), 3.83 (1 H, s, benzylic CH), 3.68 (3 H, s, OCH_3), 3.1–3.5 (1 H, m, benzylic CH), and 1.5–2.6 [12 H, m including singlets at 2.25 and 1.97 (aryl CH_3 and CH_3CO)]; mass spectrum m/e (rel intensity) 326 (4, M^+), 267 (26), 266 (100), 255 (21), 227 (61), 225 (85), 207 (45), 196 (32), 195 (45), and 155 (20).

Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.87; H, 6.66.

Registry No.—**5**, 15448-20-1; **6**, 15448-23-4; **7a**, 37741-20-1; **7b**, 37741-21-2; **8a**, 37741-22-3; **8b**, 37741-23-4; **9**, 37741-24-5; **10a**, 37741-25-6; **10b**, 37741-26-7; **11**, 37741-27-8; **12**, 37741-28-9; **13a**, 37741-29-0; **13b**, 37741-30-3; **14a**, 37741-31-4; **14b**, 37741-32-5; **15a**, 37741-33-6; **15b**, 37741-34-7; **15c**, 37741-35-8; **16**, 37741-36-9; **19**, 37741-37-0; **21a**, 37741-38-1; **21b**, 37741-39-2; **22**, 37741-40-5; **23**, 37741-41-6; **24**, 37741-42-7; **28**, 37741-43-8; **29a**, 37805-64-4; **29b**, 37741-44-9; **30**, 37741-45-0; **31**, 15448-25-6; **32**, 37741-47-2; **33**, 37805-65-5; **33** copper complex, 37818-71-6; **34**, 37741-48-3; **35**, 37741-49-4; **36a**, 37741-50-7; **36b**, 37741-51-8; **42**, 37741-52-9; β-(*o*-tolyl)propionic acid, 22084-89-5; methyl β-(*o*-tolyl)propionate, 37741-54-1; *o*-tolylsuccinic acid dimethyl ester, 37741-55-2; epiallogibberic acid, 13613-87-1.

A Study of Mechanism for the Formolysis of a 20α-Tosyloxy Steroid[1]

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The mechanism of the formolysis of 3β-acetoxy-5α-pregnan-20α-yl *p*-toluenesulfonate (**1b**) was studied with preparations containing deuterium or tritium in the 17α position. The isotopic atom was retained in the formation of 17β-methyl-18-nor-5α,17α-pregn-13-en-3β-yl acetate (**2b**). Neither of the two geometric isomers of the 5α-pregn-17-en-3β-yl acetate (**7b**, **8b**), therefore, is an intermediate in this reaction, although both are readily converted to this product (**2b**). The rate ratios, k_H/k_T, for the disappearance of the tosylate ester **1b** and for the formation of its major formolysis products were determined. The isotope effect on the rate of formolysis was higher than expected for the formation of a C-20 cation. This could be due to an accompanying 17-hydrogen-assisted formolysis yielding at least some of **2b** or due to a high rate of return from the ion pair. The latter explanation seems less likely. The unexpected formation of a uranediol derivative (**4b**) in this and a similar reaction which tentatively had been attributed by us and others to a two-step mechanism that included a methyl shift does not take this course because the deuterium that was located at C-17 in the starting compound was found at C-17a in the product **4b**. A different mechanism, analogous to a postulate made by Eschenmoser, *et al.*, for the biosynthesis of various steroids, is considered.

In a recent investigation[2] of the formolysis of 3β-acetoxy-5α-pregnan-20α-yl tosylate (**1b**) five compounds (2–6) were identified, which are listed in Table I. Questions arose about the mode of formation of the two rearrangement products, compounds **2b** and **4b**. Of these, the Δ^{13} olefin **2b** could arise by dehydration to a Δ^{17} olefin (**7**, **8**) which after protonation at C-20 would rearrange to the isolated product. Such a mechanism was first proposed by Leboeuf, *et al.*,[3] to explain the formation of a Δ^{13} olefin (**2c**) from a 20β-tosylate on prolonged boiling in benzene and was adopted by Aoyama, *et al.*,[4] to account for the formation of **2b** from a 20α-acetate on exposure to boron trifluoride etherate for several days. The following observations are consistent with such a scheme. Treatment of a 20α-tosylate (*e.g.*, **1b**, **1c**) with basic solvents

(1) Supported by U. S. Public Health Service Grants AM-9105 and K6-AM-14367.

(2) F. B. Hirschmann, D. M. Kautz, S. S. Deshmane, and H. Hirschmann, *Tetrahedron*, **27**, 2041 (1971).

(3) M. Leboeuf, A. Cavé, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 1624, 1628 (1969).

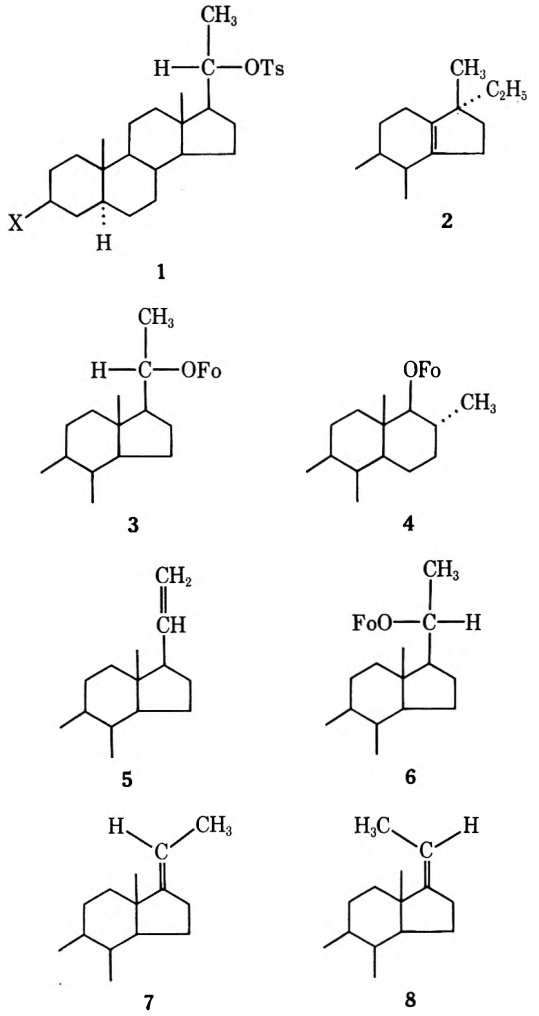
(4) S. Aoyama, K. Kamata, and T. Komeno, *Chem. Pharm. Bull.*, **19**, 1329 (1971).

TABLE I

YIELDS AND 17α-TRITIUM ISOTOPE EFFECTS FOR PRODUCTS OF FORMOLYSIS OF 3β-ACETOXY-5α-PREGNAN-20α-YL TOSYLATE

Compd	Yield from 17α-H (1b), %	$(R^i/R^0)^a$	Δ,[b] %	Yield from 17α-T, %	$(k_H^i/k_T^i)^c$
17β-Methyl-18-nor-5α,17α-pregn-13-en-3β-yl acetate (2b)	68.7	0.675[d]	0.1	46.4	2.55
3β-Acetoxy-5α-pregnan-20α-yl formate (3b)	14.9	1.67[e]	0.3	24.9	1.03
3β-Acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl formate (4b)	8.4	1.77[e]	0.4	14.9	0.97
5α-Pregn-20-en-3β-yl acetate (5b)	6.5	1.75[d]	0.4	11.4	0.99
3β-Acetoxy-5α-pregnan-20β-yl formate (6b)	1.2				
Unidentified	0.2				

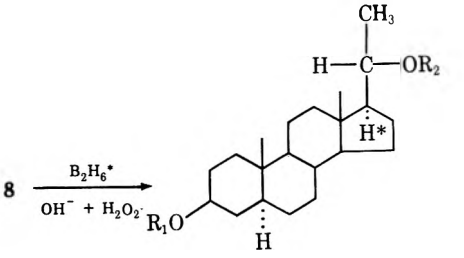
[a] *R* indicates the ratio $^3H_1/^{14}C_2$, *i.e.*, the tritium counts in channel 1 divided by the ^{14}C counts in channel 2 of the scintillation counter This ratio is calculated from the net registered counts in the two channels (N_1, N_2 respectively) by the equation $R = {}^3H_1/{}^{14}C_2 = [1 - (N_2/N_1)(1/b)]/[(N_2/N_1) - a]$, where *a* and *b* refer to N_2/N_1 for 5α-pregnane-3β,20α-diol 3-acetate containing only ^3H (9d) or ^{14}C (9e), respectively (values about 0.05 and 10). The term R^0 indicates the isotope counts ratio *R* for the starting compound (9g), and R^i for product i isolated at the end of the reaction. [b] Δ gives in per cent the (absolute value of the) difference in N_2/N_1 between the final crystals and their last mother liquor, divided by N_2/N_1 of the crystals. [c] Isotope effect for the formation of product i calculated by means of eq 9:[12] $k_H^i/k_T^i = (R^0/R^i)(k_H/k_T)$, where k_H/k_T refers to the isotope effect on the disappearance of the tosylate ester (see Table II). [d] Measured on the corresponding 3β-ol. [e] Measured on the corresponding diacetate.



Fo = HCO, Ts = *p*-$CH_3C_6H_4SO_2$

a, X = OH;
b, X = OAc;
c, X = H

(pyridine,[3,5] hexamethylphosphotriamide[3]) yielded either predominantly or exclusively the *E* isomer (**7b**, **7c**) of the Δ^{17} olefin but no Δ^{13} compound, whereas only the latter was obtained in formic acid[2] or in benzene containing boron trifluoride.[3] In methanol a mixture of **7c**, **8c**, and **2c** was obtained.[3] Finally, in formic acid[2,3,6] or in benzene containing toluenesulfonic acid,[3] either isomer of the Δ^{17} olefin was converted to **2**. These observations, however, do not preclude that at least some of the Δ^{13} olefin is formed from the 20α-substituted steroid by a hydride shift from C-17 to C-20, which would either accompany or follow the ionization step. To distinguish the Δ^{17} route from the direct mechanism we prepared 17α-deuterated 3β-acetoxy-5α-pregnan-20α-yl tosylate (**9c**) and subjected it to formolysis. If the free Δ^{17} olefin is an intermediate, the deuteron is lost into the medium, whereas a shift of deuteride would yield labeled Δ^{13} olefin.



	R_1	R_2	H*	C-4
9a	H	H	D	
b	Ac	H	D	
c	Ac	Ts	D	
d	Ac	H	T	
e	Ac	H	H	^{14}C
f	Ac	H	T	^{14}C
g	Ac	Ts	T	^{14}C

The Wittig reaction of a 17-keto steroid[7] yields predominantly[8] the *Z* isomer of the 17-ethylidene com-

(5) (a) H. Hirschmann, *J. Biol. Chem.*, **140**, 797 (1941); (b) D. M. Glick and H. Hirschmann, *J. Org. Chem.*, **27**, 3212 (1962).

(6) C. Ouannes, M. Dvolaitzky, and J. Jacques, *Bull. Soc. Chim. Fr.*, 776 (1964).

(7) G. Drefahl, K. Ponsold, and H. Schick, *Chem. Ber.*, **98**, 604 (1965).

(8) A. M. Krubiner and E. P. Oliveto, *J. Org. Chem.*, **31**, 24 (1966).

pound, which has been used for the synthesis of 5α-pregnane-3β-20α-diol by hydroboration.[8] By substituting $B_2^2H_6$ for diborane we obtained the 17α-deuterated analog **9a** of the diol which was preferentially acetylated to the 3-acetate **9b** by heating with acetic acid (*cf.* ref 5a). As the selectivity of the acetylation is only moderate, repeated recycling of the hydrolyzed diacetate and 20-monoacetate was required to provide a sufficient amount of **9b**. Its nmr spectrum verified the presence of deuterium at C-17.

As expected for either of the two mechanisms discussed above, the formolysis of the deuterated analog **9c** of the 3-acetate 20-tosylate of the 5α-pregnanediol gave the Δ^{13} olefin in diminished yield (54%). The mass spectrum of its parent alcohol, when compared with that of its unlabeled analog **2a**, showed shifts in peaks for M^+ and for M^+ − methyl by one mass unit but no change for M^+ − ethyl. The presence of deuterium in the ethyl side chain of the olefin was confirmed by the nmr spectrum of the 3 ketone, which showed at 0.775 ppm a doublet instead of the pair of doublets reported for the unlabeled 3 ketone.[2] Therefore, the deuterium atom was not eliminated but had migrated to C-20. As our starting material was only about 94% deuterated and as the formation of the deuterated olefin was slower than that of the formates, some diminution of the D/H ratio was to be anticipated for the olefin even if the formolysis of the unlabeled tosylate proceeds entirely by hydride shift. We did not consider our analysis of peak heights in the mass spectra precise enough to decide whether *any* loss of label had occurred into the medium and attempted to settle the question by conducting a formolysis of unlabeled tosylate in a medium containing HCOOT. Tritium uptake during the formation of the Δ^{13} olefin **2b** was observed but signified no Δ^{17} pathway because an unlabeled sample of **2b** showed an even larger uptake of tritium when exposed to the tritiated reaction medium.[9] Our most reliable demonstration that the formolysis does not cause any significant loss of hydrogen from C-17 came from a study of doubly labeled (4-^{14}C–17α-^{3}H) tosylate (**9g**) to be described below. The isotope ratio of the total reaction product agreed with that of the solvolyzed tosylate (Table II). Therefore, at least in the formolysis of the 20α-tosylate, only a negligibly small fraction of the reaction can proceed *via* a Δ^{17} olefin.

TABLE II
KINETIC MEASUREMENTS

Time, min	Tosylate fraction remaining (y)	Rate k_H, min^{-1}	R^t[a]	k_H/k_T[b]
0	1		1.47	
10	0.537	0.0622	1.90	1.70
20	0.313	0.0580	2.41	1.74
212			1.47[c]	
Mean		0.0601[d]		1.72

[a] R^t signifies the isotope counts ratio R as defined in Table I for the tosylate ester (9g) after t minutes of formolysis. [b] Calculated by means of eq 1:[12] $k_H/k_T = \log(1/y)/[\log(1/y) - \log(R^t/R^0)]$, where k_H/k_T and R^0 are used as defined in Table I. [c] This R value refers to the total reaction product. [d] The previously determined mean was 0.061 min^{-1} and was measured at half the concentration of the tosylate ester.[2]

This finding raised the further question as to whether the hydride shift accompanies or follows the ionization of the tosyloxy group. We have studied this problem by measuring the effects of isotopic substitution of the 17α hydrogen on the rates of disappearance of the tosylate ester and of the formation of its main products. This approach seemed promising, as it had been used with apparent success in studies of the mechanism of solvolysis of 3-methyl-2-butyl tosylate,[10,11] which resembles the steroid in having a methyl group and a methine carbon adjacent to the reacting center.

As in an earlier study,[12] we conducted the formolysis of the normal and of the isotopically substituted tosylate concomitantly. This is conveniently done if the 17α hydrogen is labeled with tritium and the reaction of its normal analog is observed by following that of tosylate labeled in the steroid nucleus with ^{14}C. The required 3-acetates of 5α-pregnanediol (**9d** and **9e**) were prepared, respectively, from **8b** by hydroboration with tritiated diborane and from 3β-hydroxy-5-pregnen-20-one-4-^{14}*C* by known procedures.[2,5b] The two preparations were mixed (**9f**), diluted with unlabeled carrier, and converted to the tosylate **9g**. In order to determine the effect of 17α-T on the rate of disappearance of the tosylate it is necessary to isolate this compound after a partial solvolysis. As has been observed repeatedly,[3,13] 20α-tosylates are destroyed by adsorption chromatography under usual conditions. They remain unaltered during partition chromatography in neutral solvents, but we were unable to take advantage of this fact because we obtained no adequate separation of the tosylate and its formolysis products with various solvent systems, including one used previously in a similar case.[12] Chromatography with acetone or methanol on Sephadex (LH-20) likewise failed to give us satisfactory separations. Eventually we obtained a useful fractionation without any sign of decomposition by chromatography on silica gel deactivated with large amounts of water. The bands of products and of tosylate still showed some overlap, but the tosylate that had separated and the fraction contaminated with products gave the same isotope ratio after recrystallization. This showed that recrystallization after the addition of carrier tosylate sufficed for the purification of the labeled tosylates and this procedure was used for the analysis of a second sample. The results of both runs (Table II) were in satisfactory agreement and indicated a rate ratio k_H/k_T of 1.7 for disappearance of the tosylate.

From this value and from the isotope ratios observed for the major reaction products isolated after a complete formolysis, the rate ratios, k_H/k_T, for the formation of these products can be calculated (Table I). They were near unity for the formates **3b** and **4b** and the Δ^{20} olefin **5b**, but high for the product (**2b**), that undergoes a shift of the isotopic hydrogen during its formation. The interpretation that can be placed

(9) The uptake of tritium in the two experiments agreed if the shorter exposure of the Δ^{13} olefin formed *in situ* is taken into account.

(10) S. Winstein and J. Takahashi, *Tetrahedron*, **2**, 316 (1958).

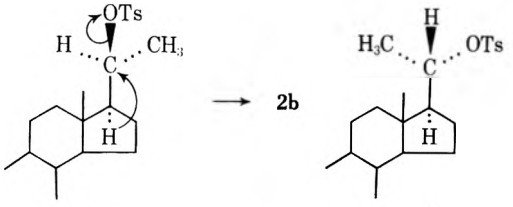
(11) V. J. Shiner, Jr., in "Isotope Effects in Chemical Reactions," C. J. Collins and N. S. Bowman, Ed., Van Nostrand-Reinhold, Princeton, N. J., 1970, pp 129–133.

(12) J. Ramseyer and H. Hirschmann, *J. Org. Chem.*, **32**, 1850 (1967).

(13) H. Lee and M. E. Wolff, *ibid.*, **32**, 192 (1967).

on these results depends on one's estimate of the isotope effect on the formation of the open C-20 cation. If this effect is comparable to the isotope effect on the formation of the products that are derived from this ion, the formation of the Δ^{13} olefin does not compete in the partitioning of the C-20 cation and, therefore, involves a different process of ionization. This could be envisaged as the migration of the 17α hydrogen in concert with the ionization of the tosyloxy group. Such a process would have a low activation energy only if the participating bonds are antiparallel, as in **10**. If **2b** forms in this manner, no loss of the labeled atom into the medium can occur.

Sunko and Borčić[14a] in a recent summary of the literature stated that deuterium substitution adjacent to the reaction center will cause in solvolytic reactions at room temperature a rate decrease of about 10–20% per atom D. Shiner, *et al.*,[15] reported a strong conformational dependence of this β-isotope effect. Thus they deduced from the noncummulative effect of successive substitution with D in a single methyl group of *tert*-butyl chloride that k_H/k_D was 1.30 for the deuterium that was anti to the chlorine, but only 1.01 if the disposition of these atoms was gauche.[16] In the case of 5α-pregnane-3β,20α-diol and presumably its esters the gauche conformation shown in **11** is more stable than the anti conformation (**10**),[17] and, if the latter



10 **11**

reacts only with participation of the 17α hydrogen, it would be appropriate to use conformation **11** as the model for estimating the isotope effect on the unassisted solvolysis (k_s). A value consistent with Shiner's deduction (k_H/k_D = 1.01 corresponds[18] to 1.02 for k_H/k_T) would be no larger than the isotope effect on the formation of **3b** and, therefore, would be consistent with a mechanism of solvolysis that yields all of **2b** by a hydrogen-assisted formolysis.

If, however, the above estimate of the gauche effect should be too low or if this low value[19] should be inapplicable to our case, some of **2b** would be derived from the C-20 cation. The relative contributions of the hydrogen-assisted (k_Δ) and unassisted solvolysis can be calculated (eq 18)[12] if one knows the magnitude of the individual isotope effects. If for the sake of illustration, $(k_H/k_T)_s$ is now assumed to be 1.2 and $(k_H/k_T)_\Delta$ is taken to be 2.55 (as was observed for the formation of **2b**), 84% of **2b** would still be formed by the hydrogen-assisted ionization. The remaining fraction of **2b** (16%) derived from the C-20 cation would be substantially reduced if the ion is tritiated, because this reaction breaks a bond with the isotopic atom. Consequently, an increased fraction of a more slowly forming ion will go to other products. An estimate showed that these effects are apt to cancel each other and that rate ratios k_H/k_T near unity could be expected as were observed. In this interpretation of our findings we have assumed that there is no significant return from the ion pair to the tosylate ester. If it should occur, this step too would be in competition with the hydride shift and, therefore, be accelerated with the tritiated ester. Consequently, the *net* formation of the cation would be more retarded than its forward component.[20] We have calculated (eq 18)[12] the fraction of return that would have to occur with the unlabeled tosylate to result in the observed k_H/k_T (1.7) for the net solvolysis if (a) there is no hydrogen-assisted formolysis; (b) the isotope effect on the forward component of the formolysis is 1.2 as before; and (c) the isotope effect on the reversal which yields the 20α-tosylate is the same as on the formation of the 20α-formate **3b**. The fraction of return thus estimated is 0.65, which implies that the intrinsic rate of the ionization of **1b** is about three times the measured rate.

It seems pertinent to compare our results with observations on the solvolysis of 3-methyl-2-butyl tosylate, as it has been concluded that its solvolysis is predominantly hydrogen assisted.[10,11] Using the data and assumptions of Winstein and Takahashi,[10] we have calculated, as above, the fraction of return needed to explain their results without invoking a hydrogen-assisted process. Although the effect of replacing the 3 H by deuterium in the methylbutyl tosylate was much higher ($k_H/k_D \sim 2.2$ for formolysis and other solvolyses) than the isotope effect in our case, the estimated fraction of return would be about the same (0.63). Shiner[11] discussed the possibility that there might be a rapid and reversible ionization followed by a rate-determining hydride shift, but considered it improbable because the rate seemed too fast to accommodate this mechanism. The rate of formolysis of the steroid was about four times faster than that of the simpler model.[21] If it is considered probable then that both compounds react in part by a hydrogen-assisted mechanism, it becomes necessary to account for the much smaller isotope effect on the disappearance of the steroid tosylate (k_H/k_T 1.72 corresponds[18] to k_H/k_D 1.46). Two factors may play a role. As C-13 of the steroid is fully substituted, the conformation favorable to participation is relatively less stable than in the model. As one would expect from this, the fraction of products formed with hydride shift is smaller for the steroid than for the model (>90%)[11] and the contribution of any k_Δ to the overall rate must be less important. Furthermore, the faster rate of the steroid might signify that its transition state of formolysis occurs earlier on the reaction coordinate and that the magnitude of the isotope effect is accordingly reduced.

(14) D. E. Sunko and S. Borčić in "Isotope Effects in Chemical Reactions," C. J. Collins and N. S. Bowman, Ed., Van Nostrand-Reinhold, Princeton, N. J., 1970: (a) pp 165, 171; (b) p 204.

(15) V. J. Shiner, Jr., B. L. Murr, and G. Heinemann, *J. Amer. Chem. Soc.*, **85**, 2413 (1963).

(16) These different contributions would result in a mean value of 1.09 for monodeuteration, which is consistent with observation and with the generalization of Sunko and Borčić.

(17) C. Altona and H. Hirschmann, *Tetrahedron*, **26**, 2173 (1970).

(18) For calculation see C. G. Swain, E. C. Stivers, J. F. Reuwer, Jr., and L. J. Schaad, *J. Amer. Chem. Soc.*, **80**, 5885 (1958).

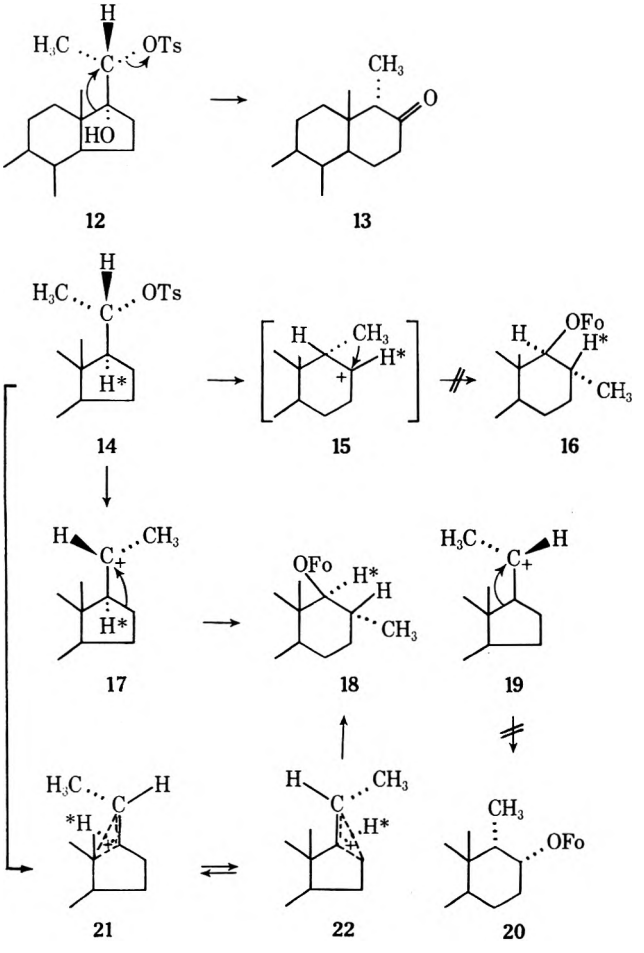
(19) A much higher isotope effect (k_H/k_T 1.37) was reported for the formolysis of 2α-tritiated androsterone tosylate.[12] However, as will be discussed below, this determination is a measurement of a gauche effect only if there was no significant return of tosylate ion, because the elimination of the 2α hydrogen is a major pathway from the cation.[12] Moreover, this solvolysis does not appear to be a simple ionization.

(20) S. G. Smith and D. J. W. Goon, *J. Org. Chem.*, **34**, 3127 (1969).

(21) S. Winstein and H. Marshall, *J. Amer. Chem. Soc.*, **74**, 1120 (1952).

Although these various considerations do not prove hydrogen participation in our case, this hypothesis seems probable enough to justify further efforts at its verification.

Another question which we investigated concerned the mode of formation of the D-homo steroid **4b**. Its presence among the reaction products was unexpected, as the solvolysis of a 17α-hydroxy-20α-tosyloxypregnane (**12**) had yielded a 17aα-methyl-17 ketone (**13**)[22] in a reaction which could be pictured as an ionization facilitated by the simultaneous attack of an antiparallel bond. In contrast, the formation of a uranediol 17aβ-formate (**4b**) from **1b** in a single step would require the far less favorable transition state of a substitution with retention of configuration.[23] We, therefore, considered two successive rearrangements.[2] The first would consist in the simultaneous ionization of the tosyloxy group and the migration of the 13–17 bond to C-20 (**14** → **15**) and therefore be analogous to the ring enlargement observed for the reaction of **12**;



the second rearrangement would consist in the migration of the axial 17aα-methyl of **15** to the equatorial α facet at C-17 and conversion to **16**. This mechanism[24] can be distinguished from a single-step ring enlargement (**17** → **18**) by the location of a deuterium atom originally located at C-17. If the reaction is two-step as shown, the deuterium would end up at C-17 of **16**. When the nmr spectrum of uranediol 3-acetate derived from 17-deuterated tosylate (**9c**) was examined it showed no change in the doublet of the 17-methyl group compared to its normal analog. A difference was seen, however, at 2.7 ppm where the doublet of the 17a hydrogen had almost disappeared. Therefore, the deuterium is at C-17a (as in **18**) and not at C-17 and the two-step pathway involving a methyl migration is disproved.

This finding calls anew for an explanation of the remarkable preference for the migration of the 16–17 bond. Electronic factors seem to favor an attack by the cation on the bond linking C-17 with the more substituted atom, C-13.[25] However, as the migration of the 13–17 bond to a C-20 cation would yield a D-homo steroid with an axial methyl (**20**) and that of the 16–17 bond one with an equatorial methyl group (**18**) in the D ring, the observed preference might be explained if the transition state of the ring enlargement resembled the product. According to Hammond's postulate[26] this is unlikely because the conversion of a pregnan-20-yl to a D-homoandrostan-17a-yl cation should release the strain energy of the trans hydrindan system and require less activation energy than the reverse process.[27] An early transition state which would resemble the initial ion seems to involve different considerations. If the plane of the C-20 cation is perpendicular to the incoming bond, some interaction between the hydrogen at C-20 and the 18-methyl results if the reacting bond is the 16–17 linkage (**17**), whereas there is no such strain in the alternative conformation (**19**).[28] We would expect, therefore, that steric and electronic factors would reinforce each other in an early transition state and lead to the preferred migration of the 13–17 bond toward a C-20 cation (**19** → **20**).[29] As this is not observed, an open C-20 carbocation may not be the intermediate. We therefore are considering also a pathway *via* two bridged ions. The first of these (**21**) would arise by partial bonding between C-13 and C-20 simultaneous with the rupture of the antiparallel carbon–oxygen bond, while the second (**22**) would involve bridging between C-16 and C-20. On reaction with solvent the latter (**22**) would yield the more stable of the D-homo steroids (**18**) whereas **21** might be attacked at C-20 to give the 20α-formate **3b**. This would account for the formation of **3b** by two successive inversions and thus provide a reasonable alternative to the explanation given before[2] for the predominant retention of configuration. The main point of interest is the transformation **21** → **22** because it would be in close analogy to a key step in the biogenesis of various steroids and triterpenoids (tirucallol, lanosterol, etc.) as postulated by Eschenmoser, *et al.*[30]

(22) K. I. H. Williams, M. Smulowitz, and D. K. Fukushima, *J. Org. Chem.*, **30**, 1447 (1965).

(23) N. L. Allinger, J. C. Tai, and F. T. Wu, *J. Amer. Chem. Soc.*, **92**, 579 (1970).

(24) An analogous proposal was made independently by Aoyama, *et al.*,[4] to explain the formation of uranediol diacetate from 5α-pregnane-3β,20α-diol diacetate in BF_3–Et_2O.

(25) H. Minato, J. C. Ware, and T. G. Traylor, *J. Amer. Chem. Soc.*, **85**, 3024 (1963).

(26) G. S. Hammond, *ibid.*, **77**, 334 (1955).

(27) In equilibration studies of *D*-homo ketols, which implicate 17-hydroxypregnan-20-ones as intermediates, the concentrations of the latter were evidently too small to be detected: N. L. Wendler, D. Taub, and R. W. Walker, *Tetrahedron*, **11**, 163 (1960).

(28) The dihedral angle of C-16–C-17 with C-20–C-21 of **19** is close to the one for the preferred conformation of pregnan-20-one, as determined by N. L. Allinger, P. Crabbé, and G. Pérez, *Tetrahedron*, **22**, 1615 (1966).

(29) See also M. Stiles and R. P. Mayer, *J. Amer. Chem. Soc.*, **81**, 1497 (1959), for examples which seem explicable on an analogous basis.

(30) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).

The β-isotope effect can be expected to be markedly reduced[14b] if the solvolysis yields a bridged (**21**) rather than a classical (**17**) ion. In a search for such distinct intermediates we compared the effects of 17 tritium on the rates of formation of **3b**–**5b** (Table I). Compounds **4b** and **5b**, the ones most apt to be derived from diverse primary ionization products, gave no indication of this, because their k_H/k_T ratios showed no significant difference. In contrast, the difference between the tritium effects on the rates of formation of **3b** and **4b** appears to be real,[31] but its sign is puzzling if both compounds are derived from the same primary ionic precursor. It seems that a different approach will be needed to ascertain whether **21** could be an intermediate in the formation of the uranediol ester **4b** from the tosylate **1b**.

Experimental Section

Ir spectra were recorded on solutions in CS_2 on a Perkin-Elmer grating photometer (Model 421). Nmr spectra were measured on solutions in $CDCl_3$ containing TMS, on a Varian HA-100 spectrometer. Results are given in parts per million downfield from TMS. Mass spectra were scanned with a Varian double-focusing M-66 spectrometer on samples introduced directly with a probe heated to 100°. Source temperature was 250°, and the ionization voltage was 70 eV for 5α-pregnanediol 3-acetate, 40 eV for the formates, and 30 eV for the Δ^{13} compound. Isotope analysis was done by the method of Biemann.[32] Radioactivity was determined on a Packard two-channel spectrometer (Model 314 EX). Conditions of measurement were as specified before.[12] Equations used for calculating the results are derived in the earlier paper.[12] Most of the symbols used are also defined in the legends to the Tables.

The melting points reported are corrected. Steroids were generally isolated by extraction with ether or with benzene (as in all formolyses) after adding water to the reaction medium. The organic phase was usually washed with dilute hydrochloric acid, sodium carbonate, and water and taken to dryness *in vacuo*. Unless otherwise specified, chromatography was done on silica gel (100–200 mesh) activated at 120°. Ir and tlc were used extensively to monitor the fractionations. For the latter, plates were made from Adsorbosil 1 (Applied Science Laboratories) which were dried at room temperature (4 hr). Steroids were detected by exposure to iodine vapors.

3β-Acetoxy-5α-pregnan-20α-ol-17α-^2H (9b).—$B_2{}^2H_6$ generated from 240 mg of sodium borodeuteride in 10 ml of dry diglyme and 3 ml of boron trifluoride etherate in 3 ml of diglyme was passed into a solution of (*Z*)-5α-pregn-17-en-3β-ol (**8a**)[7,8] (482 mg) in 8 ml of tetrahydrofuran. After standing at room temperature for 4 hr the excess of diborane-$^2H_6$ was hydrolyzed. To this mixture were added 13 ml of tetrahydrofuran and dropwise 12 ml of 10% NaOH and 8 ml of 30% H_2O_2. After being stirred at 0–10° for 1 hr the product was isolated by ether extraction and refluxed with 60 ml of glacial acetic acid for 190 min. The cooled solution was poured on crushed ice and the steroids isolated by ether extraction were adsorbed on a column of silica gel (50 g). (When the starting material of the acetylation was pure 5α-pregnane-3β,20α-diol, the respective yields of the diacetate, the 3-monoacetate, the 20-monoacetate, and the diol were 25, 33, 17, and 25%.) The diacetate and the 20-acetate were hydrolyzed with methanolic KOH, and the product was combined with diol and again acetylated. Several such fractions of 3-acetate were combined and recrystallized and had mp 132–134° (387 mg). Mass peaks shifted by +1 from those of normal 3-monoacetate were at *m/e* 363 (M^+, weak), 345, 330, 303, 288. Prominent unchanged peaks were at *m/e* 276 (base peak), 275, 216, 215, 201; ^2H, 94% of 1 atom measured for ($M^+ - 60$); nmr 0.64 (18-H), 0.82 (19-H), 1.21 (d, J = 6, 21-H), 2.01 (Ac), 3.70 (quartet, J = 6, 20-H), ~4.69 ppm (m, 3-H). These signals agreed with those of the undeuterated analog, which, however, had eight lines for the signal at 3.70 ppm.

3β-Acetoxy-5α-pregnan-20α-yl-17α-^2H Tosylate (9c) and Its Formolysis.—Compound **9c**, which was prepared from **9b** and purified as described for its unlabeled analog,[5b] had mp 142–143°. Its solution (434 mg in 9 ml of benzene) was diluted with 868 ml of formic acid and kept at 25.2° for 2 hr. Chromatography[2] of the product gave 182 mg in the olefin and 116 mg in the formate fractions. **17β-Methyl-18-nor-5α,17α-pregn-13-en-3β-ol**, isolated as described,[2] had mp 130–132° and base peak in the mass spectrum at *m/e* 273 as for its normal analog. The M^+ peak (*m/e* 303) was weak but was used for ^2H analysis after some widening of the slits; found, 90% of 1 atom. An aliquot was oxidized to the 3 ketone[2] which had nmr signals at 0.755 (d, J = 7.35 cps), 0.95, and 0.99 ppm.

The formates were effectively separated and with less loss than before[2] on long columns (425 × 13 mm) of silica gel (30 g deactivated with 1 ml of water) by elution with benzene containing 0.5% ethyl acetate. **3β-Acetoxy-5α-pregnan-20α-yl-^2H formate** (mp 153.5–155.5°) had mass peaks containing ^2H at *m/e* 391 (M^+, weak), 345, 331, 316. The peak at *m/e* 230 was not shifted from its position in the reference curve; ^2H measured for ($M^+ - 75$), 92% of 1 atom. **3β-Acetoxy-17α-methyl-*D*-homo-5α-androstan-17aβ-yl-17aα-^2H formate** had mp 217–219°, ^2H-containing peaks at *m/e* 345, 331, 316, 285, 277, 270, 231. The peak at *m/e* 215 was not shifted from reference curve of the unlabeled analog: ^2H measured for ($M^+ - 60$) or ($M^+ - 75$), 94% of 1 atom. A sample was partially hydrolyzed to the 3-acetate[33] which had mp 167–169.5° and δ 0.80, 0.955 (d, J = 6 cps), 2.02, and ~4.7 ppm (m). The residues of the peaks of the unlabeled compound at 2.66 and 2.75 ppm were too weak to be reliably distinguished from the noise. There was no other signal near 2.7 ppm.

3β-Acetoxy-5α-pregnan-20α-yl-4-^{14}C,17α-^3H Tosylate (9g).—3β-Acetoxy-5α-pregnan-20α-ol-17α-^3H (**9d**) was prepared as described for **9b** from 4.5 mg of $NaBH_4$-^3H (42 mCi) diluted with 60 mg of $NaBH_4$, 1.5 ml of BF_3–Et_2O, and 110 mg of (*Z*)-5α-pregn-17-en-3β-yl acetate. In this run, in contrast to earlier trial experiments with the same starting material, enough of the 3-acetate (63 mg of **9d**) survived the alkali treatment to make the acetylation step unnecessary. Compound **9d** was isolated by chromatography and recrystallized, mp 132–134°.

3β-Acetoxy-5α-pregnan-20α-ol-4-^{14}C (**9e**) was obtained from 6 μCi of 3β-hydroxy-5-pregnen-20-one (53 mCi/mmol) and 104 mg of unlabeled carrier by acetylation and successive hydrogenations with $Pd/CaCO_3$ and Raney nickel, and chromatography essentially as described.[5b] The final sample had mp 133–135°.

A mixture of 0.91 mg of **9d**, 25 mg of **9e**, and 475 mg of nonradioactive carrier was recrystallized until the count ratios N_2/N_1 became constant (0.726 final crystals and 0.732 and 0.728 for the last two mother liquors). This product (**9f**) was converted to the tosylate **9g** and again recrystallized to constant count ratio.[34]

To test the stability of the tosylate under the conditions of chromatography described below, another preparation of **9g** (7.2 mg) which had N_2/N_1 0.629 was mixed with 3.5 mg of unlabeled Δ^{13} olefin **2b** and 1.7 mg of an unlabeled mixture of the two principal formates **3b**, and **4b** and chromatographed. The early eluates contained mostly **2**–**4** (1.4 mg), the next fraction was a mixture having N_2/N_1 0.632, and the late fractions were mostly tosylate (4.7 mg) which after recrystallization had N_2/N_1 0.626.

Formolysis of 3β-Acetoxy-5α-pregnan-20α-yl-4-^{14}C,17-^3H Tosylate (9g).—Three experiments were conducted at the same time at 25.0°. These differ only in reaction times and size of samples (25.0 mg for the 10- and 20-min runs, and 159 mg for 212 min) whereas the solvents and concentrations were the same (1.2 ml of dry benzene/25 mg of tosylate, diluted at zero time with 50.0 ml of dried[2] formic acid). The reaction products were iso-

(31) This is indicated by the constancy of the ratio $R^{20\alpha}/R^{17a\beta}$, which was determined once for the final preparations of the formates **3b** and **4b** and after several further purification steps twice on the final crystals of the diacetates with these results: 0.951, 0.947, and 0.937. (The error of the *absolute* values of k_H/k_T for these products is larger, as it depends not only on such measurements of radioactivity but also on tosylate determinations by ir spectroscopy.)

(32) K. Biemann, "Mass Spectroscopy: Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, pp 223–226.

(33) H. Hirschmann, F. B. Hirschmann, and A. P. Zala, *J. Org. Chem.*, **31**, 375 (1966).

(34) The ratio of **9g** (N_2/N_1 0.694) was lower than that of **9f**. This probably can be attributed to the decomposition that accompanies the tosylation of the 20α-hydroxy group because any elimination reaction would be expected to be slower for the ^3H-labeled component.

lated as described for the earlier kinetic runs.[2] From each experiment an aliquot derived from 5.0 mg of tosylate was removed, freed of solvent as before,[2] and analyzed in the ir by measuring its absorbances at 813, 781, and 687 cm^{-1}. Mean tosylate fractions remaining after 10 and 20 min were calculated and are given in Table II. The remainders of each sample were processed as follows.

A. **10-Min Run.**—A solution in 0.5 ml of acetone was applied to a column (110 × 10 mm) of silica gel which was packed as a suspension in the upper phase of ligroin (bp 88–90°), methanol, and water (10:9:1). The silica gel used had been thoroughly washed with water, dried to constant weight by exposure to air, and then hydrated (silica–water, 3:1).[35] Elution with the same upper phase was completed within 30 min. Fraction 4 (1 ml) was 6.0 mg. Fractions 5 (1 ml, 4.7 mg) and 6 (5 ml, 4.4 mg), which were essentially tosylate, were combined and recrystallized until N_2/N_1 of crystals (0.559) and last mother liquor agreed (Δ 1%). Fraction 4 was diluted with 8.2 mg of unlabeled tosylate and recrystallized to give N_2/N_1 0.553 (Δ 0.5%).

B. **20-Min Run.**—As the data presented under A showed that even samples high in product could be recrystallized to give pure tosylate, the material remaining from B (15.6 mg) was mixed with 25 mg of unlabeled tosylate and recrystallized until $\Delta N_2/N_1$ was 0.7%.

C. **212-Min Run.**—No tosylate remained as even the tritiated component had formolyzed for >10 half lives. This sample (N_2/N_1 0.693 as compared to 0.694 for the starting material) was, therefore, fractionated as described for the products of 9c. To avoid any possible fractionation of the two radioactive components of any compound by chromatography, incompletely separated fractions were mixed with cold carriers and again subjected to the separation procedure. The 5α-pregn-20-en-3β-ol needed for this purpose was prepared by the method of Barton.[36] The chromatographically separated olefins were recrystallized as the 3β-ols, and the formates were recrystallized as such, hydrolyzed, recrystallized, acetylated, and recrystallized. The percentage differences in N_2/N_1 between final crystals and their mother liquors are given in Table I.

Dynamic State of 17β-Methyl-18-nor-5α,17α-pregn-13-en-3β-yl Acetate (2b) in Formolysis Medium.—A mixture of 0.66 ml of tritiated water (66 mCi) with 110 ml of dry formic acid was used to prepare solutions as follows: (a) 3β-acetoxy-5α-pregnan-20α-yl tosylate (**1b**), 25 mg in 0.6 ml of benzene and 50 ml of formic acid-^3H; (b) (*Z*)-5α-pregn-17-en-3β-yl acetate (**8b**), 12 mg in 0.3 ml of benzene, 6.0 mg of *p*-toluenesulfonic acid monohydrate, and 36 ml of formic acid-^3H; (c) 17β-methyl-18-nor-5α,17α-pregn-13-en-3β-yl acetate (**2b**) in the same medium and in the same concentration as b. All stood for 150 min at 25.0°. The 3β-hydroxy-Δ^{13} olefin was isolated from all runs by the usual procedures (except that chromatography was omitted from run b). The recrystallized products (mp 130–132°) had in channel 1 the following cpm/mg; (a) 2520, (b) 4210, and (c) 2870. In run a the fraction of **2b** available for exchange during the whole reaction period/total **2b** formed was 0.89 ($= 1 - 1/kt$, eq 14[12]), while (cpm/mg from a)/(cpm/mg from c) was 0.88.

Registry No.—**2a**, 33299-99-9; **2b**, 33300-00-4; **3b**, 37705-53-6; **4b**, 37759-63-0; **5b**, 22831-64-7; **8a**, 1159-24-6; **8b**, 1167-32-4; **9b**, 37759-67-4; **9c**, 37759-68-5; **9d**, 37759-69-6; **9e**, 33299-98-8; **9g**, 37759-71-0; 3β-hydroxy-5-pregnen-20-one 145-13-1.

Acknowledgment.—The authors wish to thank Mr. Clarence Gust for the nmr spectra reported in this paper.

(35) The ratio of water to silica had to be within narrow limits to prevent destruction and still allow separation. The optimal amount of water may not be the same for all batches of silica.

(36) D. H. R. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, 470 (1962); A. M. Krubiner, N. Gottfried, and E. P. Oliveto, *J. Org. Chem.*, **34**, 3502 (1969).

Lactonization of Methyl *o*-Formylbenzoate by Secondary Amines

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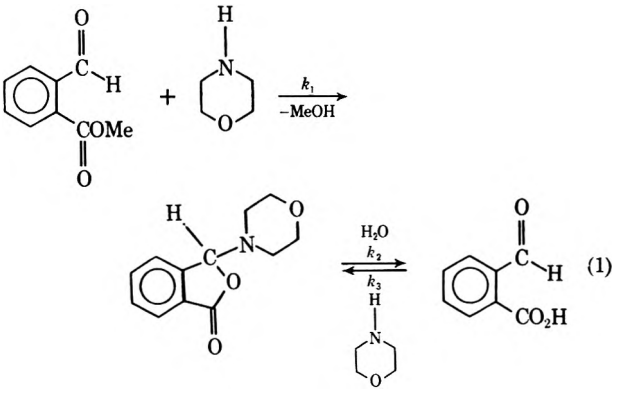
The unusual stability in dioxane of lactones formed by the reactions of MOFB with amines permitted a kinetic study of the effect of amine structure on the course of the reaction. While many classes of amines effected the reaction, the reactions of cyclic secondary amines were especially fast. The second-order rate constants for these fast reactions at 21° were dependent on ring size (pyrrolidine, 34.0 m^{-1} sec^{-1}; piperidine, 27.5; 1*H*-hexahydroazepine, <1), on ring substituents (4-pipecoline, 30.0; 3-pipecoline, 22.5; 2-pipecoline, <1; 2,6-dimethylpiperidine, 2-ethylpiperidine, and 2,6-dimethylpyrrolidine did not react), and on ring heteroatoms (piperazine, 468; 1-methylpiperazine, 7.4; morpholine, 3.7; 1,4-dimethylpiperazine did not react). With the exception of piperazine, the second-order rate constants at 25° paralleled the pK_B values according to the Brønsted relation $\log k_2 = 0.33 \log K_B + 2.39$. Thermodynamic activation parameters at 25° are given for some of the compounds.

The mechanism of ortho carbonyl group participation in the hydrolysis of methyl benzoates has in recent years received a great deal of attention.[1,2] The most extensively studied system involves the amine-assisted hydrolysis of methyl *o*-formylbenzoate.[3,4] The proposed mechanism (eq 1) for the hydrolysis of the ortho-substituted esters accounts for the enormous rate enhancement over the meta and para ester analogs.



(1)

The purpose of this investigation was to attempt to determine some of the structural requirements of the amine nucleophile which promote the rapid formation of the intermediate complex as shown in eq 1. Preliminary work with nonaqueous solvents showed that the intermediate, which quickly hydrolyzed in water, remained quite stable for periods of 24 hr or longer in dioxane solvent. Therefore, the work described below

(1) M. L. Bender and M. S. Silver, *J. Amer. Chem. Soc.*, **84**, 4589 (1962).
(2) M. S. Newman and A. L. Leegwater, *ibid.*, **90**, 4410 (1968).
(3) M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, *ibid.*, **87**, 4545 (1965).
(4) G. Dahlgren and D. M. Schell, *J. Org. Chem.*, **32**, 3200 (1967).

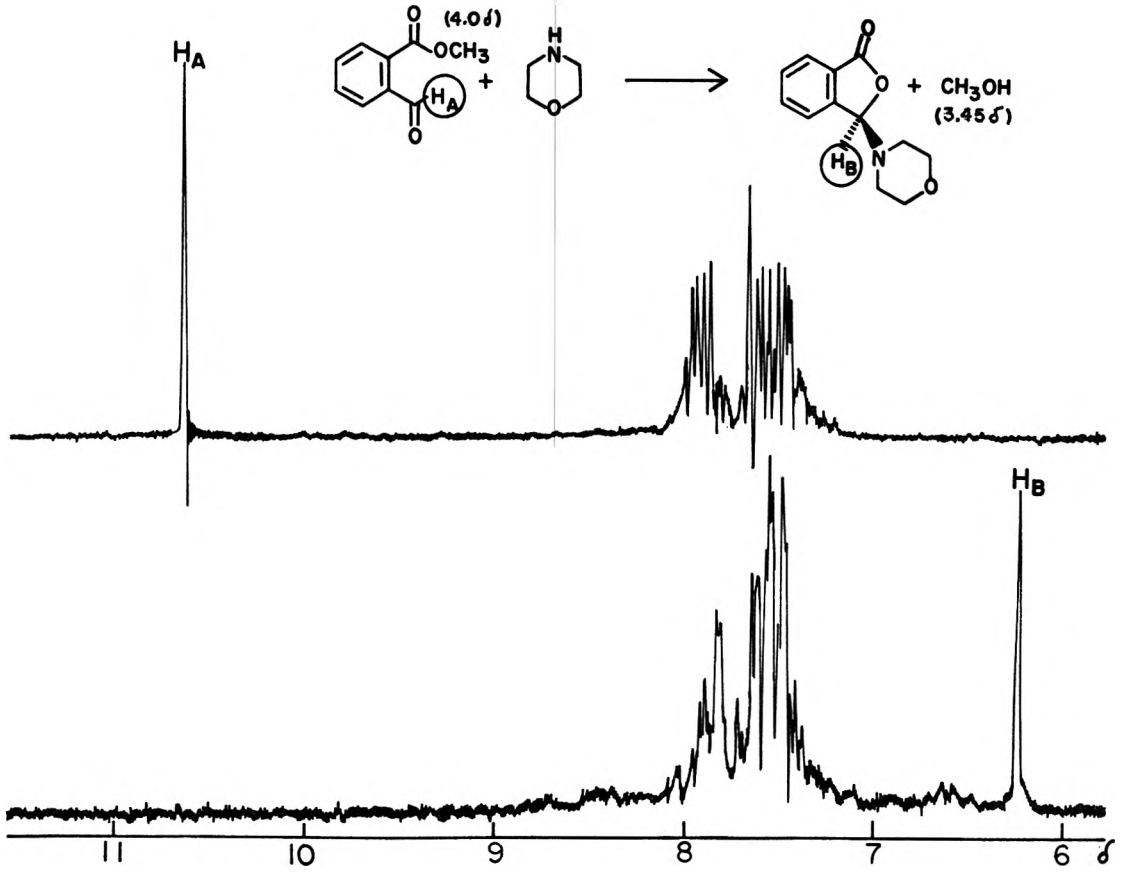


Figure 1.—Pmr spectra for lactonization of MOFB by morpholine. Upper curve represents the reactants and lower curve the products.

was done in dry dioxane solvent and involves only the formation of the lactone, as shown in the first step of eq 1.

Experimental Section

Materials. Methyl o-Formylbenzoate (MOFB) was prepared by the method of Bender and coworkers[3] using ethereal diazomethane and phthaldehydic acid (Aldrich Chemical). The MOFB product was a slightly yellow liquid and had a melting point of 14° (lit.[5] mp 14°) and boiling point of 134–135° (12 mm) [lit.[4] bp 135–136° (12 mm)]. The ir spectrum of the product showed two carbonyl stretching frequencies at 1703 and 1727 cm^{-1} in agreement with the infrared assignments of Bowden and Taylor.[6]

In some preparations the MOFB was observed to be contaminated by its pseudo ester (3-methoxyphthalide), most of which could be removed by partial liquification of the frozen sample.[3] After purification the MOFB was found to contain less than 1% pseudo ester by ir and pmr techniques.

The amines used in this study were the highest grade available and were double distilled from potassium hydroxide solutions and in the case of aromatic amines from solutions containing zinc dust[7] just prior to use.

The 1,4-*p*-dioxane solvent used in this study was prepared by the method of Fieser and Fieser.[8] Dioxane not immediately used was frozen and stored as a solid. All ultraviolet spectra were done on a Cary 14 spectrophotometer and the pmr data were obtained on a Bruker 90 spectrometer.

Kinetic Procedure.—The rate of lactonization was followed by observing the disappearance of MOFB in the region of 285 nm on a Durrum D150/D131 stopped flow/temperature jump spectrophotometer, interfaced with an AD4/IBM 1130 hybrid computer.[9] Pseudo-first-order kinetic conditions were applied throughout using a 200- to 1000-fold excess amine over MOFB concentration. The pseudo-first-order rate constants, k_0, were determined using computer averaging of at least eight individual runs. We also calculated a grand k_0 obtained by treating all of the individual accumulated points as a single run. Invariably, the average k_0 and the grand k_0 were the same within experimental error. In all cases the correlation coefficient for the least squares fit on the individual runs was at least 0.999 (<1% standard deviation on k_0). The second-order rate constants were obtained from a plot of the pseudo-first-order rate constants *vs.* the molality of the excess amine nucleophile.

Results and Discussion

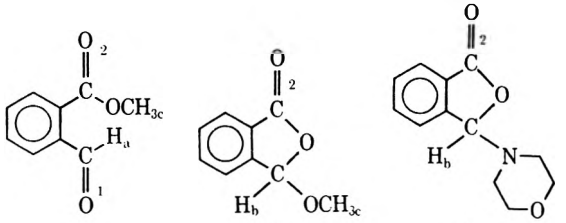
The addition of morpholine to MOFB, as observed by pmr, results in the loss of the aldehydic proton (H_A) and the appearance of the methinyl proton (H_B) (Figure 1). Equivalent changes in the infrared spectra can also be observed. The MOFB infrared spectrum is characterized by two carbonyl stretching frequencies, one at 1727 cm^{-1} for the ester carbonyl group and the other at 1703 cm^{-1} for the aldehydic carbonyl group. Morpholine addition results in the loss of both of these absorptions and is accompanied by the appearance of a new carbonyl stretch at 1780 cm^{-1}. A comparison (Table I) of the pmr and ir spectra of MOFB, the reaction product, and the pseudo ester (3-morpholinophthalide) shows that the morpholine addition has effected lactonization. Amines other than secondary cyclic showed no evidence of lactonization over the time scale of the test (reaction half-lives in the second to millisecond range). A summary of the amines studied in this work is given in Table II.

The lactonization rate was found to be sensitive to a variety of parameters related to the structure of the cyclic secondary amine. An increase in ring size

(5) K. V. Auwers and A. Heinze, *Ber.*, **52B**, 595 (1919).
(6) K. Bowden and G. R. Taylor, *J. Chem. Soc. B*, 1395 (1971).
(7) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, p 1276.
(8) Reference 7, p 333.
(9) The details of this interfacing will appear in a subsequent paper.

TABLE I

PMR AND IR DATA ON MOFB (I), 3-MORPHOLINOPHTHALIDE (II), AND MOFB–AMINE ADDITION PRODUCT (III)



I II III

	I	II	III
H_a, δ	10.4		
H_b, δ		6.3	6.2
H_c, δ	3.9	3.6	
C=O 1, cm^{-1}	1703		
C=O 2, cm^{-1}	1727	1780	1780

TABLE II

AMINE REACTIVITY IN LACTONIZATION OF MOFB IN DIOXANE AT 21°

Reactive	Nonreactive
1*H*-Hexahydroazepine	Aniline
2,5-Dimethylpyrrolidine	Butylamine
2-Pipecoline	Cyclohexylamine
3-Pipecoline	Diethylamine
4-Pipecoline	2,6-Dimethylaniline
Morpholine	2-Ethylpiperidine
Piperazine	*N*-Methylaniline
1-Methylpiperazine	*N*-Methylcyclohexylamine
Piperidine	Pyridine
Pyrrolidine	Pyrolle
	1,4-Dimethylpiperazine

from pyrrolidine (5) to 1*H*-hexahydroazepine (7) caused a 30-fold rate decrease (Table III). This behavior is consistent with the idea that the inactivity of the aliphatic secondary amines as lactonization nucleophiles is due to steric restriction at the lone pair of the nitrogen. In general, as ring size increases, the –C–N–C– bond angle increases, thereby presenting a steric inhibition to complex formation of the amine nitrogen lone pair electrons and the electron-deficient carbon of the MOFB carbonyl group. However, the modest change in rate in going from pyrrolidine to piperidine and the substantial rate change from piperidine to 1*H*-hexahydroazepine contradicts this simple structural interpretation of the rate behavior.

TABLE III

SECOND-ORDER RATE CONSTANTS FOR THE LACTONIZATION OF MOFB BY SECONDARY CYCLIC AMINES OF INCREASING RING SIZE[a]

Amine	Ring size	k_2, mol^{-1} sec^{-1}[b]
Pyrrolidine	5	34.0 ± 1.0
Piperidine	6	27.5 ± 0.6
1*H*-Hexahydroazepine	7	<1

[a] Dioxane solvent at 21°. [b] Obtained from plots of pseudo-first-order constants *vs.* molality of amine.

A similar rate reduction is observed when a methyl group is moved from the 4 to the 3 to the 2 position in the six-membered ring amine nucleophile (see Table IV). The modest rate constant differences observed in moving a methyl group from the 3 to the 4 position of the piperidine ring system (3-pipecoline and 4-pipecoline) is not considered significant. However, the lactonization rate reduction observed when a methyl group is placed in the 2 position (2-pipecoline), and the complete lack of reaction when an ethyl group is substituted for the methyl group in the 2 position (2-ethylpiperidine) and when 2 methyl groups are placed in the 2 and 6 position (2,6-dimethylpiperidine) lend support to the idea that the nitrogen lone-pair electrons are participating in the rate-determining step. Additional support was given to this notion when we examined 2,5-dimethylpyrrolidine as a lactonization nucleophile and again found no immediate reaction. However, on standing for 8 hr the MOFB was converted to the lactone. We may infer that on long standing, the 2,6-dimethylpiperidine would also effect the reaction, as would 2-pipecoline and 2-ethylpiperidine.

TABLE IV

SECOND-ORDER RATE CONSTANTS FOR THE LACTONIZATION OF MOFB BY SUBSTITUTED SECONDARY CYCLIC AMINES[a]

Amine	k_2, mol^{-1} sec^{-1}
Piperidine	27.5 ± 0.6
4-Pipecoline	30.0 ± 2.0
3-Pipecoline	22.5 ± 0.9
2-Pipecoline	<1
2,5-Dimethylpyrrolidine	*b*
2-Ethylpiperidine	*b*
2,6-Dimethylpiperidine	*b*

[a] Dioxane solvent, 21°. [b] No reaction in the millisecond to second range. Lactonization effected in 4–8 hr.

The rate of lactonization was also observed to vary as a function of the 4 heteroatom in the piperidine ring structure. In the series piperidine (–CH_2– in the 4 position), morpholine (–O–), piperazine (–NH–), 1-methylpiperazine (–NCH_3–), and 1,4-dimethylpiperazine the second-order rate constants were observed to vary over a factor of 100 (Table V). The most surprising result is the large second-order constant for piperazine. This effect was at first thought to be the result of the 5% methanol–dioxane used as the solvent rather than pure dioxane (piperazine is only very slightly soluble in dioxane). However, subsequent examination of piperidine and morpholine lactonizations in 5% methanol–dioxane gave rate constants identical with those found in pure dioxane. In these latter cases the intercept (k_s) of the first-order rate constant *vs.* molality curves, which should be the origin, did decrease in the same manner as was observed in the piperazine case. The change of intercept with change in solvent composition will be more fully examined in subsequent work.

TABLE V

SECOND-ORDER RATE CONSTANTS FOR THE LACTONIZATION OF MOFB BY RING-SUBSTITUTED CYCLIC SECONDARY AMINES[a]

Amine	k_2, mol^{-1} sec^{-1}
Piperazine	468[b] ± 9
Piperidine	27.5 ± 0.6
1-Methylpiperazine	7.4 ± 0.3
Morpholine	3.7[c] ± 0.1
1,4-Dimethylpiperazine	*d*

[a] Dioxane at 21° except piperazine, where 5% MeOH/dioxane was used. [b] Statistical correction of 2 not made. [c] Reference 3 reports a value of 11 ± 1 M^{-1} sec^{-1} in aqueous media. [d] No reaction.

The unusual rate enhancement with piperazine was observed in aqueous solution earlier by Dahlgren and Schell.[4] In that study piperazine was a factor of 665 more effective a catalyst for the complete hydrolysis of MOFB than morpholine. In the present lactonization study the second-order rate constant for piperazine is a factor of 126 larger than that for morpholine or one-half of that if we make the statistical correction for the second amine group of piperazine.

Standard equations were used to determine the activation parameters over the temperature range 21–39° and the results are recorded in Table VI. It

TABLE VI
THERMODYNAMIC FUNCTIONS OF ACTIVATION FOR THE LACTONIZATION OF MOFB BY SELECT CYCLIC SECONDARY AMINES[a]

Amine	$\Delta H^{\pm}$, kcal/mol	$\Delta G^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu
Morpholine	1.6 ± 0.2	2.8 ± 0.1	15 ± 1
Piperazine	1.2 ± 0.1[b]	2.58 ± 0.07	12.6 ± 0.6
1-Methylpiperazine	1.7 ± 0.3	3.0 ± 0.1	16 ± 2

[a] Dioxane at 21° except for piperazine where 5% MeOH/dioxane was used. [b] Reference 4 reports a value of 1.3 ± 0.1 kcal/mol in aqueous media.

is interesting to note that the enthalpy of activation determined for the piperazine-catalyzed lactonization of MOFB in dioxane is essentially the same as that for the piperazine-catalyzed hydrolysis of MOFB in water.[4]

Finally, where pK_B values were available the second-order rate constants and the pK_B's were found to obey the Brønsted relation (eq 2). That is, in the case of

$$\log k_2 = 0.33\ (\pm 0.02) \log K_B + 2.39\ (\pm 0.07) \qquad (2)$$

pyrrolidine (pK_B = 2.695),[10] piperidine (2.877),[10] 1-methylpiperazine (4.50),[11] and morpholine (5.64),[12] the rate of nucleophile attack on the carbonyl carbon of the aldehyde function of MOFB parallels the affinity of the nucleophile for the protons of water. However, piperazine (pK_B = 4.21),[10] whose second-order rate constant according to eq 2, should equal 10.2 l. mol^{-1} sec^{-1}, actually gave an observed value of 500 l. mol^{-1} sec^{-1} at 25°. It is this latter observation which has piqued our curiosity and led us to preparing bicyclic systems containing the piperazine geometry but preventing participation by the second amine group in, perhaps, a proton abstraction role.

Registry No.—I, 4122-56-9; II, 4122-57-0; III, 4195-21-5; pyrrolidine, 123-75-1; piperidine, 110-89-4; 1*H*-hexahydroazepine, 111-49-9; 4-pipecoline, 626-58-4; 3-pipecoline, 626-56-2; 2-pipecoline, 109-05-7; piperazine, 110-85-6; 1-methylpiperazine, 109-01-3; morpholine, 110-91-8.

(10) D. D. Perrin, *Aust. J. Chem.*, **17**, 484 (1964).
(11) F. Erb and N. Garot, *Bull. Soc. Pharm. Lille*, **1**, 59 (1964).
(12) H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 63 (1956).

Thermal Decomposition of Benzyl Triphenylacetate and Benzyl Diphenyl-*p*-tolylacetate. The Possibility of 1,4-Aryl Migration and α-Lactone Formation[1a,b]

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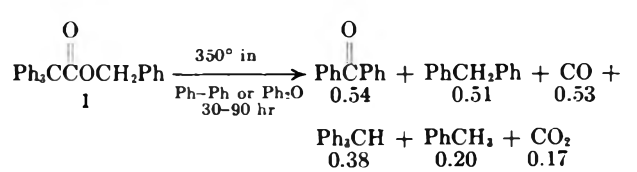
The thermal decomposition of benzyl triphenylacetate at 350° for 30–90 hr in the liquid phase gives 0.54, 0.51, and 0.53 mol/mol ester of benzophenone, diphenylmethane, and carbon monoxide, respectively, in addition to 0.38, 0.20, and 0.17 mol/mol ester of triphenylmethane, toluene, and carbon dioxide, respectively. The thermal decomposition of benzyl diphenyl-*p*-tolylacetate under comparable conditions for 30 hr gives 0.29, 0.27, 0.15, and 0.34 mol/mol ester of benzophenone, phenyl-*p*-tolylmethane, *p*-methylbenzophenone, and diphenylmethane, respectively, plus 0.30 mol/mol ester of diphenyl-*p*-tolylmethane. A mechanism is proposed for the formation of the arylphenylmethanes and benzophenones which involves a 1,4-aryl migration to produce the arylphenylmethane and α-lactone which rapidly decarbonylates to give the benzophenone.

The thermal decomposition of benzyl triphenylacetate (1) at 350° in biphenyl or diphenyl ether (*ca.* 15% 1 in solution) for 30–90 hr in a sealed tube gives rise to fairly high and approximately equal yields of benzophenone, diphenylmethane, and carbon monoxide in addition to triphenylmethane, toluene, and carbon dioxide (throughout this paper yields are given in mol/mol ester unless otherwise indicated).



Yields were determined by glpc and nmr analyses and are averages of 6–8 runs. The use of biphenyl or diphenyl ether as solvent made no significant difference. In fact, the pyrolysis of a neat sample of 1 for 5 hr at 350° gave 0.52, 0.46, and 0.25 mol/mol ester of benzophenone, diphenylmethane, and triphenylmethane, respectively. The gaseous products were collected and determined as described previously.[2]

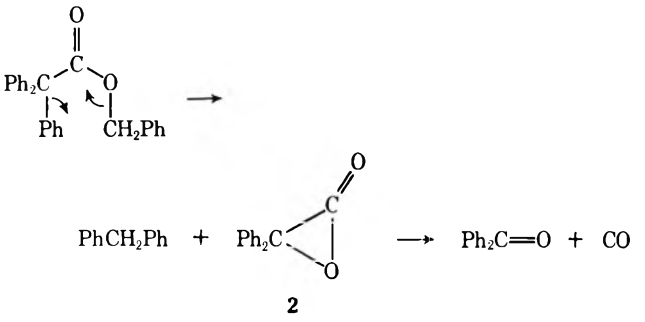
Ester 1 was reported[3] to decompose at its boiling point to give triphenylmethane, 37% carbon dioxide,

(1) (a) This research was partially supported by Public Health Service Grant GM 13799 from the National Institute of General Medical Sciences and Grant 3219-A from the Petroleum Research Fund administered by the American Chemical Society. We thank these organizations for their support. (b) Based on work by D. E. Z., and M. L.-S. L. in Partial fulfillment of the requirements for the Ph.D. and M.S. degrees, respectively, at I. S. U. (c) Alfred P. Sloan Research Fellow, 1970–1972.

(2) D. E. Zabel and Walter S. Trahanovsky, *J. Org. Chem.*, **37**, 2413 (1972), and references cited therein.
(3) J. F. Norris and A. J. Cresswell, *J. Amer. Chem. Soc.*, **56**, 423 (1934).

and 42% carbon monoxide. Because of the high yield of carbon monoxide, benzaldehyde was postulated but not demonstrated to be a pyrolysis product. We found no benzaldehyde, benzyl triphenylmethyl (trityl) ether, trityl phenylacetate, 1,1,1,2-tetraphenylethane, or **1** in the product mixture.

A possible explanation for the formation of benzophenone and diphenylmethane is that a 1,4-phenyl migration occurs giving rise to diphenylmethane and diphenylacetolactone (**2**) which rapidly decarbonylates



to give benzophenone. Triphenylmethane and toluene probably come from hydrogen abstraction reactions by the trityl and benzyl radicals, which would be produced by homolytic cleavage of the trityl–carbonyl bond of **1**

$$1 \longrightarrow Ph_3C\cdot + \cdot COOCH_2Ph \longrightarrow CO_2 + \cdot CH_2Ph$$

followed by decarboxylation of the benzyloxycarbonyl radical.[2] The sources of hydrogen atoms are probably species formed by the addition of radicals into solvent molecules.

1,4-Aryl migrations are rare but known[4] and α-lactones have been isolated at low temperatures.[5,6] The decarbonylation of α-lactones has been shown to be a primary photochemical reaction[6] and a thermal reaction of di(trifluoromethyl)acetolactone.[7] Although polymerization has been shown to be a thermal reaction of α-lactones, including **2**,[5,6] the thermal decarbonylation of **2** at high temperatures is not an unreasonable process. In fact, fair yields of benzophenone have been obtained from reactions which are thought to involve **2**, although decarbonylation of **2** has not been invoked as the route to benzophenone.[8]

Other mechanisms, such as a bimolecular one which is analogous to the above unimolecular mechanism, can be written, but a key point which they must account for is the approximately equal yields of diphenylmethane and benzophenone.

The thermal decomposition of neat benzyl diphenyl-*p*-tolylacetate (**3**) under comparable conditions gives

$$\underset{\mathbf{3}}{Tol(Ph)_2CCOOCH_2Ph} \xrightarrow[30\ hr]{350^\circ}$$

Tol ≡ *p*-$CH_3C_6H_4$

PhCOPh	+ PhCH₂Tol	+ PhCOTol	+ PhCH₂Ph
4	**5**	**6**	**7**
0.29	0.27	0.15	0.34

the products expected from both phenyl and *p*-tolyl migrations. Nmr and glpc analysis also indicated that 0.30 mol/mol ester of diphenyl-*p*-tolylmethane was produced. In Table I are presented the yields of products from runs for varying lengths of time. From these yields, it is seen that for all of these runs the ratio of **4** to **5** is *ca.* 1, as expected, but the ratio of **6** to **7** is *ca.* 0.5 for all the runs except the one which was stopped after 1 hr. For the 1-hr run, the ratio of **6** to **7** is *ca.* 1. Thus **6** seems to be unstable to reaction conditions.

TABLE I
DECOMPOSITION PRODUCTS OF BENZYL DIPHENYL-*p*-TOLYLACETATE AT 350°

Reaction time, hr	Yields,[a] mol/mol ester				
	PhCOPh	PhCH₂Tol	PhCOTol	PhCH₂Ph	Tol-(Ph)₂CH
1[b]	0.16	0.14	0.12	0.13	0.20
5	0.21	0.20	0.14	0.23	0.40
15	0.35	0.31	0.20	0.36	0.49
30	0.29	0.27	0.15	0.34	0.30
47	0.27	0.26	0.13	0.32	0.34
66	0.28	0.23	0.13	0.28	0.24
91	0.27	0.22	0.14	0.26	0.22

[a] Analysis for toluene was not carried out. [b] 61% of ester **3** was recovered.

The ratio of *p*-tolyl to phenyl migration calculated from diarylmethanes is 0.86 and that calculated from the benzophenones from the 1-hr run is 1.3. Thus the rate of migration of the *p*-tolyl is *ca.* two times that of the phenyl group taking into consideration the fact that there are two phenyl groups to every *p*-tolyl group. It is difficult to interpret these comparable rates of migration for the *p*-tolyl and phenyl groups, since the ratio of these rates has been shown to be *ca.* 1 for a radical rearrangement[9] but range from 1 to 16 for cation rearrangements.[10]

Methyl (**8**) and phenyl (**9**) triphenylacetates were thermally decomposed under similar conditions. Ester **8** gave 0.07, 0.11, and 0.56 mol/mol ester of toluene, benzophenone, and triphenylmethane, respectively. Ester **9** gave 0.70 and 0.75 mol/mol ester of phenol and triphenylmethane, respectively. Thus the methyl ester undergoes a rearrangement reaction analogous to the one observed for the benzyl ester, but the phenyl ester undergoes trityl–carbonyl bond cleavage only. These results for the thermal decomposition of **8** and **9** are consistent with previously published results.[3,11]

When **1** was pyrolyzed in the gas phase at 550° by the technique previously described[12] most of **1** was recovered, no diphenylmethane was produced, and 0.08, 0.08, 0.06, and 0.02 mol/mol ester of benzophenone,

(4) (a) G. W. Griffin and E. J. O'Connel, *ibid.*, **84**, 4148 (1962); (b) H. E. Zimmerman, H. G. C. Durr, R. G. Lewis, and S. Bram, *ibid.*, **84**, 4149 (1962); (c) O. L. Chapman, H. G. Smith, R. W. King, D. J. Pasto, and M. R. Stoner, *ibid.*, **85**, 2031 (1963); (d) T. H. Kinstle, O. L. Chapman, and M.-T. Sund, *ibid.*, **90**, 1227 (1968); (e) J. W. Wilt and T. P. Malloy, *ibid.*, **92**, 4749 (1970); (f) E. Grovenstein, Jr., S. Akabori, and J.-U. Rhee, *ibid.*, **94**, 4734 (1972).

(5) R. Wheland and P. D. Bartlett, *ibid.*, **92**, 6057 (1970).

(6) O. L. Chapman, P. W. Wojtkowski, W. Adam, O. Rodriguez, and R. Rucktäschel, *ibid.*, **94**, 1365 (1972).

(7) Personal communication from W. Adam. We thank Professor Adam for this information.

(8) (a) P. D. Bartlett and L. B. Gortler, *J. Amer. Chem. Soc.*, **85**, 1864 (1963); (b) J. K. Crandall and S. A. Sojka, *Tetrahedron Lett.*, 1641 (1972).

(9) M. S. Kharasch, A. C. Poshkus, A. Fono, and W. Nudenberg, *J. Org. Chem.*, **16**, 1458 (1951).

(10) (a) W. E. Bachmann and F. H. Moser, *J. Amer. Chem. Soc.*, **54**, 1124 (1932); (b) J. G. Burr, Jr., and L. S. Ciereszko, *ibid.*, **74**, 5426 (1952).

(11) R. Anschütz, *Justus Liebigs Ann. Chem.*, **359**, 196 (1908).

(12) Walter S. Trahanovsky, C. C. Ong, and J. A. Lawson, *J. Amer. Chem. Soc.*, **90**, 2839 (1968).

bibenzyl, triphenylmethane, and biphenyl, respectively, were obtained. Thus a different reaction must take place at the higher temperature in the gas phase.

Experimental Section

Methods and Materials.—Most equipment and methods have been previously described.[2,12] An insulated, electrically heated, aluminum block heater was used for most of the high-temperature sealed-tube pyrolyses. The heater consisted of a round block of aluminum 6 in. in diameter and 6 in. long which was wrapped with asbestos, wound with enough No. 20 Chromel heating wire to attain a maximum temperature of 500°, and again wrapped with asbestos. Ten evenly spaced holes, each 0.875 in. in diameter, 4.5 in. from the axis of the cylinder, and 5 in. deep, were drilled into the block. One hole 0.25 in. in diameter and 3 in. deep for the thermocouple was drilled between two of the sample holes. Each of the ten sample holes was expanded to 1 in. in diameter to a depth of 1 in. Ten stainless steel plugs, 1 in. deep, were ground to fit loosely in the sample holes and rest on the ledge of the inner hole. Each plug had a hook on the bottom side for attaching sample holders and a "knob" on the top for pulling out the plug (and sample). Ten sample holders were made of stainless steel tubing (22 mm) and fitted with wire bails. The block was placed in a box made of Transite insulation board; the box was filled with blown mica and covered with a Transite lid. The heating coil was connected to a Variac, and a thermocouple attached to a Leeds and Northrup potentiometer was used to measure the temperature of the block.

Benzyl triphenylacetate (1) was prepared from the acid chloride[13] and alcohol:[3] mp 98–99° (lit.[3] mp 99–99.5°); nmr ($CDCl_3$) δ 7.17 (s, 20) and 5.21 (s, 2); ir ($CHCl_3$) 1725, 1487, 1170, 1005, and 973 cm^{-1}.

Benzyl trityl ether was prepared as described previously:[14] mp 101–103° (lit.[14] mp 105.5–106°); nmr ($CDCl_3$) 7.35 (m, 20) and 4.26 (s, 2); ir ($CHCl_3$) 1490, 1375, 1150, 1085, 1053, 1000, 982, and 900 cm^{-1}.

Trityl phenylacetate was prepared in 70% yield from trityl bromide and potassium phenylacetate[15] by a method similar to a previously published one:[16] mp 69–71°; nmr ($CDCl_3$) δ 7.17 (m, 20) and 3.60 (s, 2); ir ($CHCl_3$) 1737, 1130, and 983 cm^{-1}.

Anal. Calcd for $C_{27}H_{22}O_2$: C, 85.69; H, 5.86. Found: C, 86.62, 85.05, 84.02; H, 6.05, 5.97, 6.09. (This compound appeared to be sensitive to moisture.)

Diphenyl-*p*-tolylacetic acid was prepared from benzilic acid, toluene, and anhydrous stannic chloride by a procedure similar to that previously described,[17] mp 205–207° (lit.[17] mp 205°).

Benzyl diphenyl-*p*-tolylacetate (3) was prepared by treating the acid with an ethereal solution of phenyldiazomethane.[18] The crude product was recrystallized from benzene: mp 68–69°; nmr (CCl_4) δ 7.1 (s, 14), 6.99 (s, 5), 5.15 (s, 2), and 2.3 (s, 3); ir (KBr) 1720, 1495, 1440, 1162, 971, and 813 cm^{-1}.

Anal. Calcd for $C_{28}H_{24}O_2$: C, 85.71; H, 6.12. Found: C, 85.86; H, 6.23.

Methyl triphenylacetate (8) was prepared as described previously:[3] mp 182–184° (lit.[19] mp 182°); nmr ($CDCl_3$) δ 7.11 (d, 15) and 3.67 (s, 3); ir ($CHCl_3$) 1725, 1486, 1445, 1430, and 1010 cm^{-1}.

Phenyl triphenylacetate (9) was prepared as described previously:[20] mp 124–126° (lit.[20] mp 123–124°); ir ($CHCl_3$) 1755, 1595, 1490, 1156, and 970 cm^{-1}.

Thermal Decomposition of the Esters.—Solutions of the esters in diphenyl ether or biphenyl or neat samples were placed in constricted tubes, degassed three times, and sealed. The tubes were heated in the aluminum block heater, cooled, and opened. A weighed quantity of benzil was added as a standard and the mixture was analyzed by glpc using an SE-30 or Carbowax 20M column. The products were identified by enhancement of glpc trace peaks with authentic samples[21] and nmr spectra of the product mixture. The ir spectrum of the product mixture from 1 had a peak at 1660 cm^{-1} which is characteristic of benzophenone.

Analysis of the Gases Evolved during the Thermal Decomposition of 1.—A total of 0.756 g (2.00 mmol) of 1 in 6.15 g (36.2 mmol) of diphenyl ether was placed in two thick-walled tubes and degassed three times and the tubes were sealed. The tubes were heated at 350° for 32 hr. After cooling the tubes were broken open under a funnel submerged in a large water tank and analyzed as described previously.[2] At 301° K and 707-mm pressure (corrected for water vapor) 9.00 ml of carbon dioxide and 28.40 ml of carbon monoxide were obtained (1.40 ml of gas remained). A second run gave comparable results.

Registry No.— **1**, 37173-04-9; **3**, 37173-05-0; **8**, 5467-21-0; **9**, 34823-77-3; benzyl trityl ether, 5333-62-0; trityl phenylacetate, 37173-09-4.

(13) L. W. Jones and C. D. Hurd, *J. Amer. Chem. Soc.*, **43**, 2438 (1921).
(14) E. F. Pratt and J. D. Draper, *ibid.*, **71**, 2846 (1949).
(15) M. Davies and W. J. O. Thomas, *J. Chem. Soc.*, 2858 (1951).
(16) K. D. Berlin, L. H. Gower, J. W. White, D. E. Gibbs, and G. P. Sturm, *J. Org. Chem.*, **27**, 3595 (1962).
(17) A. Bistrzycki and K. Wehrbein, *Chem. Ber.*, **34**, 3080 (1901).
(18) G. L. Closs and R. A. Moss, *J. Amer. Chem. Soc.*, **86**, 4042 (1964).
(19) J. Gyr, *Chem. Ber.*, **41**, 4308 (1908).
(20) J. Schmidlin and H. H. Hodgson, *ibid.*, **41**, 444 (1908).
(21) We thank Professor H. Gilman for a sample of phenyl-*p*-tolylmethane. The other samples were obtained from commercial sources.

Oxidation of Organic Compounds with Cerium(IV). XV. Electronic and Steric Effects on the Oxidative Cleavage of 1,2-Glycols by Cerium(IV) and Lead(IV)[1a-c]

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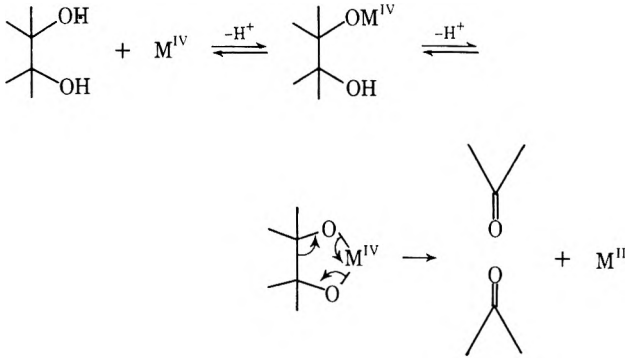
The relative rates of oxidative cleavage of a series of substituted *meso*-hydrobenzoins, *dl*-hydrobenzoin, and *erythro*-*O*-methylhydrobenzoin by cerium(IV) and lead(IV) were measured by competition studies. The relative rates of oxidative cleavage by periodate of some of these hydrobenzoins were also measured. All oxidations were carried out at 50° in 85% aqueous acetic acid. From these data ρ values of +0.016 for the lead(IV) and −1.53 for the cerium(IV) oxidations of *meso*-hydrobenzoins were calculated using σ^+ values. With lead(IV) *dl*-hydrobenzoin is oxidized nine times faster than the meso isomer, but with cerium(IV) these rates are equal. The relative rates of oxidation of *meso*-hydrobenzoin and its monomethyl ether are more similar with cerium(IV) than with lead(IV). These results support the intermediate formation of a bidentate complex with lead(IV) but not with cerium(IV) and are consistent with the mechanism for the cleavage of cerium(IV), which involves the formation of a monodentate complex followed by a one-electron cleavage to give an intermediate radical which is then further oxidized.

The cleavage of 1,2-glycols by periodic acid[2] and lead tetraacetate[3] has been known for some time. Although these two oxidants seem to be the most widely used ones to bring about 1,2-glycol cleavages,[4] several other oxidants such as sodium bismuthate,[4a,5] manganese(III) pyrophosphate,[6] phenyl iodosoacetate,[4,7] cerium(IV) salts,[4b,8] vanadium(V) salts,[4b,9] chromic acid,[10] and nickel peroxide[11] also readily cleave 1,2-glycols. A catalytic system, the silver(I)-catalyzed oxidative cleavage of 1,2-glycols by peroxy disulfate, has been reported.[12]

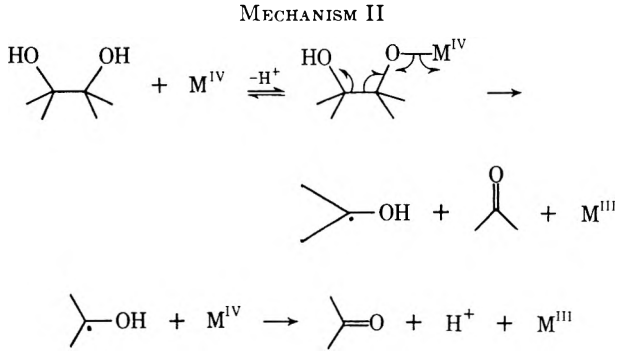
The mechanism for the cleavage of 1,2-glycols by lead(IV) is thought to involve the formation of a bidentate metal–glycol complex which then breaks down to products *via* a two-electron process[4a] (mechanism I). The main support for this mechanism comes from the fact that cis diols are more rapidly oxidized than the corresponding trans diols and threo diols are more rapidly oxidized than the corresponding erythro diols.[4a,13] Although there is no direct evidence for these cyclic lead complexes, their existence has been made more reasonable by the isolation of cyclic osmates.[14] Mechanism I is further supported by the failure to trap radical intermediates.[8e]

MECHANISM I



Other mechanisms for the cleavage of 1,2-glycols can be written, and indeed the cleavage of 1,2-glycols by cerium(IV) seems to involve coordination to only one hydroxy group followed by a one-electron oxidation to give an intermediate radical (mechanism II).[8] The main support for this mechanism is the similar rates of oxidation of 1,2-glycols and their monomethyl ethers,[8d,8j] and the successful trapping experiments[8c,8e] which indicate that an intermediate radical is formed. Some support for the intermediacy of a bidentate cerium(IV)–glycol complex has been given,[8f] but other results,[8d] including formation constants for cerium(IV) complexes

MECHANISM II



(1) (a) Part XIV: W. S. Trahanovsky and M. D. Robbins, *J. Amer. Chem. Soc.* **93**, 5256 (1971). (b) This work was partially supported by Public Health Service Grant No. GM 13799 from the National Institute of General Medical Sciences and Grant No. GP-18031 from the National Science Foundation. We are grateful for this support. (c) Preliminary communication: Abstracts, 162nd National Meeting of the American Chemical Society, New York, N. Y., Aug 1972, ORGN 13. (d) Alfred P. Sloan Research Fellow, 1970–1972.

(2) L. Malaprade, *C. R. Acad. Sci.*, **186**, 382 (1928); *Bull. Soc. Chim. Fr.*, [4], **43**, 683 (1928); [5], **1**, 833 (1934).

(3) R. Criegee, *Justus Liebigs Ann. Chem.*, **481**, 275 (1930).

(4) (a) C. A. Bunton in "Oxidation in Organic Chemistry," part A, K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, Chapter VI; (b) A. S. Perlin in "Oxidation," Vol. 1, R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter IV.

(5) W. Rigby, *J. Chem. Soc.*, 1907 (1950).

(6) (a) A. Y. Drummond and W. A. Waters, *ibid.*, 3119 (1953); (b) P. Levesley, W. A. Waters, and A. N. Wright, *ibid.*, 840 (1956).

(7) H. Beucker and R. Criegee, *Justus Liebigs Ann. Chem.*, **541**, 218 (1939).

(8) (a) F. R. Duke and A. A. Forist, *J. Amer. Chem. Soc.*, **71**, 2790 (1949); (b) F. R. Duke and R. F. Bremer, *ibid.*, **73**, 5179 (1951); (c) G. Mino, S. Kaizerman, and E. Rasmussen, *ibid.*, **81**, 1494 (1959); (d) J. S. Littler and W. A. Waters, *J. Chem. Soc.*, 2767 (1960); (e) W. S. Trahanovsky, L. H. Young, and M. H. Bierman, *J. Org. Chem.*, **34**, 869 (1969); (f) H. L. Hintz and D. C. Johnson, *ibid.*, **32**, 556 (1967).

(9) J. S. Littler, A. I. Mallet, and W. A. Waters, *J. Chem. Soc.*, 2761 (1960).

(10) (a) R. Slack and W. A. Waters, *ibid.*, 594 (1949); (b) K. B. Wiberg in "Oxidation in Organic Chemistry," part A, K. B. Wiberg, Ed., Academic Press, New York, N. Y., Chapter II.

(11) R. Konaka and K. Kuruma, *J. Org. Chem.*, **36**, 1703 (1971), and references cited therein.

(12) E. S. Huyser and L. G. Rose, *ibid.*, **37**, 851 (1972), and references cited therein.

(13) R. Criegee, E. Höger, G. Huber, P. Kruck, F. Marktscheffel, and H. Schellenberger, *Justus Liebigs Ann. Chem.*, **599**, 81 (1956).

(14) (a) R. Criegee, *Angew. Chem.*, **50**, 153 (1937); (b) R. Criegee, B. Marchand, and H. Wannowius, *Justus Liebigs Ann. Chem.*, **550**, 99 (1942).

TABLE I

RELATIVE RATES OF OXIDATIVE CLEAVAGE OF SUBSTITUTED *meso*-HYDROBENZOINS, $(ZC_6H_4CHOH-)_2$, WITH CERIC AMMONIUM NITRATE (CAN), LEAD TETRAACETATE (LTA), AND POTASSIUM PERIODATE (KIO_4)[a]

Registry no.	Z	CAN k_{rel}	LTA k_{rel}	KIO_4 k_{rel}
5173-29-5	*p*-CH_3	2.62 ± 0.36	1.023 ± 0.071	1.15
37580-80-6	*m*-CH_3	1.80 ± 0.09	1.84 ± 0.10	
655-48-1	H	(1.00)	(1.00)	(1.00)
37580-81-7	*p*-Cl	0.395 ± 0.017	1.79 ± 0.14	
37580-82-8	*p*-Br	0.446 ± 0.010	1.09 ± 0.11	
37580-83-9	*m*-Cl	0.244 ± 0.012	1.37 ± 0.12	1.13
37580-84-0	*p*-NO_2	0.0619 ± 0.0039	1.205	

[a] In 85% aqueous acetic acid at 50°. The numbers with standard deviations are based on three runs and those without are based on one run.

with glycols and their monomethyl ethers,[15] give no indication that a bidentate complex is formed.

In order to gain further support for the validity of these mechanisms and to establish the electronic effects on these mechanisms, a study of the relative rates of oxidative cleavage by cerium(IV) and lead(IV) of substituted *meso*-hydrobenzoins was undertaken. Also, the relative rates of oxidation by these oxidants of *meso*- and *dl*-hydrobenzoin were measured in order to determine if there were any steric differences between

$$\mathrm{ArCH(OH)—CH(OH)Ar} \xrightarrow{2Ce^{IV}\text{ or }Pb^{IV}} 2\mathrm{ArCH{=}O}$$

these two oxidants. A small amount of data was collected using periodate as the oxidant. All oxidations were carried out at 50° in 85% acetic acid to ensure a direct comparison of the relative rate constants.

Results

The substituted hydrobenzoins were synthesized *via* the benzoin condensation of the corresponding aldehyde.[16] The benzoin was further reduced with sodium borohydride to the hydrobenzoin.[16] The meso isomer was isolated by fractional recrystallization; the *dl* isomer, being more soluble, stayed in solution and usually one or two recrystallizations sufficed. The purity of the isomers was checked by melting point and nmr spectroscopy since the signals for the benzylic protons of the meso and *dl* isomers have large chemical-shift differences. 4,4′-Dinitrohydrobenzoin was synthesized by a different route.[17] *dl*-Hydrobenzoin was prepared by a modification of the method of Fieser.[16] The *erythro*-monomethyl ether of hydrobenzoin was prepared by methylating benzoin with methyl iodide–silver oxide in acetone[18] and reducing the methyl benzoin to the required compound with sodium borohydride.

The kinetic study was carried out by competitively oxidizing equimolar quantities of a substituted hydrobenzoin and the unsubstituted hydrobenzoin with the required oxidant. The amount of oxidant used was such that only a maximum of 5% of either of the substrates would be consumed. Since the substrate concentration at the beginning of the reaction was approximately equal to substrate concentration at the end of the reaction, the relative rate constants are given by eq 1. The ratio of the two aldehydes produced were

$$k(\mathrm{X})/k'(\mathrm{H}) = [\mathrm{X\ products}]/[\mathrm{H\ products}] \quad (1)$$

determined by glpc, making corrections for relative extraction and thermal conductivity ratios. The relative rates for *dl*-hydrobenzoin were determined against *meso*-4,4′-dimethylhydrobenzoin and the relative rates for the *erythro*-monomethyl ether of hydrobenzoin were determined against *meso*-3,3′-dichlorohydrobenzoin. The results are summarized in Tables I–III. Plots of

TABLE II

RELATIVE RATES OF OXIDATIVE CLEAVAGE OF *dl*- TO *meso*-HYDROBENZOIN WITH VARIOUS OXIDANTS[a]

Oxidant	k_{dl}/k_{meso}
CAN	0.90 ± 0.28[b]
LTA	8.29 ± 0.58[c]
KIO_4	5.16[d]

[a] In 85% aqueous acetic acid at 50°. [b] Based on three runs. [c] Based on two runs. [d] Based on one run.

TABLE III

RELATIVE RATES OF OXIDATIVE CLEAVAGE OF *meso*-HYDROBENZOIN TO ITS MONOMETHYL ETHER AND WITH VARIOUS OXIDANTS[a]

Oxidant	$k_{diol}/k_{monoether}$
CAN	6
LTA	20

[a] See footnote *a*, Table I.

the logarithms of the relative rate of each substrate by ceric ammonium nitrate (CAN) *vs.* the Hammett σ and σ^+ values[19] gave about equally good correlations with σ and σ^+ values. A least squares treatment of these data using σ^+ values gave a ρ of -1.53 ± 0.15 and using σ values gave a ρ of -1.72 ± 0.09. Similar treatment of the relative rates obtained with lead tetraacetate (LTA) using σ^+ values gave a ρ of 0.016 ± 0.14 and σ values gave a ρ of 0.010 ± 0.015.[20] Plots of the logarithms of the relative rates of each substrate by CAN and LTA *vs.* σ^+ values are shown in Figure 1. Use of the σ^+ values are

(15) L. B. Young and W. S. Trahanovsky, *J. Amer. Chem. Soc.*, **91**, 5060 (1969).

(16) L. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, Mass., 1957.

(17) T. Ukita and R. Takeshita, *Chem. Pharm. Bull.*, **9**, 600 (1961).

(18) H. Wren, *J. Chem. Soc.*, **95**, 1584 (1909).

(19) H. C. Brown and Y. Okamota, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(20) When the two abnormally high rate constants for the LTA oxidations were omitted, a ρ of 0.097 ± 0.055 using σ^+ and a ρ of 0.086 ± 0.070 using σ were calculated. We have no good explanation for the slightly higher rate constants for the *m*-methyl and *p*-chloro compounds. Possibly these compounds were slightly contaminated with their *dl* isomer, which would have been oxidized more rapidly. In any case, it is clear that there is no correlation with the rate constants for the LTA oxidations and the electronic effects of the substituents and even the abnormally high rate constants (*ca.* 1.8) are fairly close to 1.0.

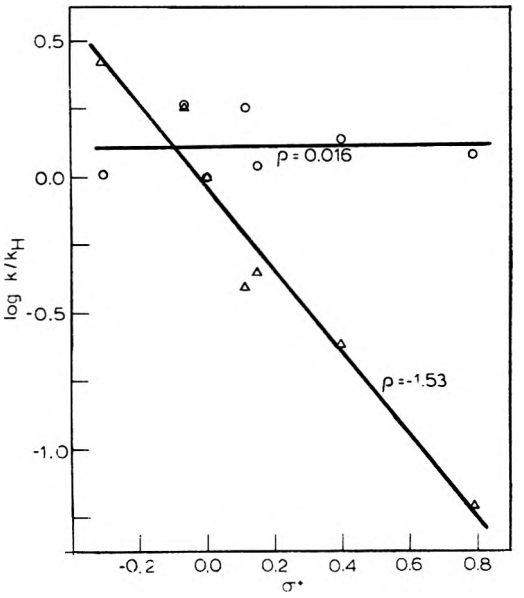


Figure 1.—Plots of the logarithms of the relative rates of oxidative cleavage of *meso*-hydrobenzoins by CAN (△) and LTA (○) *vs.* σ^+ for the substituent.

favored since oxidative cleavages have generally correlated better with σ^+ than σ.[21]

Discussion

The results of this study strongly support mechanism I for the cleavage of 1,2-glycols by lead(IV) and mechanism II for the cleavage of 1,2-glycols by cerium(IV). The contrasting results obtained for these two oxidants under comparable reaction conditions make these conclusions all the more firm.

The lack of a substituent effect (a ρ of +0.02) for the 1,2-glycol cleavage by lead(IV) indicates that the formation of the bidentate complex is rate determining, or that the decomposition of this complex is rate determining but little charge develops on the benzylic carbon atoms in the cyclic transition state. Additional support for the intermediacy of this bidentate complex comes from the observation that the *dl* isomer of hydrobenzoin was oxidized 8.3 times faster than the meso isomer by lead(IV) whereas these isomers were oxidized at comparable rates by cerium(IV), which evidently does not form a cyclic intermediate. The lead(IV) and cerium(IV) results considered together mean that the rate difference for the oxidation of these two isomers by lead(IV) must result from a difference in transition-state energies, not groundstate energies. This difference in energy is no doubt a result of the increased steric interaction between the cis phenyl groups of the meso transition state compared to the trans phenyl groups of the *dl* transition state. The more similar relative rates of oxidation of *meso*-hydrobenzoin and its monomethyl ether with cerium(IV) ($k_{diol}/k_{monoether}$ = 6) compared to the corresponding relative rates with lead(IV) ($k_{diol}/k_{monoether}$ = 20) also support the two different mechanisms for the two oxidants.

The relative rates of oxidation by LTA of a small number of tetrasubstituted benzpinacols (unsubstituted, 4-methoxy, 4-methyl, and 4-chloro) show a slight rate increase as the substituent becomes more electron donating.[22] From these results, it was concluded that the formation of the monodentate complex is rate determining. Although this conclusion is in disagreement with the results in this article and other data,[4a,13] it may be true for more hindered glycols such as the benzpinacols.[23] Because only a limited number of examples were studied and the benzpinacols possess special features which make them atypical 1,2-glycols, this study is of little use in defining a mechanism for the LTA oxidation of most 1,2-glycols.

The ρ value of −1.5 found for the cerium(IV) oxidative cleavage of substituted *meso*-hydrobenzoins is consistent with mechanism II and requires that the rate-determining step must be the decomposition of the monodentate complex to the intermediate radical and carbonyl compound. The ρ value of −1.5 is comparable to the one observed (−2.0) for the oxidative cleavage of 1,2-diarylethanols.[21] It is reasonable that the formation of benzylic radicals should be a little more sensitive to substituents than the formation of α-hydroxybenzyl radicals.

It is interesting to note that, based on orbital symmetry considerations, the cyclic mechanism, mechanism I, is a forbidden process for one-electron oxidants such as cerium(IV).[25]

The cleavage of 1,2-glycols by cerium(IV) is just a special case of the general oxidative cleavage of alcohols by cerium(IV).[21,26] The same mechanism seems to operate for all of these oxidative cleavages and as expected the α-hydroxy radicals are stable enough that alcohols which can form them (1,2-glycols) undergo rapid cleavage. The polar nature of the transition state for the cleavage reaction[21] also favors the cleavage of α-hydroxy radicals.

The favored mode of oxidative cleavages seems to be a one-electron process,[21,26,27] but the facile cleavage of 1,2-glycols by LTA is clearly a two-electron process. Most likely a facile two-electron cleavage will occur only if a special situation exists such as the possibility of forming a bidentate complex and going directly from this complex to stable organic products and a stable oxidation state of the oxidant.[12] The fact that alcohols which cannot meet these requirements undergo two-electron cleavages reluctantly[21,27] suggests that the slow oxidative cleavages by LTA of 1,2-glycols which cannot form bidentate complexes, such as *trans*-decalin-9,10-diol,[4a,13] are one-electron processes involving the intermediate formation of lead(III).

The limited results obtained with potassium periodate as oxidant are comparable to those obtained with LTA and indicate that periodate cleavage of 1,2-glycols proceeds by a mechanism similar to mechanism I, *i.e.*, one which involves a bidentate complex as an intermediate. This is in agreement with previous conclusions.[4a]

Recently the silver(I)-catalyzed cleavage of 1,2-glycols by peroxy disulfate was reported to be accomplished

(21) (a) P. M. Nave and W. S. Trahanovsky, *J. Amer. Chem. Soc.*, **90**, 4755 (1968); (b) *ibid.*, **93**, 4536 (1971).

(22) J. P. Cordner and K. H. Pausacker, *J. Chem. Soc.*, 102 (1953).

(23) Such a change in mechanism has been observed for the periodate oxidation of ethylene glycol and a series of methylated ethylene glycols.[24]

(24) F. R. Duke and V. G. Bulgrin, *J. Amer. Chem. Soc.*, **76**, 3803 (1954).

(25) J. S. Littler, *Tetrahedron*, **27**, 81 (1971).

(26) (a) W. S. Trahanovsky, P. J. Flash, and L. M. Smith, *J. Amer. Chem. Soc.* **91**, 5068 (1969); (b) W. S. Trahanovsky and J. Cramer, *J. Org. Chem.*, **36**, 1890 (1971).

(27) P. M. Nave and W. S. Trahanovsky, *J. Amer. Chem. Soc.*, **92**, 1120 (1970).

by two paths.[12] It was proposed that one path involves silver(II) which cleaves by mechanism II.

Ultilization of the above-mentioned techniques should provide a useful tool for determining the mechanism of other glycol cleaving reagents as well as giving some indication as to the stereochemistry of appropriate substrates.

Experimental Section

Methods and Materials.—Most equipment and methods have been previously described.[28] Glpc analysis was carried out on a Varian Aerograph 1700 gas chromatograph using a thermal conductivity detector and a 5 ft × 0.25 in. 20% SE-30 on Chromosorb W column.

CAN (Baker) was used as a solution in 85% aqueous acetic acid (1.0705 g/25 ml). The LTA (Analabs) solution was freshly prepared for each reaction by dissolving the solid (0.0375 g) in 85% aqueous acetic acid (5 ml). The solution was warmed to 50° before addition to the substrate mixture. The potassium periodate (Matheson Coleman and Bell) solution was freshly prepared for each reaction by dissolving the solid (0.0195 g) in water (7.5 ml). The aqueous solution, warmed to 50°, was then added to the mixture of substrates in glacial acetic acid (22.5 ml).

meso-**Hydrobenzoin** was prepared by the method of Fieser:[16] mp 135–136° (lit.[16] mp 136–137°); nmr ($CDCl_3$) δ 7.26 (s, 10), 4.81 (s, 2), and 2.70 (broad s, 2, $D_2O \rightarrow 0$).

meso-**4,4′-Dimethylhydrobenzoin** was prepared by the method of Fieser:[16] mp 143–145° (lit.[29] mp 145–146°); nmr (DMSO-d_6) δ 7.06 (s, 8), 4.96 (m, 2, $D_2O \rightarrow 0$), 4.54 (m, 2, $D_2O \rightarrow$ s), and 2.26 (s, 6).

meso-**4,4′-Dinitrohydrobenzoin** was prepared by the nitration of *meso*-diacetylhydrobenzoin[17] followed by hydrolysis of the diacetate: mp 232° (lit.[17] mp 231°); nmr (DMSO-d_6) δ 7.85 (AA′BB′ pattern, ν_a ~8.15, ν_b ~7.52, 8), 5.70 (broad s, 2, $D_2O \rightarrow 0$), and 4.79 (s, 2).

meso-**4,4′-Dichlorohydrobenzoin.**—4,4′-Dichlorobenzoin was prepared by the method of Lutz and Murphy[30] and reduced to the hydrobenzoin by the method of Fieser:[16] mp 109–110° (lit.[31] mp 151°); nmr ($CDCl_3$) δ 7.4 (AA′BB′ pattern, ν_a ~7.18, ν_b ~6.95, 8), 4.68 (s, 2), and 2.59 (s, 2).

meso-**4,4′-Dibromohydrobenzoin** was prepared by the method used to prepare the dichloro compound: mp (from 95% ethanol) 137–138°; nmr (DMSO-d_6) δ 7.29 (AA′BB′ pattern, ν_a ~7.62, ν_b ~7.16, 8), 5.38 (m, 2), and 4.53 (m, 2).

Anal. Calcd for $C_{14}H_{12}O_2Br_2$: C, 45.19; H, 3.25; Br, 42.95. Found: C, 45.10; H, 3.27; Br, 43.01.

meso-**3,3′-Dimethylhydrobenzoin** was prepared by the method used to prepare 4,4′-dichlorohydrobenzoin and purified by chromatography on a silica column, mp (from petroleum ether, bp 60–70°) 87–88°; nmr ($CDCl_3$) δ 7.05 (m, 8), 4.63 (broad s, 2), 2.29 (s, 6), and 2.17 (m, 2, $D_2O \rightarrow 0$). *Anal.* Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.41; H, 7.67.

meso-**3,3′-Dichlorohydrobenzoin** was prepared by the method used to prepare the 4,4′ isomer: mp (from benzene) 96–98° (lit.[31] mp 95°); nmr ($CDCl_3$) δ 7.07 (m, 8), 4.65 (s, 2), and 2.69 (broad s, 2).

dl-**Hydrobenzoin** was prepared by a modification of the method of Fieser.[16] Instead of purifying the crude diacetate by chromatography, it (*ca.* 2 g) was dissolved in 20 ml of carbon tetrachloride and 200 ml of petroleum ether and this solution was held at 0° for 24 hr, during which the diacetate crystallized from the solution: mp 119–120° (lit.[16] 120°); nmr ($CDCl_3$) δ 7.1 (m, 10), 4.6 (s, 2), and 3.21 (s, 2).

erythro-*O*-**Methylhydrobenzoin.**—*O*-Methylbenzoin was prepared by the method of Wren[18] and reduced to the monomethyl ether of hydrobenzoin with sodium borohydride, mp (from aqueous ethanol) 100° (lit.[32] 100–102°).

Procedure for Competition Experiments.—The two hydrobenzoins (5 × 10^{-4} mol of each) were dissolved in 85% aqueous acetic acid (28 ml for CAN, 25 ml for LTA, and 22.5 ml of glacial acetic acid for KIO_4) at 50°. To the rapidly stirred solution was added an aliquot (2 ml for CAN, 5 ml for LTA, and 7.5 ml for KIO_4) of the oxidant. The mixture was stirred at 50° for 20 min. All mixtures remained homogeneous throughout the reaction; the pale yellow color of Ce(IV) disappeared in about 1 min.

The reaction mixture was poured into water (25 ml) and extracted with benzene (2 × 25 ml). The conbined benzene extracts were washed with water (25 ml), saturated sodium bicarbonate (25 ml), and finally water (25 ml). The benzene layer was dried ($MgSO_4$) for 18 hr and filtered, and the benzene was removed on a rotary evaporator. To the residue was added 1 ml of benzene and the resultant solution was analyzed by glpc (three injections per run). The areas of the glpc peaks were determined by Xeroxing the traces and cutting and weighing the peaks. The thermal conductivity and extraction ratios were determined by preparing weighed mixtures of the authentic aldehydes in 85% aqueous acetic acid (30 ml) and performing identical extraction and area-determination procedure. At least three determinations were carried out for each standard.

Registry No.—CAN 12125-48-3; LTA, 546-67-8; KIO_4, 7790-21-8; *erythro*-*O*-methylhydrobenzoin, 6941-71-5.

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(28) W. S. Trahanovsky and M. P. Doyle, *J. Org. Chem.*, **32**, 146 (1967).
(29) J. Grimshaw and J. S. Ramsey, *J. Chem. Soc. C*, 653 (1966).
(30) R. E. Lutz and R. S. Murphy, *J. Amer. Chem. Soc.*, **71**, 480 (1949).
(31) H. D. Law, *J. Chem. Soc.*, **99**, 1115 (1911).
(32) J. C. Irvine and J. Weir, *ibid.*, **91**, 1390 (1907).

Reactions of Bismuth Triacetate with Organic Compounds

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Reaction of bismuth triacetate (1) with amines and alcohols at ~150° usually affords the respective N- and O-acetylated derivatives. Formates and formamides undergo reaction when heated with 1 at 200°; bismuth metal and the respective acetate or acetamide result. For example, formanilide is converted to acetanilide in 71% yield by this method. On the other hand, the reaction of 1 with propionanilide under these conditions does not lead to production of bismuth metal, and a mixture of amides results. Some variations of reactivity with structure are presented, and a possible reaction pathway is suggested.

In view of the elaborate elucidation of the utility of such heavy metal salts as lead tetraacetate, mercuric acetate, and thallium acetate in organic synthesis,[1] there seems a notable paucity of reports concerning the corresponding chemistry of salts of bismuth. This deficiency prompted us to study the reactions of bismuth triacetate (1) with some representative amines, alcohols, amides, and esters.

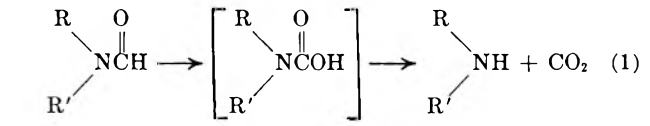
Bismuth triacetate has been a well-known compound for some 50 years. Early reports[2] were primarily concerned with its preparation and stability. More recently, it has been reported useful as a catalyst in industrial applications such as the vapor-phase conversion of acetylene to vinyl acetate,[3] a high-temperature preparation of phthalate esters,[4] and in the high-pressure air oxidation of various aliphatic hydrocarbons.[5] In 1951, Rigby reported[6] that acyloins were readily oxidized to 1,2 diketones with 1 in acetic acid (or with bismuth oxide in acetic acid) at about 100°, and suggested its general use as a mild oxidant for acyloins. Bismuth was the reduction product resulting from the bismuth(III) salt. On the other hand, refluxing solutions of other readily oxidizable substances such as hydrazine, formaldehyde, catechol, *p*-phenylenediamine, and glucose with bismuth oxide in acetic acid was claimed to give "negative results," although no effort apparently was made to isolate the products from these reactions. No other reactions of bismuth triacetate with organic substances have been reported which seem of general synthetic interest.

We initially observed that 1 reacts with formamides such as dimethylformamide (2) and formanilide (3) at bath temperatures of about 200° to produce the corresponding acetamides, with concomitant deposition of metallic bismuth. In most cases, the reaction seems complete within 24 hr. Generally, these reactions are carried out by heating an equimolar mixture of the two reactants without solvent, extracting the organic products, and purifying the organic residue after concentration of these extracts. A summary of the reactions of 1 with various formamides is shown in Table I.

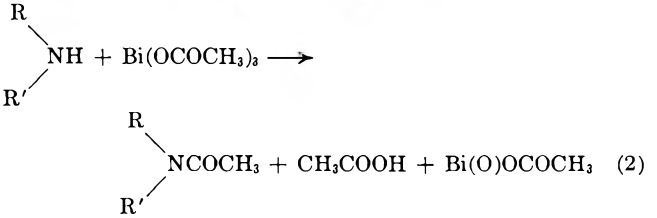
In these examples, it appears that the speed with which this reaction occurs is not a function of steric hindrance about nitrogen, since tertiary and secondary amines (*e.g.*, 4 and 3) appear to react equally readily. We believe that the slow rate of reaction of 1 with 2 is due to the fact that 2 boils at temperatures well below those we used to effect these reactions. Consequently, the temperature of the reaction mixture and the concentration of the amide in it were certainly lower than in the case of any of the other higher boiling amides shown; this would then lead to the lower apparent rate. On the other hand, the slow rate of conversion of diphenylformamide (7) does appear to be a true indication of the unreactive nature of 7 in the present reaction.

In order to test the applicability of this reaction to amides other than formamides, the interaction of 1 and propionanilide (8) was investigated. Following reaction of equimolar amounts of 1 and 8 at a bath temperature of 200° for 24 hr, formation of metallic bismuth could not be detected; the organic portion of the mixture appeared to be a mixture of starting material and acetanilide in roughly equal amounts. It thus appears that oxidation does not occur with typical amides other than formamides, although some acyl interchange clearly does result.

One likely hypothesis for the pathway of this reaction seemed to be the possibility that it proceeds *via* an amine intermediate, perhaps as shown below. In



(1)



(2)

this scheme, the carbamic acid, formed by oxidation of the formamide by bismuth(III), would be expected to decarboxylate readily, affording an amine which might then be acetylated by 1 *in situ*.

To test the viability of this hypothesis, several amines were treated with 1. Amines with appreciable nucleophilic character were found to react readily with 1 at temperatures at or below 150°, as shown in Table II.

Amines which were very reactive (such as 10 and 14) exhibited evidence of extensive decomposition when heated at 150°, and consequently these reactions

(1) See, for example, L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967.

(2) (a) E. Salkowski, *Biochem. Z.*, **79**, 96 (1917); (b) M. O. Kharmandar'yan, *J. Russ. Phys. Chem. Soc.*, **60**, 1477 (1928); (c) L. Cuny, *Bull. Sci. Pharmacol.*, **34**, 65 (1927).

(3) I. B. Vasil'eva, A. I. Gel'bshtein, I. N. Tolstikova, and W.-T. Tao, *Kinet. Katal.*, **5**, 144 (1964).

(4) J. R. Leebrick, W. J. Considine, and N. Kudisch, British Patent 1,010,175 (1965); *Chem. Abstr.*, **64**, 9645*e* (1966).

(5) C. S. Morgan, Jr., and N. C. Robertson, U. S. Patent 2,659,746 (1953); *Chem. Abstr.*, **49**, 1099*e* (1955).

(6) W. Rigby, *J. Chem. Soc.*, 794 (1951).

TABLE I

REACTIONS OF FORMAMIDES WITH BISMUTH TRIACETATE[a]

Compd	Name	Reactant ratio (1:amide)	Time, hr	Product	Yield, %[b]
2	Dimethylformamide	1:1	90[c]	Dimethylacetamide	69
3	*N*-Phenylformamide	1:1	24	*N*-Phenylacetamide	71
	N-Phenylformamide	1:2	24	*N*-Phenylacetamide	83
	N-Phenylformamide	1:3	24	*N*-Phenylacetamide	47.5
4	*N*-Methyl-*N*-phenylformamide	1:1	24	*N*-Methyl-*N*-phenylacetamide	80
5	*N*-Cyclohexylformamide	1:1	24	*N*-Cyclohexylacetamide	76
6	*N*-Formylpiperidine	1:1	30	*N*-Acetylpiperidine	69
7	*N*,*N*-Diphenylformamide	1:2	130[d]	*N*,*N*-Diphenylacetamide Diphenylamine	4.5[e]

[a] Reactions carried out at 200° unless otherwise noted. [b] Isolated yield of product after purification by distillation or recrystallization. [c] Reaction incomplete at 18, 40, and 60 hr. [d] Reaction carried out at 210–220°. [e] A 20% yield of sublimed diphenylamine was obtained prior to recrystallization.

TABLE II

REACTIONS OF AMINES WITH BISMUTH TRIACETATE[a]

Compd	Name	Temp, °C	Time, hr	Product	Yield, %[b]
9	Aniline	150	3	Acetanilide	86
10	*p*-Anisidine	105	24	*p*-Acetaniside	34
11	*p*-Bromoaniline	170	3.5	*p*-Bromoacetanilide	38
12	Benzylamine	150	2.5	*N*-Benzylacetamide	70
13	*p*-Nitroaniline	150	5	[c]	
14	Phenylhydrazine	80	24	Hydracetin	27
15	Hydrazobenzene	130[d]	3	Azobenzene	60

[a] Approximately equimolar amounts of reactants employed in all reactions. [b] After recrystallization of the product. [c] No obvious reaction; starting material recovered. [d] Carried out under nitrogen.

TABLE III

REACTION OF BISMUTH TRIACETATE WITH FORMATES AND ALCOHOLS[a]

Compd	Name	Temp, °C	Time, hr	Product	Yield, %[b]
16	Dodecanol	150	24	Dodecyl acetate	60
17	Benzyl alcohol	185	24	Benzyl acetate	58
18	Cholesterol	160	25	Cholesteryl acetate	48
19	Dodecyl formate	190	24	Dodecyl acetate	58
20	Benzyl formate	190	25	Benzyl acetate	72
21	Cholesteryl formate	190	48	Cholesteryl acetate	87

[a] Equimolar ratios of 1 to substrate employed. [b] After recrystallization or distillation of the product.

had to be run at lower temperatures. Reactivity appeared to be directly related to the nucleophilicity of the amine, and the very poor nucleophile **13** did not react at all. Not unexpectedly, oxidation rather than acetylation occurred with **15**, and azobenzene was the only observable product. The development of extensive color in many of these reactions and the highly variable yields of amides obtained contrasted with the results from the reaction of **1** with formamides.

Inasmuch as the formyl group was implicated as the oxidized moiety in the reactions of formamides with **1**, we then extended our investigation to consider the reactivity of **1** with alcohols and formate esters. The results of these experiments are summarized in Table III.

In these experiments, we found that bismuth metal was produced in the reaction of **1** with formates at temperatures of 190° with concomitant formation of the corresponding acetates, paralleling the results obtained in the reactions of **1** with formamides. Although we investigated only a few examples, there seems no reason why yields of 70–80% of the analogous acetate should not normally be expected in this reaction.

Alcohols reacted with **1** to form the respective acetates. The yields obtained from the reaction of **1** with various alcohols are generally lower than those from its reactions with the corresponding formates, although they do not appear to be variable in the way that yields from reactions of **1** with amines of different types are.

Discussion

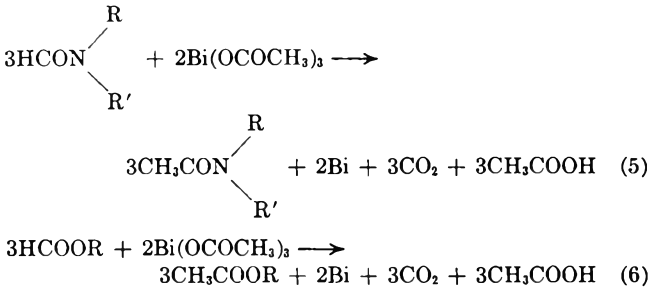
The inorganic residue isolated from the reactions of **1** with the amines and alcohols was identified as bismuthyl acetate. This enables us to propose the following overall representations for these two reactions.

$$Bi(OCOCH_3)_3 + HN(R)(R') \longrightarrow CH_3CON(R)(R') + Bi(O)OCOCH_3 + CH_3COOH \quad (3)$$

$$Bi(OCOCH_3)_3 + HOR \longrightarrow CH_3COOR + Bi(O)OCOCH_3 + CH_3COOH \quad (4)$$

Although carbon dioxide was not identified among the products of the reaction of **1** with formates and formamides, this seems the most reasonable result from the

oxidation–reduction reaction involved. Hence, these two overall reactions may be written as follows.



$$3HCONR_2 + 2Bi(OCOCH_3)_3 \longrightarrow 3CH_3CONR_2 + 2Bi + 3CO_2 + 3CH_3COOH \quad (5)$$

$$3HCOOR + 2Bi(OCOCH_3)_3 \longrightarrow 3CH_3COOR + 2Bi + 3CO_2 + 3CH_3COOH \quad (6)$$

Because reactions 3 and 4 seem to be examples of one type of reaction of **1**, whereas 5 and 6 are examples of a different type, each type of reaction is discussed separately below.

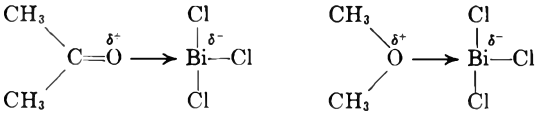
Reactions of 1 with Amines and Alcohols.—Inasmuch as it had been previously reported that **1** decomposes into bismuthyl acetate upon heating,[2a] it seemed attractive initially to postulate a two-step procedure in which acetic anhydride was produced from the decomposition of **1**, and that the anhydride subsequently acetylated the amine or alcohol in the reaction mixture, as shown (for a primary amine).

$$Bi(OCOCH_3)_3 \xrightarrow{\Delta} Bi(O)OCOCH_3 + (CH_3CO)_2O \quad (7)$$

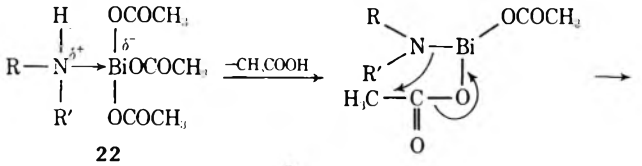
$$(CH_3CO)_2O + RNH_2 \longrightarrow CH_3CONHR + CH_3COOH \quad (8)$$

However, in our hands, bismuth acetate, when heated to temperatures as high as 190° under nitrogen (*i.e.*, in the absence of water), does not decompose. No acetic anhydride can be detected, and the ir spectrum of the salt remains unchanged. This makes this hypothesis seem improbable at best.

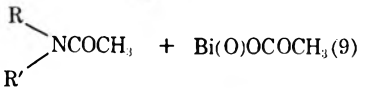
Recently, a number of complexes formed by reaction of organic substances with bismuth(III) salts have been reported.[7-10] These reflect the ability of the latter to function as Lewis acids; two examples may be represented as follows.[7]



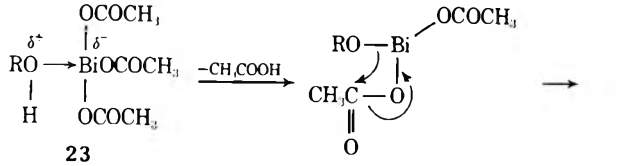
It seems reasonable to believe that reaction of amines and alcohols with **1** would afford initially the structures **22** and **23** analogous to the complexes shown above.



22



$$+ Bi(O)OCOCH_3 \quad (9)$$



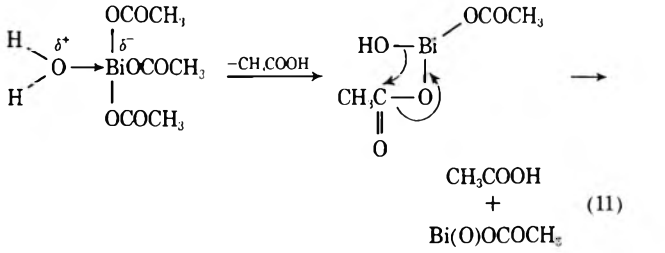
23

$$ROCOCH_3 + Bi(O)OCOCH_3 \quad (10)$$

(7) G. O. Doak, L. D. Freedman, and G. G. Long, "Kirk-Othmer Encyclopedia of Chemistry and Technology," 2nd ed, Vol. 3, 1964, p 535.

By elimination of the elements of acetic acid, followed by a four-centered reaction, these could then decompose to the observed products.

These reactions appear to be completely analogous to the reaction of **1** with water, which may be formulated in a similar way.

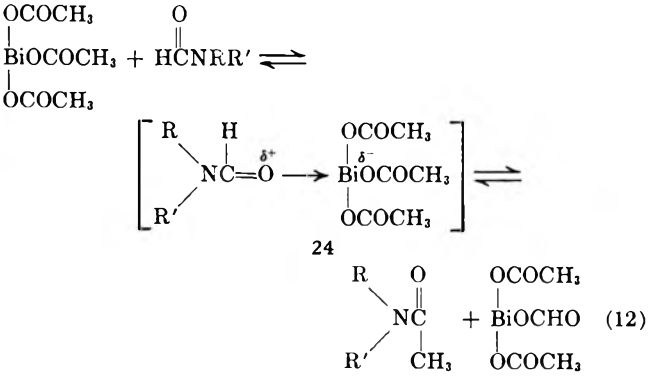


$$CH_3COOH + Bi(O)OCOCH_3 \quad (11)$$

Reactions of 1 with Formamides and Formates.—A hypothesis for the sequence of reactions involved in these transformations which initially appeared attractive involved initial oxidation of the formyl moiety to a carboxylic acid function, affording either a carbamate or a carbonate. These products would then be expected to readily lose carbon dioxide to afford the corresponding amine or alcohol; the latter could then be acetylated by additional **1** in the mixture, or perhaps by the acetic acid formed, as shown in eq 1 and 2, for a formamide example.

This sequence, however, predicts that no more than 3 mol of a formamide can react with 2 mol of bismuth triacetate, even if the latter does not itself acylate the amine. Additional excesses of the formamide should remain unattacked. However, in the reaction of **1** with formanilide (**3**), it was observed that a 2:1 ratio of **3** to **1** afforded an 83% yield of recrystallized acetanilide, even though, by this mechanism, a 75% yield is the maximum possible. The inescapable conclusion is that oxidation of the formyl group is *not* a necessary prerequisite to its replacement by an acetyl function. The additional observation that propionanilide also reacts with **1** to form substantial amounts of acetanilide in the product mixture, even though in this case no formyl group is present and no bismuth metal can be detected in the product mixture, also suggests that two different, unrelated reactions are being observed.

We believe, therefore, that **1**, through a reversible reaction with acyl groups (see eq 12), can effect acyl



24

$$+ BiOCHO \quad (12)$$

interchanges on amides and esters. In contrast with most such interchanges, the decomposition of the formyl group through its oxidation by bismuth(III) drives

(8) B. V. Tronov, A. A. Zhelnov, and G. V. Gavrilin, *Zh. Obshch. Khim.*, **37**, 576 (1967).

(9) S. J. Kuhn and J. S. McIntyre, *Can. J. Chem.*, **43**, 375 (1965).

(10) A. K. Mishra and K. N. Tandon, *Inorg. Chem.*, **10**, 1896 (1971).

this reaction to completion of exchange and the resultant relatively high yields observed in such cases.

A crystalline addition product directly analogous to the proposed intermediate **24** has been isolated from the reaction of dimethylformamide with bismuth(III) chloride at room temperature.[10] However, acyl interchanges of the type proposed have not previously been reported for bismuth salts.

This analysis does not preclude the possibility that *some* of the reaction takes place through initial oxidation of the formamide or formate. The fact that the acetylations of various amines by **1** which we investigated led to extremely variable yields and to highly colored by-products—in contrast to reactions of the latter with a variety of formamides—leads us to believe (in conjunction with our earlier reasoning) that this sequence is not likely to account for a very large portion of the reaction.

Continuing studies in these laboratories are directed toward investigating the nature of these reactions when other bismuth(III) salts are used. Our expectation is that such studies may clearly delineate the scope and allow more definitive mechanistic formulations for the reactions of bismuth(III) salts with various organic substances.

Experimental Section

Materials and Equipment.—Melting points were determined using a Hoover capillary melting point apparatus, and are corrected. Boiling points are uncorrected. Infrared spectra were obtained with a Beckman Model IR-8 spectrophotometer and absorptions are reported in inverse centimeters. Gas–liquid chromatography (glc) was carried out on a Bendix Model 2200 gas chromatograph equipped with an 8 ft × 0.125 in. stainless steel column packed with 10% Carbowax 20M, h.p., on Chromosorb W, 60–80 mesh, unless otherwise noted. Nuclear magnetic resonance spectra were obtained using a Varian Associates A-60A nuclear magnetic resonance spectrometer. All spectra are reported in parts per million relative to tetramethylsilane (δ).

Bismuth triacetate (**1**) was prepared from bismuth oxide following the procedure of Rigby,[6] and identified as authentic by comparison of its infrared spectrum[11] with that reported by Donaldson, *et al.*[12] The white crystals thus obtained were filtered, washed with ethyl acetate, and sucked dry. Prolonged passage of air through the crystals or heating of the crystals in a humid atmosphere led to loss of characteristic infrared absorption at 1550, 1030, and 950 cm^{-1}. A sample heated in this manner at 75° for 15 hr appeared to be bismuthyl acetate, $Bi(O)OCOCH_3$. *Anal.* Calcd for $C_2H_3BiO_3$: C, 8.45; H, 1.06. Found: C, 8.31; H, 0.98. Presumably this change is due to its reaction with moisture present in the air, since a sample of **1** appeared unchanged in its physical appearance and infrared spectrum after having been heated at 150° under a nitrogen atmosphere for 6.5 hr, contrary to a previous report of its thermal instability.[2a]

Reactions of 1 with Formamides. A. General Procedure.—An intimate mixture of 5.00 g (0.0143 mol) of formanilide and 15.94 g (0.0413 mol) of **1** was heated for 24 hr in a bath maintained at 200°. After the formanilide melted, the solution became mushy. After a few hours, an amber liquid began to form above a gray, mushy solid which gradually darkened and became more metallic. At the end of the reaction, this solid was almost wholly metallic.

The mixture was allowed to cool and was then triturated with two 50-ml portions of chloroform. The organic extracts were washed with saturated aqueous $NaHCO_3$ and evaporated to dryness, and the solid residue was then recrystallized from carbon tetrachloride. A second crop was obtained by concentration of the mother liquors, total yield, 3.96 g (71%), mp 111–113.5° (reported[13] mp 113.9–114.4°). The ir ($CHCl_3$) and nmr ($CDCl_3$) spectra of the product were identical with those of authentic acetanilide.

B. With Dimethylformamide (DMF).—A mixture of 10.0 g (0.137 mol) of DMF and 47.9 g (0.124 mol) of **1** was heated in a bath maintained at 200°. The mixture refluxed vigorously; gradually a yellowish liquid formed above a grayish solid mush. Prior studies of this reaction, employing equimolar amounts of **1** and DMF under the same conditions, had shown (based on glc analysis of the crude reaction mixture[14] and comparison of peak areas due to DMF and dimethyl acetamide) that conversion of DMF to dimethyl acetamide after 18, 40, 60, and 90 hr was, respectively, 22, 46, 70, and 100%. Consequently, the reaction mixture was allowed to cool after 90 hr and then extracted with two 75-ml portions of ether. The combined extracts were carefully concentrated to an oil, 500 ml of benzene was added, and any residual acetic acid was then removed by azeotropic distillation at atmospheric pressure. The residue was then fractionally distilled at a pressure of 19 mm to afford 2.2 g of pure dimethylacetamide, bp 60–69°, identical by ir spectrum (CCl_4) and glc retention time[14] with an authentic sample of dimethylacetamide. Two slightly higher boiling fractions, bp 69–71° (19 mm), showed, by glc analysis,[14] a peak identical in retention time with dimethylacetamide and a much smaller second peak with a longer retention time. Redistillation of these combined fractions afforded additional dimethylacetamide, bp 59–68° (18 mm), and, again, a fraction, bp 68–69° (18 mm), which exhibited two peaks on glc analysis.[14] This second peak was shown clearly not to be acetic acid, DMF, or acetic anhydride; attempted collection, however, failed and it was not conclusively identified. Total yield of distilled dimethylacetamide, including amounts calculated from the glc analysis of the high-boiling mixture isolated from the second distillation, was 8.25 g (69%).

C. With Diphenylformamide.—A mixture of 5.00 g (0.0254 mol) of *N*,*N*-diphenylformamide and 4.90 g (0.0127 mol) of **1** was heated in a bath maintained at 210–220° for 130 hr. The resultant solution was black; in addition, some bismuth metal had precipitated. The mixture was triturated with four 25-ml portions of chloroform; these extracts were decanted, filtered, combined, and concentrated to a black oily residue. This residue was then extracted with small portions of hot hexane. Further separation by decantation from oily residues which appeared on slight cooling was necessary; additional cooling of these hexane extracts afforded 0.51 g of brownish, flaky crystals in two crops, mp 96–100°.

The residues from this purification were again combined and reconcentrated. Hot petroleum ether (bp 30–60°) was added to the residue. Cooling afforded another crop of brownish crystals, mp 99.5–101°, and subsequent concentration of the mother liquors yielded still another crop, mp 99–101°. The total yield of these two crops of crystals was 0.69 g.

The crystals obtained from hexane showed no depression of melting point when mixed with those obtained from petroleum ether. The ir spectra ($CHCl_3$) of all of these crops of crystals were superimposable, and confirmed the identity of the samples as somewhat impure diphenylacetamide (reported[15] mp 101–102°). These spectra were similar to that of diphenylformamide, but differed in that a peak near 2900 cm^{-1} typical of formyl CH absorption was absent and a peak at 1375 cm^{-1} indicative of the new CCH_3 linkage was now present. The total yield of diphenylacetamide, mp 96–101°, was 1.20 g (22.4%).

The brown mother liquors from these crystallizations were placed in a small sublimation apparatus and sublimed at 0.5 mm (bath temperature 130°). A crystalline, whitish substance containing some brown specks, weight 0.875 g, mp 35–50°, sublimed from the residue and was collected. An ir spectrum ($CHCl_3$) of this sublimate showed only very weak absorption at 1665 cm^{-1}; in all other respects, the spectrum was identical with that of an authentic sample of diphenylamine. Recrystallization of the sublimate from hexane afforded a low yield of white crystals, mp 45.5–49°, with an ir spectrum identical with that of authentic diphenylamine, mp 53–55°.

Reaction of 1 with Propionanilide.—An intimate mixture of

(11) Obtained as a mull in Nujol.

(12) J. D. Donaldson, J. F. Knifton, and S. D. Ross, *Spectrochim. Acta*, **21**, 275 (1965).

(13) L. W. Winkler, *Arch. Pharm. (Weinheim)*, **266**, 45 (1928).

(14) Carried out on a Carbowax 20M column programmed at 100° for 7 min, then to 130° in 1 min, and 130° subsequently.

(15) O. Wallach and I. Kamensky, *Justus Liebigs Ann. Chem.*, **214**, 234 (1882).

5.00 g (0.0335 mol) of propionanilide and 12.96 g (0.0336 mol) of 1 was heated for 24 hr in an oil bath maintained at 200°. At the conclusion of this period, there was no evidence of bismuth metal in the reaction mixture. The mixture was allowed to cool, and was then extracted with three 50-ml portions of chloroform. The organic extracts were filtered, combined, washed with saturated aqueous $NaHCO_3$, and concentrated to afford a black, oily residue (4.99 g).

This residue was dissolved in hot carbon tetrachloride. Cooling of this solution afforded a brown, flocculent precipitate (1.52 g) which was filtered from the mother liquors. This brown solid was then extracted with hot hexane; the solution, on cooling, deposited whitish crystals (A), weight 0.41 g. The mother liquors obtained from filtration of the flocculent precipitate were concentrated, yielding, on cooling, a black, crystalline mass. Several recrystallizations of this mass from hexane afforded two additional crops of off-white crystals B, 1.65 g, and C, 0.33 g.

Solids A, B and C all exhibited melting points with a wide range in the area between 79 and 95°, and nmr ($CDCl_3$) of all three contained the same general features: δ 8.2 (s, NH), 7.35 (m, ArH), 2.33 (q, J = 7 Hz, CH_3CH_2CO- of propionanilide), 2.10 (s, CH_3CO- of acetanilide), and 1.17 (t, J = 7 Hz, CH_3-CH_2CO- of propionanilide). All of these peaks with these characteristics were observed in the nmr of pure acetanilide and/or propionanilide. Ratios of the integration of the area under the peak at 2.10 to that under the peak at 1.17 were found to be 40:60, 49:51, and 50:50 for A, B, and C, respectively. Since these areas should be proportionate measures of the population of each of the two amides, it seems clear that about half of the propionanilide was converted to acetanilide.

Reaction of 1 with Amines. Representative Procedure (Aniline).—A mixture of 1.18 g (0.0127 mol) of aniline and 3.94 g (0.0102 mol) of 1 was heated at 150° for 3 hr. The mixture was allowed to cool and was then extracted with three 30-ml portions of chloroform. These extracts were filtered and concentrated to afford a white, crystalline residue, yield after drying, 1.46 g (86%), mp 113.5–115° (reported[13] for acetanilide, mp 113.9–114.4°). An ir spectrum ($CHCl_3$) of the product was identical with that of authentic acetanilide. The inorganic solid remaining after initial extraction of the reaction mixture with chloroform was filtered and pressed dry. Its ir spectrum[11] was essentially the same as that of bismuthyl acetate, $Bi(O)OCOCH_3$, described earlier.

For more reactive amines, it was necessary to carry out the reaction at lower temperatures in a nitrogen atmosphere; thus, reaction of *p*-anisidine at 105° for 24 hr under nitrogen afforded a 34% yield of recrystallized *N*-acetyl-*p*-anisidine, mp 127–128.5°, undepressed on admixture with an authentic sample, ir ($CHCl_3$) identical with that of authentic *p*-acetanisidide.

Reaction of 1 with Hydrazobenzene.—A mixture of 0.421 g (2.29 mmol) of hydrazobenzene and 1.09 g (2.84 mmol) of 1 was heated at 130° under nitrogen for 3 hr. The mixture was then allowed to cool and was extracted with three 30-ml portions of chloroform. The organic extracts were filtered, combined, and concentrated, affording an orange, crystalline residue. Recrystallization of the solid product from an ethanol–water mixture afforded orange crystals (0.220 g, 53%) of azobenzene: mp 68–70°, undepressed on admixture with an authentic sample; ir ($CHCl_3$) identical with that of authentic azobenzene.

Reaction of 1 with Alcohols. Representative Procedure (Dodecanol).—A mixture of 2.10 g (0.0113 mol) of dodecanol and 4.82 g (0.0124 mol) of 1 was heated at 150° for 24 hr. After the mixture was allowed to cool, it was extracted with three 30-ml portions of methylene chloride. The residual inorganic solid was rinsed with methylene chloride and pressed dry; its ir spectrum[11] identified it as bismuthyl acetate. The organic extracts were washed with saturated aqueous $NaHCO_3$, concentrated, and distilled to afford 1.53 g (60%) of a clear, colorless liquid: bp 94° (0.30 mm) [reported[16] bp 139–140° (9 mm)]; ir ($CHCl_3$) 1750 (ester C=O), 1370 cm^{-1} (CH_3C).

Reaction of 1 with Formates. Representative Procedure (Cholesteryl Formate).—A mixture of 4.87 g (0.0126 mol) of 1 and 5.18 g (0.0125 mol) of cholesteryl formate was heated at 190° for 48 hr. After the reaction mixture was allowed to cool, the resultant mixture of bismuth metal and brown solid was extracted with three 30-ml portions of methylene chloride. The organic extracts were dried ($MgSO_4$) and concentrated to yield 5.05 g of a brown solid. This was recrystallized from 95% ethanol to afford 4.68 g (87%) of yellow-white crystals: mp 112–113.5° (reported[17] mp 114°); ir ($CHCl_3$) (identical with that of the product isolated from reaction of cholesterol with 1) exhibits increases in absorption at 1025, 1190–1250, and 1370 cm^{-1} compared with the spectrum of the starting formate; nmr (CCl_4) δ 1.94 (s, CH_3CO-). The addition of a small amount of benzoyl peroxide to a parallel reaction under conditions similar to these appeared to have no measurable effect on either the course or speed of the reaction.

Registry No.—1, 22306-37-2.

Acknowledgment.—The financial support of the National Science Foundation Undergraduate Research Participation Program for this work is gratefully acknowledged.

(16) M. Stoll and A. Rouvé, *Helv. Chim. Acta*, **27**, 950 (1944).
(17) A. H. Milburn and E. V. Truter, *J. Chem. Soc.*, 1736 (1956).

Fluorinated Cyclopropenes and Cyclopropenium Ions[1]

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Tetrachlorocyclopropene (1) was fluorinated with potassium fluoride in tetramethylenesulfone at 160–180° to give 1,2,3-trichloro-3-fluorocyclopropene (2), 1,2-dichloro-3,3-difluorocyclopropene (3), 1-chloro-2,3,3-trifluorocyclopropene (4), plus two ring-opened products, the pentafluoropropene 5 and the pentafluoropropane 6. Tetrabromocyclopropene (7) was fluorinated under similar conditions to give 1,2-dibromo-3,3-difluorocyclopropene (8), 1-bromo-2,3,3-trifluorocyclopropene (9), 5, and 6. The fluorocyclopropenes 3, 4, 5, and 6 reacted with antimony pentafluoride to give the fluorocyclopropenium hexafluoroantimonates, 15, 16, 17, and 18, respectively. The physical properties of the compounds herein described are compared with those of analogous, known species. A mechanism for the fluorination of 1 and 7 by potassium fluoride is proposed.

The Preparation of Fluorocyclopropenes.—Tetrachloro- and tetrabromocyclopropenes 1 and 7 undergo halogen exchange readily in the presence of Lewis acids through the intermediacy of the corresponding trihalocyclopropenium ions, which have been isolated and studied in some detail.[2] Thus tetrachlorocyclopropene (1) reacts with an excess of boron tribromide to give tetrabromocyclopropene (7).[3] Both 1 and 7 can be fluorinated at the allylic position by antimony trifluoride to give 1,2,3-trichloro-3-fluorocyclopropene

(1) Taken in part from the Ph.D. thesis of D. C. F. Law, University of Wisconsin, 1967, also presented at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, Abstract of Papers, S52.

(2) R. West, A. Sadô, and S. W. Tobey, *J. Amer. Chem. Soc.*, **88**, 2488 (1966).
(3) S. W. Tobey and R. West, *ibid.*, **88**, 2481 (1966).

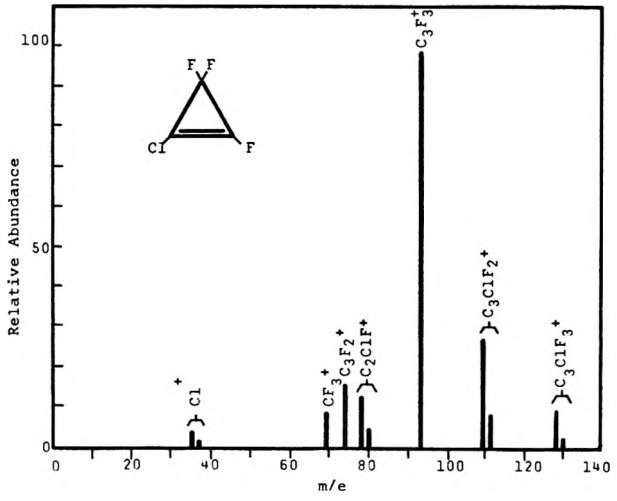


Figure 1.—Mass spectrum of 1-chloro-2,3,3-trifluorocyclopropene (4).

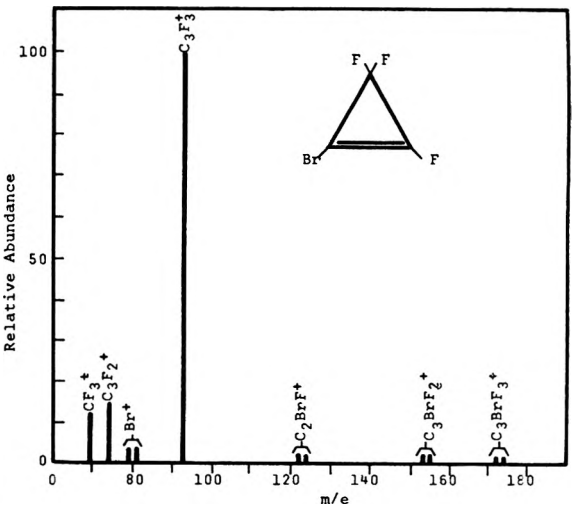
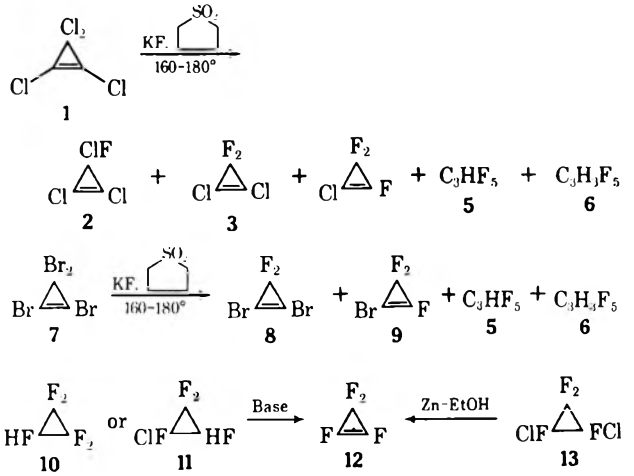


Figure 2.—Mass spectrum of 1-bromo-2,3,3-trifluorocyclopropene (9).

(2), 1,2-dichloro-3,3-difluorocyclopropene (3), and 1,2-dibromo-3,3-difluorocyclopropene (8), respectively.[3]

Since the fluorination of 1 and 7 by antimony trifluoride effects halogen exchange at the allylic position only without affecting the vinylic halogens, we decided to investigate the same reaction using a nucleophilic fluorinating reagent. With potassium fluoride in tetramethylenesulfone at 180°, fluorination of 1 and 7 occurred not only at the allylic position, but also at one of the vinylic positions. Thus tetrachlorocyclopropene (1) reacted to yield 2, 3, 1-chloro-2,3,3-trifluorocyclopropene (4), and two ring-opened products, the pentafluoropropene 5 and the pentafluoropropane 6 (the last two compounds have not been completely characterized). Under similar conditions, tetrabromocyclopropene (7) was fluorinated by potassium fluoride to give 1,2-dibromo-3,3-difluorocyclopropene (8), 1-bromo-2,3,3-trifluorocyclopropene (9), 5, and 6.

After this work was completed, Sargeant and Krespan reported that tetrafluorocyclopropene (12) was prepared by the dehydrohalogenation of pentafluorocyclopropane (10) or 1-chloro-1,2,2,3-tetrafluorocyclopropane (11), and most conveniently by the dechlorination of 1,2-dichloro-1,2,3,3-tetrafluorocyclopropane (13).[4]



(4) P. B. Sargeant and C. G. Krespan, *J. Amer. Chem. Soc.*, **91**, 415 (1969).

Therefore, except for the iodocyclopropenes, which are expected to be very unstable,[5] most of the perhalocyclopropenes have now been prepared and characterized.

The Properties of Fluorocyclopropenes.—1,2,3-Trichloro-3-fluorocyclopropene (2), bp 96°, 1,2-dichloro-3,3-difluorocyclopropene (3), bp 58°, and 1,2-dibromo-3,3-difluorocyclopropene (8), bp 105°, were identified by their boiling points, ir, and ^{19}F nmr data, which are identical with those of the authentic samples previously reported.[3] The structural assignments of 1-chloro-2,3,3-trifluorocyclopropene (4), bp 28°, and 1-bromo-2,3,3-trifluorocyclopropene (9), bp 38°, are based on evidence described below.

The mass spectra of 4 and 9 are shown in Figures 1 and 2, respectively. The fragmentation patterns of 4 and 9 are very similar except that species containing a chlorine are relatively more abundant than those containing a bromine. Both 4 and 9 give base peaks corresponding to the rearrangement ion, $C_3F_3^+$ (*m/e* 93), and molecular ions corresponding to $C_3ClF_3^+$ (*m/e* 128) and $C_3BrF_3^+$ (*m/e* 172, 174), respectively.

The infrared spectra of 4 and 9 are strikingly similar (see Experimental Section). The bands at 1860 and 1850 cm^{-1} shown by 4 and 9, respectively, can be attributed to the C=C stretching vibration and may be compared to the corresponding ir active bands found for other cyclopropenes (Table I). Among the per-

TABLE I
CARBON–CARBON DOUBLE BOND STRETCHING VIBRATION FREQUENCIES OF CYCLOPROPENES

Cyclopropene	$\nu_{C=C}$, cm^{-1}
C_3H_4	1641[a]
C_3Br_4 (7)	1757
C_3Cl_4 (1)	1810
C_3Cl_3F (2)	1820
C_3BrF_3 (9)	1850
C_3ClF_3 (4)	1860
C_3F_4 (12)	1945[b]

[a] Reference 6. [b] Reference 4.

halocyclopropenes, hypsochromic shifts of the C=C stretching frequency accompany a decrease in the mass

(5) An unsuccessful attempt to prepare 1,2-diiodo-3,3-dichlorocyclopropene was reported by H. M. Cohen and A. H. Keough, *J. Org. Chem.*, **31**, 3428 (1966).

of the halogen substituents. A parallel mass effect is also observed in some vibrational frequencies of the perhalocyclopropenium ions (see Table IV).

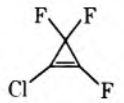
The ^{19}F nmr data of the fluorocyclopropenes are summarized in Table II. The ^{19}F nmr spectrum of **4**

TABLE II
^{19}F NMR DATA FOR FLUOROCYCLOPROPENES

Cyclopropene	Chemical shift, ppm	J_{F-F}, cps	$J_{^{13}C-F}$, cps
 **2**	99.8		
 **3**	99.8		292
 **8**	98.1		320 ± 5
 **4**	(a) 98.5 (doublet) (b) 127.8 (triplet)	41.4	(a) 292.8 (b) 445.2
 **9**	(a) 97.2 (doublet) (b) 124.2 (triplet)	41.1	(a) 292.9 (b) 444.5
 **12**	(a) 96.7 (triplet)[a] (b) 145.1 (triplet)	43.5	

[a] Reference 4.

is consistent with the structure of 1-chloro-2,3,3-trifluorocyclopropene, but excludes the alternative isomeric structure, 3-chloro-1,2,3-trifluorocyclopropene (**14**). The two allylic fluorines of **4** appear as a doublet

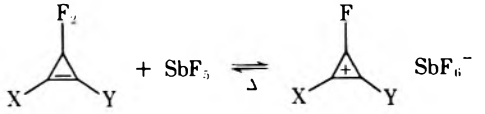

14

(J_{F-F} = 41.4 cps) at 98.5 ppm, which is consistent with the chemical shifts of allylic fluorines in other fluorocyclopropenes (see Table II). The vinylic fluorine of **4** appears as a triplet at 127.8 ppm. The unknown isomer **14** would be expected to show a doublet for the vinylic fluorines at *ca.* 145 ppm, and a triplet for the allylic fluorine at *ca.* 99 ppm. Furthermore, the pattern of the satellites due to $^{13}C-^{19}F$ couplings in the spectrum of **4** provides definitive proof of the assigned structure, as they consist of a pair of doublets about the main doublet ($J_{^{13}C-F}$ = 292.8 cps) and a pair of triplets about the main triplet ($J_{^{13}C-F}$ = 445.2 cps). In the case of structure **14**, the satellites of the main doublet would be expected to appear as a pair of quartets owing to the nonequivalence of the vinylic fluorines in the ^{13}C-labeled species. The structure of **9** can also be unambiguously assigned on similar ^{19}F nmr evidence (see Table II). The $^{13}C-^{19}F$ and $^{13}C-^{12}C-^{19}F$ spin–spin couplings in fluorocyclopropenes are relatively insensitive to the variation of halogen substituents on the ring, as shown by the data in Table III.

Diels–Alder reactions of all the perhalocyclopropenes mentioned above have already been reported.[6,7] It is interesting to note that the relative rate-enhancing effect of halogen substituents on the cyclopropene's dienophilic reactivity toward furan is Br > Cl > F. This trend is consistent with the observation that small ring systems are stabilized by fluorine substitution relative to chlorine substitution.[7]

Fluorocyclopropenium Ions.—Cyclopropenium ions are now well known as stable aromatic species with two π electrons, and a variety of more or less stable salts of substituted cyclopropenium ions have been prepared,[8] including some perhalocyclopropenium salts.[3,4]

When the fluorocyclopropenes **3**, **4**, **8**, and **9** were treated with antimony pentafluoride, an allylic fluorine was removed from the cyclopropene and the corresponding trihalocyclopropenium hexafluoroantimonates, **15**, **16**, **17**, and **18**, could be isolated. These complexes are the first examples of stable, unsolvated fluorocarbonium ion salts. Sargeant and Krespan also reported that **12** reacted with antimony pentafluoride to give the complex **19** in antimony pentafluoride solution.[4]



3. X = Y = Cl — 15, X = Y = Cl
4. X = Cl; Y = F — 16, X = Cl; Y = F
8. X = Y = Br — 17, X = Y = Br
9. X = Br; Y = F — 18, X = Br; Y = F
12. X = Y = F — 19, X = Y = F

That the integrity of the three-member ring is preserved in these complexes is proved by the observation that upon gentle heating, the original tetrahalocyclopropenes could be regenerated from the corresponding complexes. Further proof is provided by ir, ^{19}F nmr, and chemical evidence (*vide infra*).

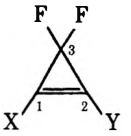
The infrared spectra of the cyclopropenium ion salts are listed in the Experimental Section. The solvent, antimony pentafluoride, has no absorptions between 4000 and 800 cm^{-1} but absorbs strongly below 750 cm^{-1}. In each spectrum, bands due to the parent cyclopropenes are entirely absent. The infrared spectra of **15** and **17**, and of **16** and **18**, are very similar, indicating that the infrared absorption is due principally to C–C and C–F modes. Frequencies of the two vibrational fundamentals characteristic of perhalocyclopropenium ions are listed in Table IV. For trichlorocyclopropenium ion, the band at 1791 cm^{-1} is the totally symmetric ring stretching mode, of class A, inactive in the infrared but observed in the Raman spectrum.[2] The lowered symmetry of the partly fluorinated cyclopropenium ions allows observation of the corresponding band in the infrared. The lower frequency band, at 1312 cm^{-1} in $C_3Cl_3^+$, is assigned to a mode involving mostly ring expansion and compression.[2] Both bands shift somewhat to higher frequencies as the heavier halogens are replaced by fluorine.

The ^{19}F nmr data for the fluorocyclopropenium ions in either SO_2 or SO_2–SbF_5 solutions are summarized in Table V. In all cases, a singlet between 62.0 and 63.6 ppm (referenced to external trichlorofluoro-

(6) K. B. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, **83**, 1266 (1961).
(7) D. C. F. Law and S. W. Tobey, *ibid.*, **90**, 2376 (1968).
(8) For a review of cyclopropenium ion chemistry, see A. W. Krebs, *Angew. Chem., Int. Ed. Engl.*, **4**, 10 (1965).

TABLE III

^{13}C–F AND ^{13}C–C–F COUPLINGS IN FLUORINATED TETRAHALOCYCLOPROPENES



X	Y	C_3–F J, cps	C_3–F I.S.,[a] ppm	C_2–F J, cps	C_2–F I.S., ppm	C_1–C_3–F J, cps	C_1–C_3–F I.S., ppm	C_1–C_2–F J, cps	C_1–C_2–F I.S., ppm	C_2–C_3–F J, cps	C_2–C_3–F I.S., ppm	C_3–C_2–F J, cps[b]
Cl	F	292.8	0.123	445.2	0.116	20.6	0.023	20.6	0.051	15.3	0.028	7.5
Cl	Cl	293.3	0.123			17.5	0.025			17.5	0.025	
Br	F	293.0	0.123	444.6	0.117	21.4	0.021	17.8	0.049	14.9	0.028	7.7
Br	Br	320 ± 5										

[a] I.S. = isotopic shift. [b] Maximum possible, J = 10.5 cps; minimum possible, J = 4.5 cps.

TABLE IV

CHARACTERISTIC VIBRATIONAL FREQUENCIES OF TRIHALOCYCLOPROPENIUM IONS

Cyclopropenium ion	Band 1, cm^{-1}	Band 2, cm^{-1}
$C_3Cl_3^+$	1791[a]	1312[a]
$C_3Cl_2F^+$ (15)	1880	1400 (broad)
$C_3ClF_2^+$ (16)	1960	1450
$C_3Br_3^+$		1276[a]
$C_3Br_2F^+$ (17)	1870	1390, 1370 (doublet)
C_3BrF_2 (18)	1940	1420

[a] Reference 2.

TABLE V

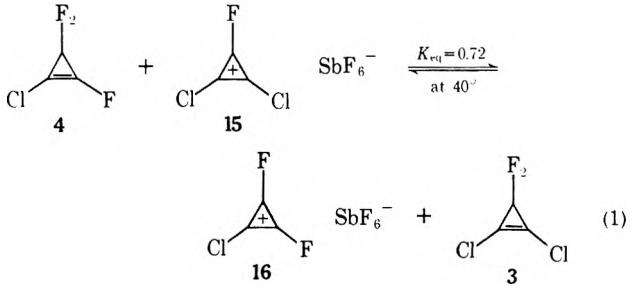
^{19}F NMR DATA OF FLUORINATED TRIHALOCYCLOPROPENIUM IONS

Cyclopropenium ion	Chemical shift, ppm
$C_3Cl_2F^+$ (15)	63.39
$C_3ClF_2^+$ (16)	63.58[a]
$C_3Br_2F^+$ (17)	62.0
$C_3BrF_2^+$ (18)	62.6
$C_3F_3^+$ (19)	63.1[b]

[a] $J_{^{13}C-F}$ = 458 cps; J_{F-F} = 3.5 cps. [b] Reference 4.

methane) was observed which does not change significantly in the temperature range −70 to 40°. For example, $C_3ClF_2^+SbF_6^-$ (16), dissolved in SO_2, shows a singlet at 63.58 ppm which is due to the two equivalent fluorines in $C_3ClF_2^+$, and a pair of satellites about the main singlet ($J_{^{13}C-F}$ = 458 cps). Each of the satellites consists of a doublet due to spin–spin coupling of adjacent fluorines (J_{F-F} = 3.5 cps). The observation of ^{13}C–F spin–spin coupling at room temperature is conclusive evidence that the spectrum is due to the fluorocyclopropenium ion alone and that fluorine exchange between the latter and SbF_6^- is slow relative to the nmr time scale.[9] We failed to observe a signal due to SbF_6^-, probably because of rapid fluorine exchange between the latter and a certain amount of SbF_5 present in the sample, with resultant broadening of the fluorine resonance signal.[10]

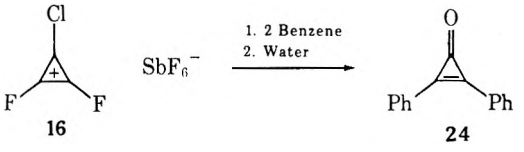
When a mixture of 1-chloro-2,3,3-trifluorocyclopropene (4) and 1,2-dichloro-3-fluorocyclopropenium hexafluoroantimonate (15) was dissolved in SO_2 in a sealed tube, an equilibrium mixture of 4, 15, 16, and 3 was established rapidly and the ^{19}F nmr spectrum due to each species was observed individually, indicating that fluorine exchange between the fluorocyclopropenes and the fluorocyclopropenium ions is also slow relative to the nmr time scale. The equilibrium constant, K_{eq}, for the following reaction (eq 1) was determined



by the integrated nmr spectral intensities to be 0.72 at 40°.

The ^{19}F nmr signal of the fluorines in the fluorocyclopropenium ions is shifted downfield by 35 ± 1 ppm from the allylic fluorines and by 61–82 ppm from the vinylic fluorines in the corresponding fluorocyclopropenes (*cf.* Table II and Table IV). These downfield shifts are consistent with the deshielding effect observed in other fluorocarbonium ions such as difluorophenyl- and fluorodiphenylcarbonium ions.[11]

1-Chloro-2,3-difluorocyclopropenium hexafluoroantimonate (16) underwent Friedel–Craft reaction with an excess of benzene followed by hydrolysis to give diphenylcyclopropenone (24).[12] Similar reactions of



trichloro- and tribromocyclopropenium ions with aromatic compounds have been reported.[13]

Discussion

The halogen substituents on the perhalocyclopropenes are either allylic or vinylic. Under the conditions used in our investigation, the displacement of the allylic halogens (from here on, the term halogen refers to chlorine or bromine as distinguished from fluorine) by fluoride ions could conceivably arise *via* SN1, SN2, SN2′, or a carbanion mechanism analogous to a nonconcerted "SN2′" reaction. However, an SN2 mech-

(9) N. S. Ham, E. A. Jeffery, T. Mole, and S. N. Stuart, *Chem. Commun.*, 254 (1967).

(10) Sargeant and Krespan also failed to observe a signal due to SbF_6^-; see ref 4.

(11) G. A. Olah, C. A. Cupas, and M. B. Comisarow, *J. Amer. Chem. Soc.*, **88**, 362 (1966).

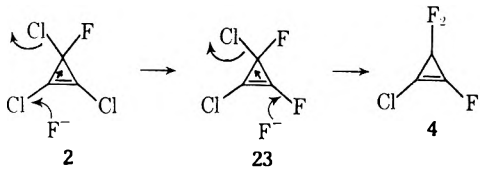
(12) R. Breslow, T. Eicher, A. Krebs, R. A. Peterson and J. Posner, *ibid.*, **87**, 1320 (1965).

(13) (a) R. West, D. Zecher, and W. Goyert, *ibid.*, **92**, 149 (1970); (b) R. West, D. Zecher, and S. W. Tobey, *ibid.*, **92**, 168 (1970).

anism is highly unlikely because of the excessive steric strain that would develop in the transition state involving a three-membered ring.[14] On the other hand, there is indirect evidence to suggest that the SN1, SN2′, or carbanion mechanisms might play a role either individually or collectively.

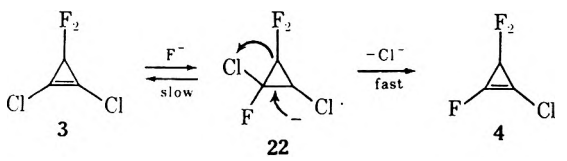
The SN1 pathway would involve the initial ionization of an allylic halogen to form an aromatic trihalocyclopropenium ion, the stability of which has been demonstrated (*vide supra*). The observation that the hydrolysis of **1** in 75% dioxane–25% water in the presence of excess hydroxide ion followed first-order kinetics[15] also lends support to the SN1 mechanism in the fluorination of **1** or **7** by potassium fluoride in the strongly polar solvent tetramethylenesulfone.

At present, no data are available for our system or analogous systems to distinguish between a truly concerted SN2′ mechanism and an analogous, nonconcerted mechanism involving a carbanion intermediate. Either of these mechanisms might be involved, since it is well known that nucleophilic attack of perhalocycloalkenes (having four, five, and six carbons) by alkoxide ions may result in displacement with rearrangement of the double bond.[16–18] Such reactions could lead to a hitherto unobserved product **23** through



the attack of **2** by fluoride. The absence of **23** can be explained by the extreme susceptibility of a fluorine-carrying trigonal carbon toward nucleophilic attack.[17] Thus any **23** formed would be expected to react rapidly with fluoride to give **4**. The latter, though possessing also a fluorine-carrying trigonal carbon, should be less reactive than **23** toward fluoride because it has no labile halogen to be displaced (*vide infra*) and is therefore isolable.

The displacement of a vinylic halogen in a perhalocyclopropene by a fluoride ion could arise through the initial addition of the fluoride to the double bond to form a carbanion intermediate, followed by the elimination of a halide ion from an adjacent carbon, as for example in the sequence **3**, **22**, and **4**. A similar mechanism has



been postulated to explain the nucleophilic attack of perhalocycloalkenes (having four, five and six carbons) by alkoxide ions.[16–18]

(14) E. L. Eliel in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 122.

(15) S. W. Tobey and A. M. McGinnis, presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 9–14, 1967, Abstracts of Papers, 0–153.

(16) J. D. Park, J. R. Lacher, and J. R. Dick, *J. Org. Chem.*, **31**, 1117 (1966).

(17) J. D. Park, R. J. McMurtry, and R. Sullivan, *ibid.*, **33**, 33 (1968).

(18) A. B. Clayton, J. Roylance, D. R. Sayers, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 7358 (1965).

On the basis of exchange reactions of various "haloforms,"[19] the stabilization of carbanions by α substituents is in the order I $\sim$ Br > Cl > F > OEt while nmr studies[20] have established the following order of "apparent electron-withdrawing power" for α substituents: I > Br > Cl > F $\gg$ CF_2Br > CF_2Cl > CF_3. The attack on **4** or **9** by fluoride would necessarily be directed exclusively at the fluorine-carrying trigonal carbon because the developing negative charge could be stabilized by the chlorine or bromine at the adjacent carbon. The fate of the resulting carbanions, which have no labile leaving group for elimination, is apparently ring opening, leading eventually to **5** and **6**.

In contrast, chlorinated cyclopentenes and cyclohexenes, which have no tendency to ring open, can undergo relatively facile and complete fluorination by potassium fluoride. Maynard reported that, under conditions similar to ours, perchlorocyclopentene (**26**) was completely fluorinated to give perfluorocyclopentene (**27**) in *ca.* 74% yield, while 1,2-dichloro-3,3,4,4,5,5,6,6-octafluorocyclohexene (**28**) gave perfluorocyclohexene (**29**) in 71% yield.[21] As the steric strain of the cyclic compounds increases by the introduction of more double bonds, fluorination apparently becomes more difficult and less complete. Thus 1,2,4,5-tetrachloro-3,3,6,6-tetrafluoro-1,4-cyclohexadiene (**30**) reacted with potassium fluoride to give a mixture of perfluoro-1,4-cyclohexadiene (**31**) (10% yield) and 1-chloro-2,3,3,4,5,5,6,6-heptafluoro-1,4-cyclohexadiene (**32**) (10% yield), whereas perchlorocyclopentadiene (**33**) gave only intractable resinous products.[21]

Experimental Section

Materials.—Tetrachlorocyclopropene (**1**) and tetrabromocyclopropene (**7**) were prepared by the method of Tobey and West.[2] Tetramethylenesulfone was obtained from Eastman Organic Chemicals and was dried over calcium hydride and distilled under vacuum before use. Anhydrous potassium fluoride was obtained from Allied Chemical and dried by heating at 150° under vacuum for 4 hr before use. Antimony pentafluoride was obtained from Allied Chemical Corp. and distilled under a nitrogen atmosphere (bp 140°, lit. bp 149.5°) before use. Anhydrous sulfur dioxide was obtained from Matheson Chemical Co. and used directly from the cylinder.

Instrumentation.—Infrared spectra were obtained on a Perkin-Elmer 237 spectrophotometer. The fluorocyclopropenes were sampled in a 10-cm gas cell equipped with sodium chloride windows at a pressure of about 4 Torr. The ir spectra of the fluorocyclopropenium hexafluoroantimonates were taken as solutions in antimony pentafluoride as a film between Irtran 2 (zinc sulfide) plates. Mass spectra were determined on a CEC 21-110 spectrometer. ^{19}F nmr spectra were obtained on a Varian A56-60 spectrometer at 56.4 MHz. All chemical shifts are referenced to external trichlorofluoromethane. Some of the ^{13}C–^{19}F spin–spin coupling data were obtained on a Varian HA-100 nmr spectrometer at 94.1 MHz. Gas chromatographic separations employed a 20 ft × 0.25 in. stainless steel column packed with 30% dinonyl phthalate on 45–60 mesh Chromosorb W.

The Fluorination of Tetrachlorocyclopropene (1).—Anhydrous potassium fluoride (63.6 g, 1.1 mol) and dry tetramethylenesulfone (130 ml) were placed in a 500-ml three-necked flask equipped with a Teflon blade stirrer, an addition funnel, and an air-cooled reflux condenser, the outlet of which was connected to a series of two cold traps immersed in solid carbon dioxide–acetone and liquid nitrogen, respectively. The flask was half immersed

(19) (a) J. Hine, N. W. Burske, M. Hine, and P. B. Langford, *J. Amer. Chem. Soc.*, **79**, 1406 (1957); (b) J. Hine, R. Wiesboeck, and R. G. Ghirardelli, *ibid.*, **83**, 1219 (1962); (c) L. H. Slaugh and E. Bergman, *J. Org. Chem.*, **26**, 3158 (1961).

(20) G. V. D. Tiers, *J. Amer. Chem. Soc.*, **78**, 2914 (1956).

(21) J. T. Maynard, *J. Org. Chem.*, **28**, 112 (1963).

in an oil bath which was maintained at 160–180°, while a slow stream of dry nitrogen was passed into the addition funnel, through the flask, the condenser, the cold traps, and out of a bubble counter filled with mineral oil. A solution of tetrachlorocyclopropene (1) (33.4 g, 0.188 mol) in 20 ml of tetramethylenesulfone was slowly added from the addition funnel into the flask with vigorous stirring over a period of 5 hr. About 5 ml of liquid product was collected in the cold traps and subsequently fractionated through a 10-cm Vigreux column. As the crude product warmed to room temperature, a gaseous distillate was collected in a Dry Ice trap and subsequently analyzed by gas chromatography. The following liquids boiling above room temperature were obtained by distillation.

1-Chloro-2,3,3-trifluorocyclopropene (4) had bp 28° (2 g, 7%); mol wt 128 (mass spectrum); ir (gas) 1860 (m), 1360 (s), 1290 (m), 1210 (s), 1120 (s), 880 (m), and 840 cm^{-1} (m); ^{19}F nmr, a doublet at 98.5 (2 F) and a triplet at 127.8 ppm (1 F), J_{F-F} = 41.4 cps.

1,2-Dichloro-3,3-difluorocyclopropene (3) had bp 58° (2.5 g, 8%); ir (gas) 1330 (s), 1300 (w), 1130 (w), 1100 (s), 850 (m), and 760 cm^{-1} (m); ^{19}F nmr, a singlet at 99.8 ppm.

1,2,3-Trichloro-3-fluorocyclopropene (2) had bp 96° (2.5 g, 7%); ir (liquid film) 1820 (w), 1270 (w), 1270 (w), 1240 (m), 1150 (w), 1095 (s), 1070 (w), 960 (s), 760 (w), and 700 cm^{-1} (s); ^{19}F nmr, a singlet at 99.8 ppm.

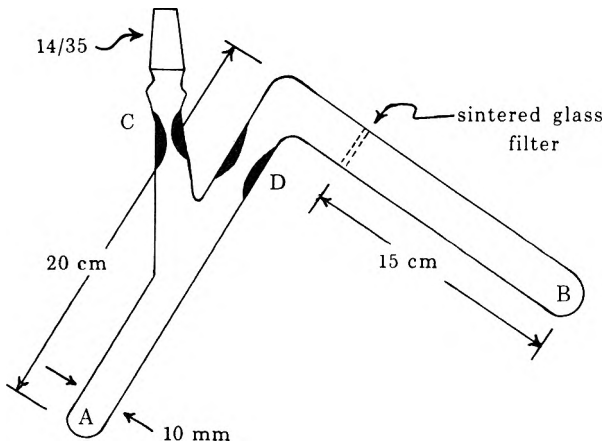
Two gaseous products were isolated by glc: the pentafluoropropene 5, mol wt 132 (mass spectrum), ir (gas) 1760 (s), 1370 (s), 1330 (s), 1250 (w), 1170 (m), 1110 (s), 930 (s), and 890 cm^{-1} (w); and the pentafluoropropane 6, mol wt 133 (mass spectrum), ir (gas) 1530 (w), 1410 (m), 1320 (m), 1250 (s), 1180 (w), 1120 (m), 970 (m), 920 (w), 840 (w), and 790 cm^{-1} (w).

The Fluorination of Tetrabromocyclopropene (7).—The apparatus and procedure are the same as described in the preceding section. A solution of tetrabromocyclopropene (7) in 20 ml of tetramethylenesulfone was slowly added with vigorous stirring to a mixture of anhydrous potassium fluoride (44.5 g, 0.768 mol) and 130 ml of tetramethylenesulfone at 160–180° under a nitrogen stream. About 5 ml of liquid product was collected in the cold traps. Separation by glc and distillation of the crude product gave, in addition to 5 and 6, the following fluorocyclopropenes.

1-Bromo-2,3,3-trifluorocyclopropene (9) had bp 38° (1.55 g, 7%); mol wt 172, 174 (mass spectrum); ir (gas) 1850 (s), 1390 (w), 1365 (s), 1295 (m), 1275 (m), 1240 (w), 1200 (s), 1145 (m), 1115 (s), 880 (m), and 820 cm^{-1} (m); ^{19}F nmr, a doublet at 97.2 ppm (2 F) and a triplet at 124.2 ppm (1 F, J_{F-F} = 41.1 cps).

1,2-Dibromo-3,3-difluorocyclopropene (8) had bp 105° (2.1 g, 7%); ir (gas) 1325 (s), 1110 (s), 1090 (w), 835 (m), 820 (w), and 740 cm^{-1} (w); ^{19}F nmr, a singlet at 98.1 cps.

The Preparation of Fluorocyclopropenium Hexafluoroantimonates.—Analytically pure samples of the fluorocyclopropenium hexafluoroantimonates were prepared by means of the Pyrex device shown below.



One volume (*ca.* 0.5 ml) of freshly distilled antimony pentafluoride was placed in arm A of the device, which was then attached to a vacuum line through the 14/35 joint, and four volumes of a fluorocyclopropene and eight volumes of sulfur dioxide were successively condensed into arm A at liquid nitrogen temperature. The device was then sealed off under vacuum at the thickened part, C. The reaction mixture was allowed to warm up slowly and gently shaken, whereupon an exothermic reaction occurred and a pale yellow solution with a colorless layer of excess cyclopropene on top resulted. The device was then tilted so that the solution was allowed to filter through the sintered glass filter into arm B, which was cooled in liquid nitrogen. While the solution in arm B was warmed up to room temperature, sulfur dioxide and the excess cyclopropene were distilled back into arm A by immersing the latter in liquid nitrogen. When finally only a dry solid residue remained in arm B, the device was sealed off at the thickened part, D. Arm B, containing the fluorocyclopropenium hexafluoroantimonate complex, was broken open in a drybox filled with dry helium and the hygroscopic complex was handled in the absence of moisture. The following elemental analyses were obtained. *Anal.* Calcd for $C_3Cl_2F^+SbF_6^-$ (15): C, 9.96; Cl, 19.61; F, 36.77; Sb, 33.66. Found: C, 10.01; Cl, 19.30; F, 36.90; Sb, 33.54. Calcd for $C_3ClF_2^+SbF_6^-$ (16): C, 10.44; Cl, 10.27; F, 44.03; Sb, 35.27. Found: C, 10.31; Cl, 10.40; F, 44.51; Sb, 35.03. Clacd for $C_3Br_2F^+SbF_6^-$ (17): C, 8.00; Br, 35.47; F, 29.51; Sb, 27.02. Found: C, 7.97; Br, 35.08; F, 30.07; Sb, 26.82. Calcd for $C_3BrF_2^+SbF_6^-$ (18): C, 9.25; Br, 20.51; F, 39.00; Sb, 31.24. Found: C, 9.16; Br, 20.51; F, 39.40; Sb, 31.20.

The ^{19}F nmr samples of 15–18 were prepared as sulfur dioxide solutions in sample tubes sealed under vacuum while the samples were frozen under liquid nitrogen. A capillary containing trichlorofluoromethane placed inside the sample tube served as the external standard.

The ir spectra of 15–18 taken in SbF_5 solutions as a film between Irtran 2 plates are as follows. $C_3Cl_2F^+$ SbF_6^- (15): 1880 (s), 1830 (w), 1750 (w), 1660 (w), 1620 (w), 1550 (w), 1410 (s), 1150 (w), 940 (m) and 890 cm^{-1} (m). $C_3ClF_2^+SbF_6^-$ (16): 1960 (s), 1930 (w), 1900 (w), 1620 (s), 1590 (w), 1550 (s), 1500 (w), 1450 (s), 1410 (w), 1380 (w), 1280 (w), 1260 (w), 970 (m) and 920 cm^{-1} (m). $C_3Br_2F^+SbF_6^-$ (17): 1870 (s), 1780 (w), 1550 (w), 1440 (w), 1390, 1370 (s, doublet), 1260 (w), and 910 cm^{-1} (m). $C_3BrF_2^+SbF_6^-$ (18): 1930 (s), 1900 (w), 1870 (w), 1830 (w), 1610 (s), 1570 (w), 1520 (s), 1490 (w), 1450 (w), 1420 (s), 1300 (w), 1280 (w), 1260 (m), 1240 (w), 1140 (w), 1040 (w), 970 (m), 930 (w), and 900 cm^{-1} (s).

The Regeneration of Tetrahalocyclopropenes from Trihalocyclopropenium Hexafluoroantimonates.—A microspatula of $C_3Cl_2F^+SbF_6^-$ (15) was placed in a Pyrex tube attached to a vacuum line. The whole system was evacuated and closed. A thermometer was hung beside the sample, which was heated to *ca.* 80° by means of a hot air blower. The sample darkened and liquefied, and the pressure in the closed system rose to 30 Torr. An infrared spectrum of the collected gaseous product was identical with that of 1,2-dichloro-3,3-difluorocyclopropene (3).

The Preparation of Diphenylcyclopropenone (24) from 16.—One gram of $C_3ClF_2^+SbF_6^-$ (16) was added to 5 ml of benzene in a test tube, which was then loosely stoppered with a cork. The mixture was stirred and gently heated for 15 min, during which time a gas evolved. After the mixture was cooled to room temperature, cold water (10 ml) and solid sodium carbonate were successively added to neutralize the acidic mixture, which was then extracted with ether. The ether extract was dried over calcium chloride and evaporated to give a solid residue. The latter was then recrystallized from cyclohexane to give colorless diphenylcyclopropenone (24), mp 121–121.5° (lit. mp 121.5–122°), which had ir and uv spectra identical with those of an authentic sample.[12]

Registry No.—1, 6262-42-6; 2, 6262-44-8; 3, 6262-45-9; 4, 24921-89-9; 5, 37145-46-3; 6, 37145-47-5; 7, 6262-43-7; 8, 6262-46-0; 9, 29777-44-4; 15, 37145-74-7; 16, 37396-42-2; 17, 37396-43-3; 18, 37145-73-6.

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Solvation of the Polymer Matrix. Source of Truncated and Deletion Sequences in Solid Phase Synthesis[1]

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An automated procedure utilizing hydrogen chloride-36 for monitoring the free amine in automated solid phase synthesis was developed. Discrepancies were found between the values determined by this procedure and those from amino acid analysis in the synthesis of a peptide, residues 63–74, of acyl carrier protein. These results led to a hypothesis of dynamic solvation changes of the polymer matrix as synthesis proceeds. The effects of chain termination by acetylation were also in agreement with the hypothesis. Dynamic solvation changes of the polymer matrix leads to the sequence-dependent problems of solid phase synthesis, both truncated and deletion sequences. It may also be responsible for difficulties encountered with monitoring procedures and with attempts to terminate unreacted peptide chains. Based on these observations, a modified procedure of solid phase peptide synthesis was developed which significantly improved the synthesis of residues 63–74 of acyl carrier protein.

Since the introduction of the solid phase method for peptide synthesis by Merrifield in 1962,[5] an enormous number of peptides have been prepared.[6] A more striking achievement, however, has been the synthesis by the solid phase procedure of several large proteins with high biological activity, *e.g.*, ribonuclease A,[7] fragment P_2 of *Staphylococcus aureus* nuclease T,[8] soybean trypsin inhibitor,[9] and acyl carrier protein.[10]

Despite these impressive achievements, many peptides have not been prepared in an adequate yield and the cause of such failures is still not clear despite extensive studies of the sequence-dependent[11] problems of solid phase synthesis.[6,12–15] Most failures in the method have been attributed to incomplete coupling and deprotection steps.[6,16–21] Fortunately, a wide variety of methods has been established for the formation of a peptide bond,[18] and recently several new resin supports have been developed.[6a] One could expect, therefore, that many of these synthetic problems could be overcome by a judicious choice of the polymeric support, side chain and α-amino protecting groups, the method of removal of the α-amino protecting group, and the reagent used for mediating the coupling reaction. Some recent studies[16] have indicated that difficult coupling reactions may be facilitated by the use of a mixed solvent or the addition of urea to the reaction mixture.

The formation of truncated peptides[22] by incomplete coupling and deprotection steps is a problem in that the overall yield of the synthesis is decreased. The regrowth of partially complete sequences, with the formation of deletion sequences,[23] poses a much greater threat to the success of the synthesis of a large molecule, as the separation of the desired peptide from a large number of very similar products may be beyond the scope of present methods of protein purification. Bayer[12] has established that such deletion sequences can occur in specialized cases, and by analogy it has been suggested that the larger synthetic proteins must contain such products. Also the formation of deletion sequences places a severe limit on the size of the peptide that can be synthesized.[13,24]

Two approaches which have been taken to reduce the occurrence of deletion sequences are either to increase the yield of the coupling reactions, by multiple couplings, for example, or to terminate truncated sequences by treatment of the resin, after completion of the coupling reaction, with a very reactive acylating reagent, *e.g.*, acetic anhydride[14,25] or other reagents.[26–28] It has yet to be demonstrated, however, that such reagents, because of their reactivity, will not cause side

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(4) Established Investigator, American Heart Association.

(5) R. B. Merrifield, *Fed. Proc.*, **21**, 412 (1962).

(6) (a) G. R. Marshall and R. B. Merrifield, "Biochemical Aspects of Reactions on Solid Supports," Academic Press, New York, N. Y., 1971; (b) A. Marglin and R. B. Merrifield, *Ann. Rev. Biochem.*, **39**, 841 (1970).

(7) B. Gutte and R. B. Merrifield, *J. Biol. Chem.*, **246**, 1922 (1971).

(8) D. A. Ontjes and C. B. Anfinsen, *Proc. Nat. Acad. Sci. U. S.*, **64**, 428 (1969).

(9) K. Noda, J. S. Terada, N. Mitsuyasu, M. Waki, T. Kato, and N. Izumiya, *Naturwissenschaften*, **58**, 147 (1971).

(10) (a) W. S. Hancock, D. J. Prescott, W. L. Nulty, J. Weintraub, P. R. Vagelos, and G. R. Marshall, *J. Amer. Chem. Soc.*, **93**, 1799 (1971); (b) W. S. Hancock, D. J. Prescott, G. R. Marshall, and P. R. Vagelos, *J. Biol. Chem.*, **247**, 6224 (1972).

(11) It has been established that these failures are not necessarily associated with a particular amino acid residue, and therefore are described as sequence-dependent problems.

(12) E. Bayer, H. Eckstein, K. Hagele, W. A. Konig, W. Bruning, H. Hagemaier, and W. Parr, *J. Amer. Chem. Soc.*, **92**, 1735 (1970).

(13) E. Bayer, H. Hagenmaier, G. Jung, W. Parr, H. Eckstein, P. Hunziker, and R. E. Sievers, "Peptides 1971," North-Holland Publishing Co., New York, N. Y., 1971, pp 65–73.

(14) H. Hagenmaier, *Tetrahedron Lett.*, 283 (1970).

(15) R. C. Sheppard, "Peptides 1971," North-Holland Publishing Co., New York, N. Y., 1971.

(16) F. C. Westall and A. B. Robinson, *J. Org. Chem.*, **35**, 2842 (1970).

(17) F. Chuen-Heh Chou, R. K. Chawla, R. F. Kibler, and R. Shapira, *J. Amer. Chem. Soc.*, **93** 267 (1971).

(18) R. B. Merrifield, *Advan. Enzymol.*, **32**, 221 (1969).

(19) S. Karlsson, G. Lindeberg, J. Porath, and U. Ragnarsson, *Acta Chem. Scand.*, **24**, 1010 (1970).

(20) J. Scotchler, R. Lozier, and A. B. Robinson, *J. Org. Chem.*, **35**, 3151 (1970).

(21) K. Lubke, "Peptides 1969," North-Holland Publishing Co., New York, N. Y., 1971, pp 154–156.

(22) A truncated peptide is defined as a peptide which becomes unavailable for reaction at some stage in the synthesis and does not add any further amino acids.

(23) A deletion sequence is defined as a truncated peptide which resumes growth at some later stage in the synthesis.

(24) (a) For example, the synthesis of human growth hormone (188 amino acids) would require an average coupling yield of 99.5% if the desired protein was to be the major product of the synthesis. Such calculations, however, are based on the assumption that all truncated sequences become deletion sequences and grow at the same rate as the correct sequence. (b) J. M. A. Baas, H. C. Beyerman, B. van de Graff, and E. W. B. de Leer, "Peptides 1969," North-Holland Publishing Co., New York, N. Y., 1971, pp 173–176.

(25) R. B. Merrifield, *J. Amer. Chem. Soc.*, **85**, 2149 (1963).

(26) L. B. Markley and L. C. Dorman, *Tetrahedron Lett.*, 1787 (1970).

(27) T. Wieland, C. Birr, and H. Wissenbach, *Angew. Chem., Int. Ed. Engl.*, **8**, 764 (1969).

(28) H. Wissmann and R. Geiger, *ibid.*, **9**, 909 (1970).

reactions that are deleterious to the synthesis, *e.g.*, acetic anhydride.[29] Also it is unclear whether the amino groups which are resistant to coupling will react with the terminating reagent.

Before these variations in procedure can be rationally applied, it is necessary to have a reliable means of quantitation for both the coupling and deprotection steps, and in fact numerous assay procedures have been reported,[6a] most of which depend on monitoring the free amino group. The automation of the solid phase synthetic method has added the further requirements that the analytical procedure must be rapid enough in order to monitor and perhaps control the progress of the automated synthesizer. At this stage, the potentiometric method of Brunfeldt[30] is the procedure which seems most applicable for use with an automated synthesizer.

Little progress has been made in understanding the cause of the sequence-dependent problems of solid phase synthesis, although several possible explanations have been advanced. The effect of steric hindrance of the amino terminus of the growing peptide chain has often been discussed with relevance to solid phase synthesis.[15,17,21] The environment of the peptide can be dramatically effected by the solvent used, as it has been found that only solvents which swell the resin and provide a reasonably polar environment will allow an efficient coupling reaction, *e.g.*, dimethylformamide and chloroform, but not benzene.[25] Since both the polymerization of the polystyrene support and the chloromethylation reaction are random processes, one could expect a heterogenous environment due to the random distribution of cross-links and reactive sites so that some reactive sites would be more sensitive than others to steric hindrance.

It has been noted[12] that solid phase synthesis is a heterogenous reaction and as such depends on the rate of diffusion of reagents in the resin. One could expect, however, that diffusion should normally be a rapid process, as the swollen beads contain 80–90% solvent.[25]

In a recent review,[6a] it was stressed that as a synthesis proceeds the physical properties of the resin reflect the change from that of hydrophobic polystyrene to that of a mixed polystyrene–protein matrix. One might then expect a change, perhaps dramatic, in local solvation of the heterogeneous polymer matrix as the synthesis proceeds. If the solvation was decreased, then the accessibility of the heterogenous population of sites could also decrease with a consequent drop in the yield. It was difficult to evaluate such a concept because of the lack of published examples of this phenomenon; in fact only two well-documented examples have been described.[6a,20]

At the beginning of our investigations on acyl carrier protein, it became clear that the synthesis of the initial sequence, residues 74–63 (see Figure 1), was a good example of the sequence-dependent problems of solid phase synthesis—the yield of growing peptide at the end of the sequence was only 20% of the initial glycine value. It was decided to examine monitoring procedures and methods for minimizing truncated and deletion sequences before proceeding further. The synthesis was then repeated under a variety of conditions and followed by analysis of the yield of both the coupling and deprotection steps.

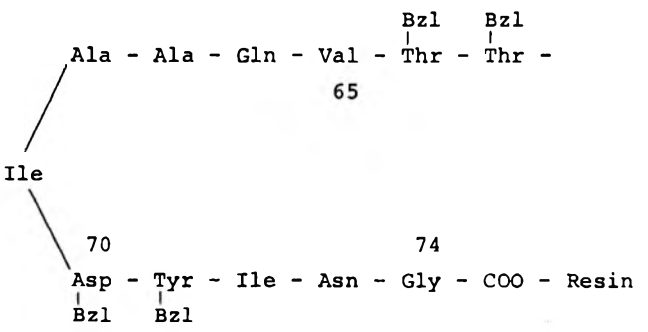

Figure 1.—Fully protected partial sequence 74–63 of acyl carrier protein.

For these analytical studies, the method developed by Dorman[31] was adapted so that the progress of an automated synthesis could be followed. From these studies, a modified synthetic procedure was derived that overcame to a considerable extent the problems originally observed in the synthesis of this peptide, and which was subsequently applied to the synthesis of acyl carrier protein. Of more general significance was the evidence which indicated that the difficulties observed in this synthesis can be attributed to changes in solvation of the peptide resin at different stages in the synthesis, which give rise to both truncated and deletion sequences. With change in the accessibility of the free amino group, monitoring methods must be used with extreme caution.

Results and Discussion

The sequence 74–63 of ACP (see Figure 1) was synthesized by the stepwise addition of suitably protected amino acids to 0.66 mmol of *tert*-butyloxycarbonyl (BOC)-glycine (0.33 mmol of amino acid per gram of peptide resin) esterified to a 1% cross-linked polystyrene resin support. The procedures used are similar to those described by Merrifield for solid phase synthesis,[32] and the specific details are described in the Experimental Section.

Although the synthesis of the initial C-terminal sequence of ACP, 74–63, would appear straightforward, early attempts to synthesize this peptide by standard procedures were discouraging (Figure 2). The addition of asparagine$_{73}$, isoleucine$_{72}$, and tyrosine$_{71}$ gave a progressive decrease in the yield of the growing peptide chain, which implies truncation. Steric hindrance of the coupling of amino acids with bulky protecting groups should be greatest at the beginning of the synthesis,[33] and this could account for these initial difficulties, especially in the case of isoleucine, with its bulky isobutyl side chain.

The most significant feature of the growth profile of the sequence 74–63 is the dramatic increase in yield for

(29) J. Halstrom, K. Brunfeldt, and K. Kovacs, *Experientia*, **27**, 17 (1971).

(30) K. Brunfeldt, P. Roepstorff, and J. Thomsen, "Peptides 1969." North-Holland Publishing Co., New York, N. Y., 1971, pp 148–153.

(31) L. C. Dorman, *Tetrahedron Lett.*, 2319 (1969).

(32) (a) R. B. Merrifield, *J. Amer. Chem. Soc.*, **85**, 2149 (1963); (b) R. B. Merrifield, *Advan. Enzymol.*, **32**, 221 (1969).

(33) The initial amino acid, glycine, was attached to the resin under conditions that are much more vigorous (100°, 24 hr) than one uses for peptide bond formation. It could be expected therefore, that some of the reaction sites would be located in the more hindered regions of the resin matrix. This conclusion is supported by the frequent observation that cleavage of the peptide from the resin releases significant quantities of the initial amino acid.

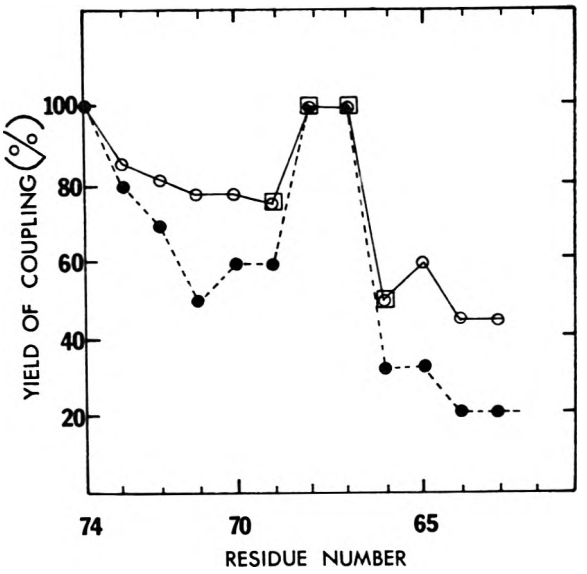

Figure 2.—The growth profile for the synthesis of the sequence 74–63 of ACP by two different synthetic procedures. The yield of each synthesis was determined by amino acid analysis of the peptide resin after the addition of each amino acid. The data present are the average of two syntheses in which the standard solid phase synthetic procedures were used (●) and four syntheses in which the modified procedures were used (○). All duplicate syntheses gave essentially the same results. If the resin peptide was acetylated after the addition of Ile_{68}, and then the synthesis was continued as for the modified procedure, the incorporation of the subsequent residues is shown by the points ⊐.

the addition of $alanine_{68}$ and $alanine_{67}$, which implies regrowth and formation of deletion sequences. However, the next amino acid, glutamine, was incorporated with a much lower yield, which again implied truncation.

It was clear at this stage that the synthesis had to be followed by some analytical technique which allowed quantitation of the yield of both the coupling and deprotection steps. The Dorman[31] procedure was chosen, which measures the amount of chloride bound to the resin by conversion of free amino groups to their corresponding hydrochlorides on treatment of the resin with pyridine hydrochloride. The chloride is displaced from the resin with triethylamine and measured by titration. However, it was decided that the use of chloride-36 would greatly increase both the speed and sensitivity of the assay. Instead of a laborious titration procedure, the chloride could be simply measured by radioactivity, while a very small amount of bound chloride (as would be expected for an efficient coupling reaction) could be accurately determined by a suitable increase in the specific radioactivity of the chloride-36. Table I indicates that both methods of chloride determination gave the same values for BOC and deprotected glycine resin, and, therefore, the chloride-36 procedure was used in all subsequent assays.

It was found necessary to modify some of the washes that were used in the original Dorman procedure so that the chloride-36 could be accurately measured. In Table II, the two procedures are compared and it is clear that the modifications do not effect the amount of bound chloride. Dimethylformamide was not a suitable solvent to remove the excess pyridine hydrochloride, presumably due to traces of dimethylamine in the solvent which displaced some of the bound chloride, and as a consequence the level of chloride-36 in the

TABLE I

COMPARISON OF METHODS USED FOR THE MEASUREMENT OF CHLORIDE[a]

	Chloridimeter	^{31}Cl radioactivity
BOC-Gly resin	30	26
Total recovery, %	98	103
Gly resin	762	725
Total recovery, %	98	97

[a] Gly resin (0.66 mmol) was treated with pyridine hydrochloride (7.5 mmol). The excess chloride was removed by a series of washes and the bound chloride was displaced with triethylamine (see Experimental Section). The chloride was then determined by titration of the chloride with a chloridimeter or by measurement of the ^{36}Cl radioactivity as described in the Experimental Section. Each value in the table is an average of three determinations (error for both assays was ±5%).

TABLE II

DORMAN ANALYSIS OF DEPROTECTED GLYCINE RESIN[a]

Original procedure			Modified procedure		
No. of wash	Reagent	^{36}Cl dpm in wash	No. of wash	Reagent	^{36}Cl dpm in wash
1	Pyr HCl[b]	29,420	1a	Pyr HCl	28,580
2	CH_2Cl_2	12,643	2a	CH_2Cl_2	13,195
3	CH_2Cl_2	4,898	3a	CH_2Cl_2	4,956
4	CH_2Cl_2	933	4a	CH_2Cl_2	741
5	DMF	612	5a	*t*-BuOH	906
6	DMF	194	6a	*t*-BuOH	486
7	DMF	115	7a	*t*-BuOH	131
8	DMF	120	8a	*t*-BuOH	23
9	DMF	90	9a	CH_2Cl_2	20
10	DMF	70	10a	CH_2Cl_2	0
11	DMF	80	11a	CH_2Cl_2	0
12	Et_3N[c]	4,906	12a	Et_3N[d]	3,370
13	DMF	587	13a	Et_3N	1,835
14	DMF	306	14a	Et_3N	306
15	DMF	63	15a	CH_2Cl_2	257
			16a	CH_2Cl_2	61
			17a	CH_2Cl_2	23
Total dpm 1–15		55,037			54,890
Total dpm 12–17		5,862			5,852
Recovery of total ^{36}Cl, %		100			100

[a] Gly resin (0.66 mmol) was treated with pyridine hydrochloride (7.5 mmol, 1.4×10^6 dpm). In two determinations the resin was treated with the washes 1–15 and 1a–17a, each wash was collected in a 25-ml volumetric flask, and the sample was made up to the mark with dichloromethane. A 1-ml sample was counted for ^{36}Cl radioactivity. [b] The abbreviations used in the diagram are Pyr HCl = pyridine hydrochloride, CH_2Cl_2 = dichloromethane, DMF = dimethylformamide, Et_3N = triethylamine. [c] 10% (v/v) triethylamine dissolved in dimethylformamide. [d] 3% (v/v) triethylamine dissolved in dichloromethane.

washes would not fall to zero (see washes 5–11). This problem was solved by the substitution of an alcohol wash in steps 5a–8a. The resin was then washed with dichloromethane (steps 9a–11a) to prevent loss of peptide from the resin by transesterification caused by traces of alcohol present contaminating the triethylamine wash.[34] Triethylamine, at the concentrations used by Dorman, was found to severely quench the counting of chlorine-36. However, it was found that three washes of a lower concentration of triethylamine were sufficient to displace all of the bound chloride, and allow satisfactory counting of the sample (steps 12a–14a).

(34) The possibility of this side reaction was reduced further by the substitution of the more sterically hindered *tert*-butyl alcohol for ethanol in steps 5a–8a.

The assay was found to be quite reproducible and, in all cases, the recovery of chloride-36 was excellent (98%). Moreover, the procedure was easily adapted to monitor an automated synthesis. An automated synthesizer[35] was modified to accommodate a fraction collector, which was used to collect the effluent from the reaction flask. In order to quantitate effluent collection, it was necessary to drain by nitrogen pressure rather than by vacuum filtration. The machine was readily programmed to execute a Dorman analysis after each coupling and deprotection step, especially as pyridine hydrochloride was the only reagent that was not already used in the synthetic procedure. Washes 1a–11a and 12a–17a (Table II) were collected in separate containers and a sample of each was then counted. The volume and pH of the fractions collected were used as a check on the operation of the synthesizer. The results of the analyses performed during the synthesis of the peptide 74–67 of ACP are shown in Table III.

TABLE III
CHLORIDE BINDING DATA[a] FOR THE SYNTHESIS OF THE PEPTIDE 74–67

Residue	1st Coupling in CH_2Cl_2	2nd Coupling in CH_2Cl_2	3rd Coupling in CH_2Cl_2–DMF (1:1)	Acetylation[b]	1st Deprotection[b]	2nd Deprotection[b]
74 Gly	38[c]				782[f]	
73 Asn[d]	300	240			675	
72 Ile	362	370	304		765	
71 Tyr[d,e]	431	411	430	380	390	415
70 Asp	84	88		178	360	
69 Ile	186	187			374	
68 Ala		47			267	320
67 Ala	106	92			275	

[a] Expressed as μmoles of free amino groups as measured by the Dorman analysis. [b] As described in the Experimental Section. [c] Result of analysis of the initial *t*-BOC-glycine resin. [d] Both active ester couplings were carried out in DMF. [e] Dorman analysis after a fourth coupling in benzene gave 425 μ*M* of chloride bound. The peptide 74–67 of ACP (Figure 1) was synthesized using the standard procedure described in the Experimental Section. The yield of each coupling reaction was estimated by the procedure of Dorman. [f] The amino acid analysis of the BOC-glycine resin indicated that 660 μmol of amino acid was esterified to the resin.

The yield of each coupling step was also followed by amino acid analysis and the results of the two analytical techniques are compared in Figure 3.

The two measurements agreed well for the addition of the first three amino acids, but after the addition of aspartic$_{70}$ there was a sharp drop in the amount of bound chloride, although the incorporation of aspartic$_{70}$ had not increased. Furthermore, the analysis of each amino acid addition and deprotection was complicated by a background of bound chloride,[36] which was superimposed on the amount of *chloride bound to* the free amino groups, although the value would remain constant after repeated couplings of that particular residue (see Table III). A disturbing feature was that, as the synthesis proceeded, the amount of chloride bound after deprotection showed a steady decrease (see Figure 2). The monitoring of the synthesis of the sequence 74–63 was repeated four times on different preparations with

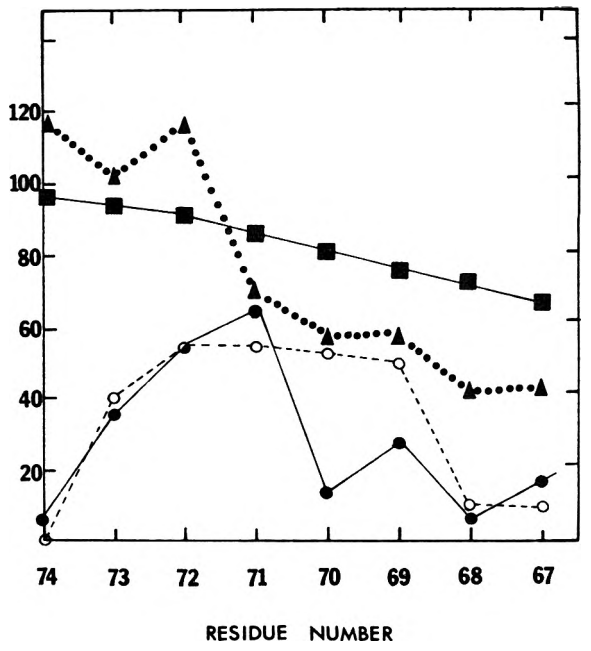

Figure 3.—The yield of the synthesis of peptide 74–63 as measured by amino acid analysis. The values recorded in the graph were an average of three separate syntheses which gave essentially the same results and are expressed as per cent of total free amine converted to the hydrochloride. The analyses were carried out as described in the Experimental Section. The amount of free amine after deprotection was determined by Dorman analysis (▲). The free amine by Dorman analysis (●) after double coupling is compared with the free amine which should be present (○) based on amino acid analysis. The per cent polystyrene (■) present in the polymer–peptide matrix is also shown.

essentially the same results. The constant background observed after several additions of a particular acid suggests that this effect is caused by a change in the properties of the polymer rather than a random accumulation of by-products from the coupling reaction.[37] A similar background effect due to the resin was also found by Beyerman[38] when *N*-(2-^{14}*C*-BOC) amino acids were used to follow the progress of a coupling reaction, or ^{35}*S*-sulfuric acid was used to determine the peptide content.

In Figure 3, it can be seen that the amount of chloride bound by the deprotected peptide decreased as the synthesis proceeded. Bayer noted a similar effect in the synthesis of ferredoxin.[39] This decrease could be caused by the cleavage of the peptide from the resin during the deprotection steps, or the pyridine hydrochloride wash in the case of the Dorman analysis, or by a decrease in the background of bound chloride as the properties of the resin change.

One of the problems of the Dorman analysis is that repeated treatment of the resin peptide with pyridine hydrochloride may cause cleavage of some of the peptide from the resin or other undesirable side reactions due to the acidic nature of this reagent. In Figure 4, the yield of the synthesis of the peptide 74–69 is compared with an identical synthesis that has been analyzed at each coupling and deprotection step with the Dor-

(35) Based on the design of R. B. Merrifield, J. M. Stewart, and N. Jernberg, *Anal. Chem.*, **38**, 1905 (1966).

(36) This background is presumably due to binding of chloride by the resin, perhaps, by continued formation of quaternary amine by exposure of the residual chloromethyl groups to triethylamine.

(37) For example, dicyclohexylurea and other by-products have been observed to give a positive test with ninhydrin reagent.

(38) H. C. Beyerman, P. R. M. van der Kamp, E. W. B. de Leer, W. Maassen van den Brink, J. H. Parmentier, and J. Westerling, "Peptides 1971," North-Holland Publishing Co., New York, N. Y., 1972.

(39) E. Bayer, G. Jung, and H. Hagenmeier, *Tetrahedron Lett.*, 4853 (1968).

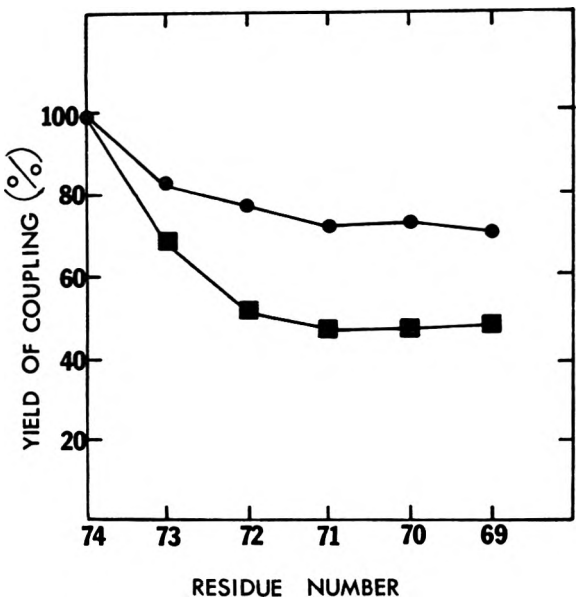

Figure 4.—The effect of the Dorman analysis on the yield of the synthesis of the sequence 74–69 of ACP. The yield of each synthesis was determined by amino acid analysis of the peptide resin after the addition of each amino acid. The data presented are the average of three syntheses that have been followed by the Dorman analysis (■) and four unmonitored syntheses (●). All duplicate syntheses gave essentially the same results. Both procedures involved the same number of coupling and deprotection steps.

man method. It is clear that the analytical procedure has caused a significant drop in the yield of the synthesis.

The variable background of bound chloride makes it difficult to use the Dorman analysis to follow the yield of a synthesis, unless the coupling of a particular amino acid is repeated until the amount of bound chloride remains constant. Although this background has been observed elsewhere,[38,40,41] several studies have not noted this problem.[14,31] This difference, however, may be due to the wide variation in properties that has been observed for different resin preparations.[7,42] Dorman[31] used a hydroxymethyl resin and did not comment on any background due to the resin binding chloride. Beyerman[38] noted that a chloromethyl resin, which had been treated with triethylamine, took up a considerable amount of ^{35}S-sulfuric acid, while a hydroxymethylated resin, or a chloromethylated resin in which the esterification of the amino acid was carried out with sodium carbonate instead of triethylamine, did not react with ^{35}S-sulfuric acid. Therefore, if the correct resin is chosen, the problem of a variable background may be overcome. The procedure should still be used with caution, however, as it can lower the yield of the synthesis (see above).

The variable background of bound chloride observed during the synthesis can be understood only if one considers that the solvation of the resin changes with the nature of the peptide–polystyrene matrix. For example, the sharp decrease in the amount of chloride bound by the resin after the addition of aspartic$_{70}$ (see Figure 3) can be explained by a decrease in solvation of the resin with a corresponding loss of chloride binding sites. These observations are consistent with studies on the rate of release of various amino acids, esterified to a chloromethyl resin, with acidic hydrolysis in a variety of solvents.[16] It was found that some sites on the resin were less accessible than others, and the effect of improper solvation during hydrolysis was to close off completely the less accessible sites, rather than generally decrease the rate of reaction at all sites by similar amounts.

The hydrophobic nature of the polystyrene resin requires that a relatively nonpolar solvent is used to allow swelling of the resin and penetration of the reagents into the matrix. As the length of the peptide chain increases, however, one would expect the requirement of a polar solvent for correct solvation of the peptide chains. In fact, in two published examples,[6a,20] a sudden drop in yield of the synthesis was overcome by the use of a polar solvent, and these studies led to the proposal that the use of a mixture of dichloromethane and dimethylformamide might be used for difficult amino acid additions. In Table III, the chloride binding data indicated that the use of this solvent mixture gave an increased incorporation of isoleucine$_{72}$.

This problem of a variable background of chloride (see Table III) could be explained if the resin contained a constant number of binding sites for chloride whose exposure was variable. If the degree of solvation of the resin changed significantly after the addition of a particular amino acid, then one would expect a change in the measured number of binding sites. If this assumption is correct, it should be possible to expose some of the buried sites by treatment of the resin with a series of washes which alternately shrink and swell the polymer matrix. The availability of previously buried sites could be readily tested by treatment of the resin with triethylamine, which should displace some further chloride from the resin. The development of the modified Dorman procedure was ideally suited for this purpose, as the use of chloride-36 allowed the measurement of very small quantities of chloride.

Three such studies at different stages of the synthesis are shown in Table IV and, in each case, it was found that further chloride-36 could be displaced from the resin after a series of shrink and swell washes. The amount of chloride trapped by the resin was not sufficient to affect the overall recovery of chloride in the assay (maximum amount of chloride released by the extra washes was only 1–5% of the total chloride added to the resin), but it was sufficient to prevent the accurate determination of small amounts of free amino groups. The same result was obtained if the original method of Dorman was followed (washes 1–15 in Table II) so that this effect was not a result of our modifications to the washing procedure.

It is clear from the growth profile of the peptide 74–63 (see Figure 2), synthesized by standard procedures for solid phase synthesis, that the synthesis has several problems which lead to a very low yield of the completed peptide. The analytical studies (see Table III) indicated, however, that variation in the conditions of coupling and deprotection could significantly improve the yield of the synthesis. More significantly, the studies described in Table IV indicated that a swell–shrink–swell wash cycle could expose buried functional

(40) R. B. Merrifield, unpublished observations.

(41) B. Mehlis, W. Fischer, and H. Niedrich, "Peptides 1969," North-Holland Publishing Co., New York, N. Y., 1971, pp 146–147.

(42) We have noted different backgrounds for glycine resins which were obtained commercially and those that were prepared in our laboratory.

TABLE IV

REEXPOSURE OF CHLORIDE BINDING SITES AT DIFFERENT STAGES OF THE SYNTHESIS OF THE PEPTIDE 74–67[a]

Number of wash	Reagent	BOC-Gly_{74} ^{36}Cl dpm in washes	BOC-Ala_{67} ^{36}Cl dpm in washes	Deprotected Ala_{67} ^{36}Cl in washes
12	Et_3N	206	427	1,809
13	Et_3N	65	167	241
14	Et_3N	10	43	
15	CH_2Cl_2	5	25	
16	CH_2Cl_2		16	
17	CH_2Cl_2			
18	*t*-BuOH			
19	*t*-BuOH			
20	*t*-BuOH			
21	CH_2Cl_2			
22	CH_2Cl_2			
23	CH_2Cl_2			
24	Et_3N	73	213	630
25	Et_3N	16	75	112
26	CH_2Cl_2		20	19
Total dpm in wash 11–15		286	778	2,050
Total dpm in wash 23–25		89	308	761
% of dpm in wash 23–25 relative to wash 11–15		31	40	37

[a] The resin peptide was treated with pyridine hydrochloride (7.5 mmol, 1.4×10^6 dpm) and the excess pyridine hydrochloride was removed by the same washes (1a–11a) as described in Table II. All available chloride was then displaced by the washes 12–17 as shown in this table. The resin was then subjected to washes 18–23 in an attempt to expose buried regions of the resin that had bound chloride, and in fact the second triethylamine treatment washes 24–26 did liberate more chloride. Samples of the washes were counted for chloride-36 in the manner described for Table II.

groups. These considerations led to the development of a modified synthetic procedure.

The chloride binding data described in Table III suggested that the coupling of $isoleucine_{72}$ was improved if the coupling reaction was carried out in a mixed solvent of dichloromethane and dimethylformamide, while the yield of addition of $asparagine_{73}$ was also increased if the coupling reaction was repeated. A second deprotection after the addition of $tyrosine_{71}$ and $alanine_{68}$ increased the amount of free amine as detected by the chloride binding measurements. If these data were an accurate estimate of the amino groups that were available for a coupling reaction, then it was clear that persistent efforts to ensure reaction at the less accessible sites on the resin were necessary to achieve a good yield in the synthesis.

In an attempt to meet these conditions, all coupling reactions were repeated with a 1:1 mixture of dichloromethane and dimethylformamide as the solvent, and the deprotection step was repeated in an attempt to ensure complete deblocking of the peptide chain. Also the swell–shrink–swell wash was used between all coupling and deprotection steps (the exact sequence of washes used is described in the Experimental Section).

The sequence 74–63 of ACP was then resynthesized with this new procedure (see Experimental Section) and the progress of the synthesis was followed by amino acid analysis. As is shown in Figure 2, the modifications were successful, as the yield of completed peptide at the end of the synthesis was doubled.

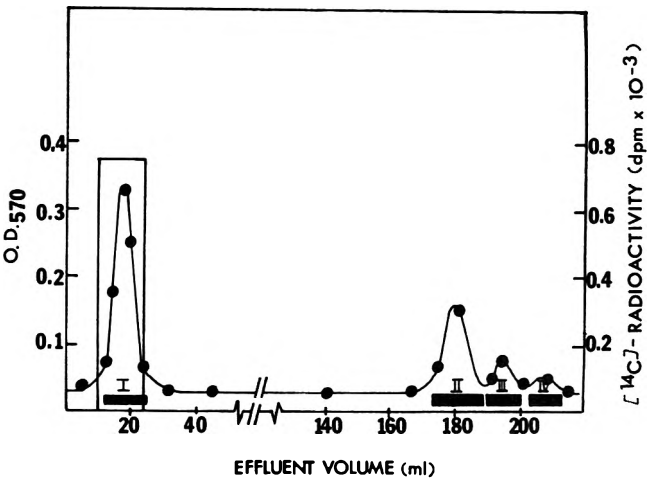

Figure 5.—Separation of the products from the synthesis of the sequence 74–69 of ACP. This figure shows the separation on a Dowex 50-X8 column (0.9 × 17 cm) of the products from the synthesis of the peptide 74–69. The column was developed at 30 ml/hr with a pyridine acetate gradient at 55°, and 6-ml fractions were collected. The progress of the column was monitored by ninhydrin analysis (570 mm) of the alkaline hydrolysate of a sample of each fraction. A portion (6%) of each fraction was checked for ^{14}C radioactivity.

However, the decrease in yield of the synthesis for the addition of $asparagine_{73}$, $isoleucine_{72}$, and $tyrosine_{71}$, as well as the regrowth of partially complete sequences after the addition of $alanine_{68}$ and $alanine_{67}$ was still evident (see Figure 2). It was decided that these problems would serve as an excellent test for the effectiveness of acetylation as a reagent for the termination of incomplete sequences. If the peptide resin was acetylated after the addition of $tyrosine_{71}$ and the peptide cleaved from the resin, one could expect to obtain *N*-acetylglycine, *N*-acetylaspartylglycine, and *N*-acetylisoleucylaspartylglycine. Alternatively, if the resin was acetylated after the addition of Ile_{69}, then the yield of addition for Ala_{68} and Ala_{67} should not be greater than that of $isoleucine_{69}$.

The peptide 74–63 (Gly-Asn-Ile-Tyr-Asp-Ile-Ala-Ala-Gln-Val-Thr-Thr) was synthesized with an identical procedure used for the synthesis depicted in Figure 2 except that the peptide resin (0.3 mmol) was acetylated with a large excess of ^{14}C-acetic anhydride (3 mmol, 5.4×10^6 dpm/mmol) for 20 min after the coupling of $isoleucine_{69}$. Despite this treatment, the synthesis gave the same regrowth of incomplete peptides with the coupling of $alanine_{68}$ and $alanine_{67}$.

Peptide 74–63 (Gly-Asn-Ile-Tyr-Asp-Ile) was synthesized as before, except that acetylation with ^{14}C-acetic anhydride was performed after the addition of $tyrosine_{71}$. A sample of the peptide resin (50 mg, 16 μmol of glycine esterified to the resin) was cleaved by a HBr and trifluoroacetic acid treatment and the product was isolated (see Experimental Section). The peptides were chromatographed on Dowex 50-X8 and the column was monitored by ninhydrin analysis after alkaline hydrolysis of a sample of each fraction (see Figure 5). The absorbance at 570 nm indicated that four fractions were present and these were numbered consecutively by Roman numerals. A portion (6%) was checked for ^{14}C radioactivity while the rest was subjected to an acid hydrolysis and the amino acid content was determined (see Table V). The analysis in-

TABLE V

COMPOSITION OF THE MIXTURE OF PEPTIDES FROM THE SYNTHESIS OF THE SEQUENCE 74–69 OF ACP[a]

Peak no.	Amino acid composition, μmol Gly	Asp	Ile	Tyr	Peptide[b]	^{14}C dpm
I	1.0	2.0	0.81	0.79	125	1,500[c]
II	1.0	0.1			38	
III	1.0	0.95	0.75		17.5	
IV	1.0	0.98	0.15		3.1	
Resin peptide[d]	1.0	1.41	1.36	0.6	306	

[a] Peptide 74–69 (0.3 mmol), which had been acetylated with ^{14}C-acetic anhydride (3 mM, 5.2 × 10^3 dpm/μmol) after the addition of Ile$_{72}$, was cleaved from the resin and fractionated on Dowex 50-8 (see results and Figure 4). The amino acid composition and ^{14}C radioactivity of the pooled peaks were then determined. [b] Based on μmoles of glycine. [c] This corresponds to the acetylation of 2.3 μmol of peptide. [d] The amino acid analysis of the resin peptide at different stages of the synthesis indicated that amino acids were added with the following yields: Asn$_{73}$, 78%; Ile$_{72}$, 71%; Tyr$_{71}$, 59%; Asp$_{70}$, 63%; Ile$_{69}$, 65%.

dicated that peak I consisted of the complete peptide 74–69 and acetylated peptides while peaks II–IV were the products of incomplete coupling of asparagine$_{73}$, isoleucine$_{72}$, and tyrosine$_{71}$, *i.e.*, Gly, Gly-Asx, and Gly-Asx-Ile, respectively. The quantities of these peptides corresponded closely to the values of truncated sequences expected from the amino acid analysis of the peptide resin, and the recovery of material was good (60% of the glycine esterified to the resin was recovered from the Dowex 50 column). The finding that only a small fraction (4%) of the incomplete peptides present in this sample had been terminated with the acetic anhydride treatment is consistent with the hypothesis that incomplete coupling and/or deprotection reflects sites which are not solvated by the reagents and may be inaccessible to chain-terminating reagents or to titration as well as to coupling.

As the yield of addition of isoleucine$_{69}$ is only 60% of the value for the initial amino acid, one would expect that up to 40% of peptide chains would be available for acetylation, but this was obviously not the case, as all of the incomplete peptide chains coupled with both alanine$_{68}$ and alanine$_{67}$. Therefore, on deprotection of the α-amino group of the isoleucyl peptides, the solvation of peptide–polymer matrix must undergo a dramatic change so that the amino groups that were unavailable for acetylation can readily form a peptide bond. On the addition of glutamine$_{66}$, the yield then dropped to the level of the synthesis before the addition of alanine$_{68}$ and alanine$_{67}$.

Acetylation of the peptide resin after the addition of tyrosine$_{71}$ occurred with only a small fraction (4%) of the truncated peptides formed by the incomplete coupling of asparagine$_{73}$, isoleucine$_{72}$, and tyrosine$_{71}$ despite the use of a large excess (tenfold) of acetic anhydride (see Figure 5 and Table V). Bayer made a similar observation from studies with model peptides,[12] where it was found that only part of the uncoupled free amino groups could be acetylated.

Therefore, one cannot expect that repeated couplings of an amino acid will increase the yield of a difficult step if the unreactive amino groups are buried. This conclusion is supported by the data presented in Table III, where it is clear that four couplings of tyrosine, carried out in a variety of solvents, did not decrease the amount of free amino groups (as measured by the amount of bound chloride), although amino acid analysis after the four couplings indicated that tyrosine had reacted with only 60% of the peptide chains. Similar observations about the ineffectiveness of repeated couplings have been made in the synthesis of (Leu-Ala)$_6$[14] and of a tetrapeptide.[25] In the synthesis of lysozyme, it was found that repeated couplings resulted in the growth of peptides on partially deprotected side chains.[43]

The use of an insoluble support allows the solid phase method to have considerable advantages over protein synthesis carried out in solution, such as the facile removal of excess reagents, tremendous savings in time, and avoidance of the problems of insolubility of large fragments. At the same time, the use of a polymeric support introduces a new set of problems which still require extensive investigation before the solid phase method can be used routinely for any particular peptide sequence. If the use of a polystyrene support is to be completely successful, then an analytical method will have to be developed which allows the rapid determination of the yield of both coupling and deprotection reactions. This goal may be difficult to achieve, as the properties of the polymeric support may distort the analytical results, either by masking some of the functional groups or by trapping by-products of the coupling reaction which will react with the assay reagents. By a similar argument, the use of terminating reagents, such as acetic anhydride, has only limited application in stopping the regrowth of partially complete sequences. The problems of the solid phase synthetic procedure, however, cannot be so general or so serious as the various analytical studies[13,14,17] would suggest, because of the enormous number of peptides that have been synthesized successfully by the method. In fact, the success of the method would suggest that in most syntheses, truncated peptides, when formed, do not regrow to any significant extent during the rest of the synthesis.

An alternative to the problems of a polystyrene resin is the use of a special polymer in which a thin layer of styrene is localized on the surface of an inert bead. Several successful syntheses have been carried out with such a support either on Teflon[44] or on glass[45] and these achievements point to a possible solution to the sequence-dependent problems of solid phase synthesis. Other physical forms of polystyrene, such as the macroreticular resins,[46] should also be further investigated. A different approach to this problem proposed by Sheppard[15] would be the use of a polymer support whose solvation properties would be similar to that of the protected polypeptide which was being synthesized in order to minimize solvation charges as synthesis progresses. Once the problem of dynamic solvation changes is overcome, then monitoring procedures can be rationally applied to overcome the sequence-dependent problems which hinder the application of solid phase synthesis.

(43) J. J. Sharp, A. B. Robinson, and M. D. Kamen, *Fed. Proc.*, **30**, 1286 (1971).

(44) G. W. Tregear, H. D. Niall, J. T. Potts, S. E. Leeman, and M. M. Chang, *Nature (London), New Biol.*, **232**, 87 (1971).

(45) (a) E. Bayer, G. Jung, I. Halasz, and I. Sebastian, *Tetrahedron Lett.*, 4503 (1970); (b) W. Parr and K. Grohmann, *ibid.*, 2633 (1971).

(46) S. Sano, R. Tokunaga, and K. A. Kun, *Biochim. Biophys. Acta*, **244**, 201 (1971).

Experimental Section

Reagents.—*tert*-Butyloxycarbonyl (BOC)-amino acids and BOC-glycine which was esterified to a polystyrene–1% divinylbenzene resin were purchased from Schwarz BioResearch. The following side-chain blocking groups were used—aspartic acid, β-benzyl ester; threonine and tyrosine, benzyl ethers; glutamic acid, γ-benzyl ester—while the BOC group was used for α-amino protection. Hydrogen chloride-36 and ^{14}C-acetic anhydride were purchased from New England Nuclear. All other chemicals, of reagent grade or better, were purchased from common sources.

A Packard liquid scintillation spectrometer, Model 544, was used for measurement of radioactivity. Amino acid analyses were measured with a Beckman Spinco amino acid analyzer, Model MS. Automated syntheses were performed on a synthesizer based on the design of Merrifield.[47] A Cotlove chloridometer was used in addition to Volhard titrations for chloride determinations.

Preparation of the Pyridine Hydrochloride Reagent.—Pyridine hydrochloride (0.3 mol) was dissolved in dichloromethane (1 l.) and the chloride content was checked by chloridimetry. Pyridine hydrochloride (^{36}Cl) was prepared in exactly the same manner except that $H^{36}Cl$ (25 μCi) was added to the solution to give a specific radioactivity of 183 dpm/μmol of chloride.

Estimation of Bound Chloride.—The peptide resin (2 g) was washed with dichloromethane (3 × 1 ml) and then treated for 15 min with 25 ml of the standard pyridine hydrochloride solution (0.3 *M*, measured with a volumetric pipette). The excess reagent was then removed by the following washes: (1) dichloromethane (3 × 20 ml, each for 2 min); (2) ethanol or *tert*-butyl alcohol[48] (3 × 20 ml, each for 2 min); (3) dichloromethane (4 × 20 ml, each for 2 min). All washes were removed by drying the resin under nitrogen pressure (1 min). Washes 1–3, as well as the remainder of the pyridine hydrochloride solution, were collected in a 250-ml volumetric flask made up to volume with dichloromethane and a sample was taken for chloride measurements. The amine hydrochloride, that had been formed by the pyridine hydrochloride treatment, was neutralized by two triethylamine–dichloromethane washes (1.5% triethylamine, 2 × 20 ml, each for 10 min). The peptide resin was then washed with dichloromethane (3 × 20 ml, each for 2 min). These washes were combined with triethylamine washes in a 100-ml volumetric flask and a sample was taken for chloride measurements.

Measurement of Chloride with the Chloridimeter.—Although the chloridimeter was developed by Cotlove, *et al.*,[49] for the determination of chloride in serum and urine, it was found that the chloride was quantitatively extracted from dichloromethane into the aqueous phase under the conditions of the assay.

The sample (1 ml), dissolved in dichloromethane, was added to a mixture of 0.1 *M* nitric acid and 1.7 *M* acetic acid (3 ml) and gelatin reagent (0.2 ml). The assay mix was then added to the reaction vessel of the chloridimeter and the chloride concentration was determined. A sodium chloride solution (1.6 mg/l.) was used to calibrate the instrument, while the blank value was measured with dichloromethane (1 ml) and the assay mix (3.2 ml).

Calculation of Chloride by ^{36}Cl Radioactivity.—The sample (1 ml) was added to Bray's solution (10 ml) and the sample was counted in a Packard liquid scintillation spectrometer, Model 544, which had been programmed to present the data as disintegrations per minute of chloride-36. As several of the reagents used in the washes, particularly triethylamine and pyridine hydrochloride, caused strong quenching of the radioactivity, it was necessary to calibrate the program with quenching standards.

Procedure for Acetylation of Incomplete Peptides.—Peptide resin (2 g, 0.66 mmol) was treated with a solution of 3 mmol of ^{14}C-acetic anhydride (specific radioactivity 5.4 × 10^3 dpm/μmol) and 3 mmol of triethylamine dissolved in dichloromethane (CH_2Cl_2, 20 ml) for 20 min. It was found that the following washing procedures were necessary for adequate removal of the excess reagent (all washes 20 ml and for 2 min unless otherwise specified): 3 × CH_2Cl_2, 3 × *tert*-butyl alcohol, 3 × CH_2Cl_2, 3 × triethylamine (1.5% v/v in CH_2Cl_2), 3 × CH_2Cl_2, 3 × *tert*-butyl alcohol, 3 × CH_2Cl_2. All the washes were combined and an aliquot was counted for ^{14}C radioactivity to check that all of the excess acetic anhydride had been removed.

Standard Procedure for the Coupling of BOC-Amino Acids.—As both triethylamine and ethanol were used in each cycle of the synthesis, a small loss of peptide chain by transesterification may occur repeatedly during a long synthesis. To minimize this possibility, the sterically hindered alcohol, *tert*-butyl alcohol, was substituted for ethanol and the concentration of triethylamine was reduced from 10 to 3% (v/v). The *tert*-butyl alcohol was found to be efficient in shrinking the resin even when 5% CH_2Cl_2 was added to prevent freezing of the alcohol.

The following sequence of reactions was used to prepare the peptide resin for a coupling reaction (all washes 20 ml and 2 min unless otherwise specified): 3 × CH_2Cl_2, trifluoroacetic acid–CH_2Cl_2, (1:1, v/v, 20 ml, 2 min), 6 × CH_2Cl_2, 3 × triethylamine (3% v/v in CH_2Cl_2), 3 × CH_2Cl_2. The coupling step was carried out with a threefold excess of the appropriate amino acid (0.2 *M*) and dicyclohexylcarbodiimide (DDC, 0.2 *M*) as the coupling reagent, except for glutamine and asparagine, which were added in the same concentration as the *p*-nitrophenyl ester. All couplings were left for 6 hr, except for active esters which were coupled for 12 hr. After coupling the excess reagents were removed by 3 × CH_2Cl_2 washes.

Modified Procedure for the Coupling of BOC-Amino Acids.—The BOC group was removed and the peptide resin was prepared for coupling by the following sequence of washes (20 ml and for 2 min unless specified): 3 × CH_2Cl_2, trifluoroacetic acid–CH_2Cl_2 (1:1, 2 × 10 ml, 2 and 20 min), 3 × CH_2Cl_2, 3 × *tert*-butyl alcohol, 3 × CH_2Cl_2, 2 × triethylamine (3%, v/v in CH_2Cl_2), 3 × CH_2Cl_2, 3 × *tert*-butyl alcohol, 3 × CH_2Cl_2, 3 × dimethylformamide (only for couplings in that solvent). The coupling procedure was the same as described above, except that the time of reaction was reduced to 2 hr for DCC-mediated couplings. First, couplings were routinely carried out with dichloromethane as the solvent. The by-products from the reaction were removed by the following washes: 3 × CH_2Cl_2, 3 × *tert*-butyl alcohol, 3 × CH_2Cl_2, 3 × triethylamine (3% v/v), 3 × CH_2Cl_2, 3 × *tert*-butyl alcohol, 3 × CH_2Cl_2, 3 × dimethylformamide. The second coupling was carried out in a mixed solvent of dichloromethane and dimethylformamide (1:1) and left for 2 hr. The following washes then completed the procedure: 3 × dimethylformamide, 3 × CH_2Cl_2, 3 × *tert*-butyl alcohol, 3 × CH_2Cl_2, 3 × triethylamine (3% v/v), 3 × CH_2Cl_2, 3 × *tert*-butyl alcohol, 3 × CH_2Cl_2.

Preparation of Samples for Amino Acid Analysis.—Peptide resin (2 mg) was hydrolyzed with a mixture of HCl (12 *N*) and propionic acid (1:1, 2 ml) for 2 hr at 130° according to the method of Scotchler, *et al.*[20] Free peptides were hydrolyzed with 6 *N* HCl in sealed, evacuated tubes for 24 hr at 110°.

HBr–Trifluoroacetic Acid Cleavage of the Peptide from the Resin.—Peptide resin (1 g) was added to a mixture of trifluoroacetic acid (30 ml) and anisole (0.3 ml) in a cleavage apparatus as described by Stewart, *et al.*[50] HBr bubbled through the solution for 30 min at 25°, and the trifluoroacetic acid was removed from the resin by filtration. The resin was then washed with trifluoroacetic acid (3 × 10 ml) and the filtrate was combined with these washes. The trifluoroacetic acid was immediately removed by evaporation under reduced pressure and the residue was dissolved in 0.01 *M* Tris-HCl, pH 7.3 (10 ml). The cleavage was then repeated on the peptide resin under exactly the same conditions as before, except that the time of reaction was increased to 1 hr. The two products were then combined.

Registry No.—Pyridine hydrochloride-^{36}Cl, 22069-61-0; hydrochloric-^{36}Cl acid, 36640-18-3; sequence 74–63, 37746-85-3; sequence 74–69, 37746-86-4.

(47) R. B. Merrifield and J. M. Stewart, *Nature (London)*, **207**, 522 (1965).

(48) The *tert*-butyl alcohol used in this paper has 5% (v/v) dichloromethane added to prevent freezing.

(49) E. Cotlove, H. V. Trantham, and R. L. Bowman, *J. Lab. Clin. Med.*, **50**, 358 (1958).

(50) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis," W. H. Freeman, San Francisco, Calif., 1969, pp 40–41.

N-Terminal Groups in Mass Spectrometry of Peptides. A Study Including Some New and Useful Derivatives

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In an effort to find volatile peptide derivatives with mass spectrometric fragmentation characteristics suitable for peptide sequencing studies, 20 new N-terminal blocking groups were used to derivatize the test peptide Val-Ile-Ala. Electron impact mass spectra were obtained for the derivative esters and compared to the previously reported spectra of the test peptide in terms of relative intensity of molecular and N-terminal sequence ions. Thirty-four derivatives were compared in all. The most successful of these in terms of ease of interpretation were the 5-(*N*,*N*-dimethylamino)naphthalenesulfonyl, *p*-dimethylaminobenzylidene, and 4-(*N*,*N*-dimethylamino)naphthylidene derivatives. The intensities of the molecular ions were 10–100 times greater relative to the base peak than in previously reported spectra of derivatives of Val-Ile-Ala. The M − 56 ions, ascribed as arising from a McLafferty rearrangement and loss of C_4H_8 from the isoleucyl residue, did not appear from most of the derivatives displaying relatively intense molecular ions. The apparent inverse relationships between the relative intensities of molecular ions and the corresponding M − 56 ions was attributed to ionization potential effects. Selection of the appropriate derivatives of the more complex peptides, Pro-Val-Ile-Ala, Met-Val-Ile-Ala, Glu-Try-Glu, Gly-Pro-Gly-Gly, Gly-Gly-Gly-Gly-Gly-Gly, and the gastrin C-terminal fragment, Try-Met-Asp-Phe-NH_2 led to mass spectra containing sufficient information to allow sequence assignment in every instance; however, the amino acid composition was required in some cases.

The application of mass spectrometry to structure elucidation of complex molecules is limited by a number of factors, one of which is the tendency of the molecule to fragment along an increasing number of routes with increasing size and complexity of the molecule. There appears to be an inverse relationship between molecular weight within a homologous series and the probability of observing the parent ion or larger fragments in the electron-impact (EI) induced mass spectra of any given series. This problem is acute in mass spectrometry of peptides and is further accentuated by the occurrence of side-chain related fragmentation patterns.

It would appear that any factor tending to yield stable ionic species in which the charge and/or energy is localized to a significant degree on some center in the ion that does not participate in elimination or cleavage processes should result in a relative increase in the intensity of parent and some large fragment ions. It would be expected that any such center possessing a low ionization potential could be, in fact, the site of charge localization. We report here three peptide derivatives which give parent and sequence ions of 10–100 times the relative intensity of previously reported derivatives as well as diminished side-chain cleavage. These are the dansyl [5-(*N*,*N*-dimethylamino)naphthalenesulfonyl] (DNS), *p*-dimethylaminobenzylidene (DMB), and the 4-(*N*,*N*-dimethylamino)naphthylidene (DMN) derivatives of the peptide amino groups.[1]

Experimental Section

Materials.—The peptides Val-Ile-Ala and Met-Phe-Gly were obtained from Cyclo Chemical Corp. The peptides Glu-Try-Glu and Try-Met-Asp-Phe-NH_2 and DNS-Gly were obtained from Mann Research Laboratories. The peptide Leu-Ala was obtained from Nutritional Biochemicals Corp. DNS-Pro and DNS-Met were obtained from Sigma Chemical Co. The aldehydes and ketones were obtained from Aldrich Chemical Co., except *p*-dimethylaminobenzaldehyde and acetylacetone (Matheson Coleman and Bell) and 4-dimethylamino-1-naphthaldehyde which was prepared as described.[2]

Syntheses.—The phthalyl and naphthalene-1,8-dicarboxyl peptide derivatives were prepared essentially by the method of King and Kidd.[3] Dansyl amino acids and peptides and 1-naphthalenesulfonyl-Val-Ile-Ala-OCH_3 were prepared essentially by the method of Gray.[4] The Schiff base peptide ester derivatives were prepared by heating equivalent amounts of the aldehyde and peptide ester in glacial acetic acid at 118° for 5–15 min. The 1- and 2-naphthoyl peptide esters were prepared from the *N*-hydroxysuccinyl esters of the acids and Val-Ile-Ala-OC_2H_5. Permethylation of the peptide DNS-Val-Ile-Ala-OCH_3 was accomplished essentially by the method of Thomas.[5] Esterification of peptides was accomplished by refluxing the peptide in the appropriate alcohol for 10 min after addition of thionyl chloride.

The peptide derivatives DNS-Gly-Val-Ile-Ala-OC_2H_5, DNS-Pro-Val-Ile-Ala-OC_2H_5 and DNS-Met-Val-Ile-Ala-OC_2H_5 were synthesized from the corresponding *N*-hydroxysuccinyl-DNS-amino acid and Val-Ile-Ala-OC_2H_5. DNS-Leu-Ala-Val-Ile-Ala-OC_2H_5 was prepared by coupling equimolar amounts of DNS-Leu-Ala and Val-Ile-Ala-OC_2H_5 with an equivalent amount of dicyclohexylcarbodiimide; the hexapeptide derivatives DMB-Val-Ile-Ala-Val-Ile-Ala-OC_2H_5 and DMB-Val-Ile-Ala-Met-Phe-Gly-OC_2H_5 were prepared in an analogous fashion.

Mass Spectra.—The spectra reported were obtained with a Hitachi Perkin-Elmer RMU-7 mass spectrometer. The samples were introduced through the solid inlet system. Inlet temperatures at which the spectra were recorded are indicated in the description of the spectra. In all cases the inlet temperature was raised gradually until the relative intensities of the peaks were nearly constant; in some cases higher temperatures were required, presumably because of some impurities of greater volatility. An ionizing voltage of 70 eV was used in obtaining all spectra reported.

Results

Figure 1 shows the mass spectra of the 1-naphthalenesulfonyl, DNS, and permethylated DNS esters of Val-Ile-Ala (**1**). The relative intensities of the sequence and molecular ions show a significant variation among the derivatives. The spectrum of 1-naphthalenesulfonyl-Val-Ile-Ala methyl ester contains a molecular ion (*m/e* 505) of relatively low intensity and a prominent ion of *m/e* 449 corresponding to the product ion of the McLafferty rearrangement of the Ile side chain

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(1) For preliminary accounts of this work, see J. P. Lehman, H. Falter, and R. A. Day, Abstracts, Third Central Regional Meeting of the American Chemical Society, Cincinnati, Ohio, June 6–8, 1971, No. 178; H. Falter, J. P. Lehman, and R. A. Day, Abstracts Volume, XXIII International Congress of Pure and Applied Chemistry, Boston, Mass., July 25–30, 1971, p 90.

(2) J. C. Banerji and S. N. Sanyal, *Indian J. Chem.*, **6**, 346 (1968).

(3) F. King and D. Kidd, *J. Chem. Soc.*, 3315 (1949).

(4) W. R. Gray, "Methods in Enzymology," Vol. 11, Academic Press, New York, N. Y., 1967, pp 142, 143.

(5) D. W. Thomas, *Biochem. Biophys. Res. Commun.*, **33**, 483 (1968).

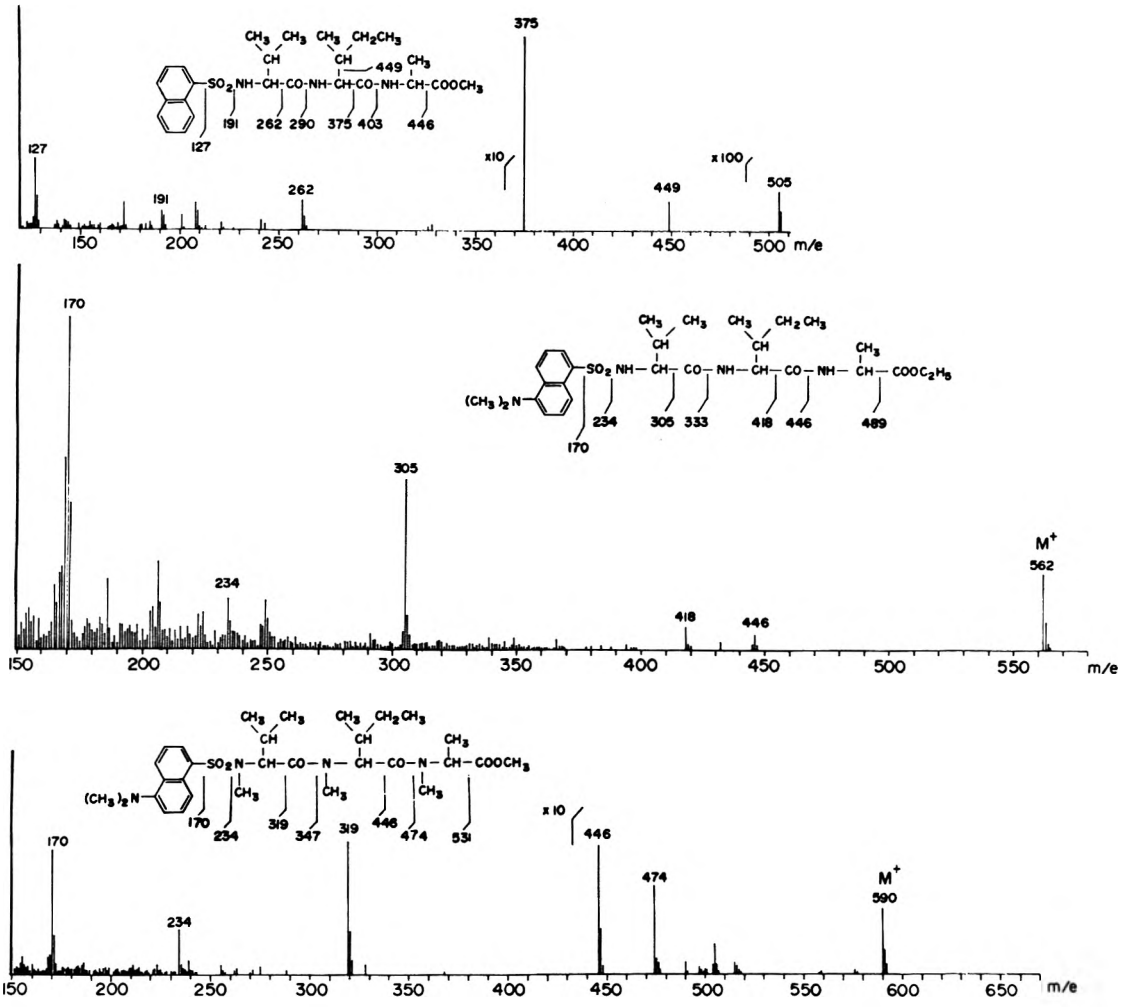


Figure 1.—Mass spectra of naphthalenesulfonylvalylisoleucylalanine derivatives: top, spectrum of 1-naphthalenesulfonyl-Val-Ile-Ala-OCH_3 obtained with an inlet temperature of 320°; middle, spectrum of DNS-Val-Ile-Ala-OC_2H_5, inlet temperature of 440°; bottom, spectrum of permethylated DNS-Val-Ile-Ala-OCH_3, inlet temperature of 250°.

with loss of isobutylene. The DNS derivative has a relatively more intense molecular ion (*m/e* 562) and no detectable ion at *m/e* 506, the expected value of the McLafferty product ion. All derivatives show many, but not all, of the sequence ions. The permethylated derivative was significantly more volatile[6] and the distribution of ion intensities was similar to that of DNS-Val-Ile-Ala-OC_2H_5 except that the relative intensity of the molecular ion was less.

The DMB ethyl (Figure 2, top) and the DMN methyl (Figure 2, bottom) esters of **1** display intense molecular ions. The distribution of intensity among sequence and molecular ions for the latter is perhaps the most uniform of any derivative of **1** shown or tabulated in Table I. It was amenable to gas–liquid partition chromatography. Table I contains a comparison of the relative intensities of the sequence and molecular ions for a number of drivatives of **1**. The spectrum of the phthalyl methyl ester of **1** was prepared in this laboratory for comparison with that reported by Prox and Sun[7] in order to determine differences in observed spectra due to differing instrumental and operational parameters.

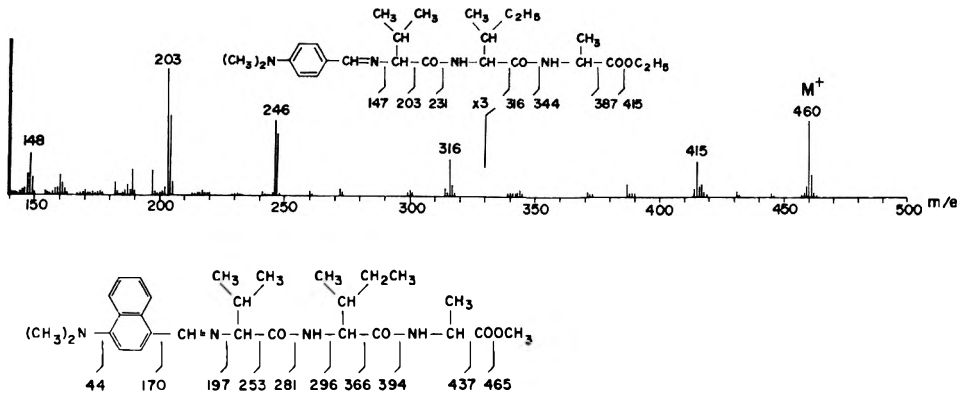
Mass spectra of the DNS ethyl esters of Pro-Val-Ile-Ala (Figure 3), Met-Val-Ile-Ala (Figure 4), Gly-Val-Ile-Ala, and Leu-Ala-Val-Ile-Ala were obtained at inlet temperatures higher than that required for DNS-Val-Ile-Ala-OC_2H_5. The mass spectra of these derivatives contain relatively intense molecular ions with the exception of the last one, and none contain the ion fragments expected from a McLafferty rearrangement. A sequence peak at one or both sides of each carbonyl group was found in all cases.

The mass spectra of the DMB triethyl ester (Figure 5) and the DMN trimethyl ester (Figure 6) derivatives of Glu-Try-Glu both contain the molecular and sequence ions. Side-chain cleavage of the tryptophan residue from the former as the indolylmethyl is indicated by the presence of an *m/e* 547 (M − 130). The *m/e* 577 corresponds to loss of $CH_2CHCO_2C_2H_5$ from glutamyl side chains by a McLafferty rearrangement. The *m/e* 447 corresponds to a sequence peak and loss of both fragments from the molecular ion. High-resolution analysis would be required to determine the processes contributing to *m/e* 447. The spectrum contains several prominent ions which are not N-terminal fragments. Most of these may be rationalized as corresponding to C-terminal fragments and to fragments having arisen by two single bond cleavages.[8] The second derivative gave a spectrum (Figure 6) with a smaller number of ions; the most

(6) This derivative was readily purified by gas–liquid partition chromatography. Experiment performed by Dr. J. MacGee, V. A. Hospital, Cincinnati, Ohio.

(7) A. Prox and K. K. Sun, *Z. Naturforsch. B*, **21**, 1028 (1966).

(8) Patil, *et al.*, *Org. Mass Spectrom.*, in press.



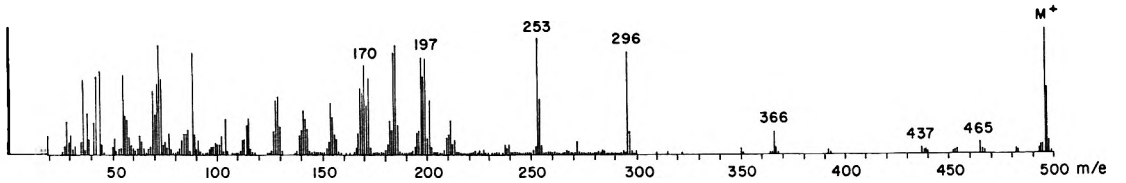


Figure 2.—Spectra of DMB-Val-Ile-Ala-OC_2H_5 and DMN-Val-Ile-Ala-OCH_3; inlet temperatures 220 and 120°, respectively.

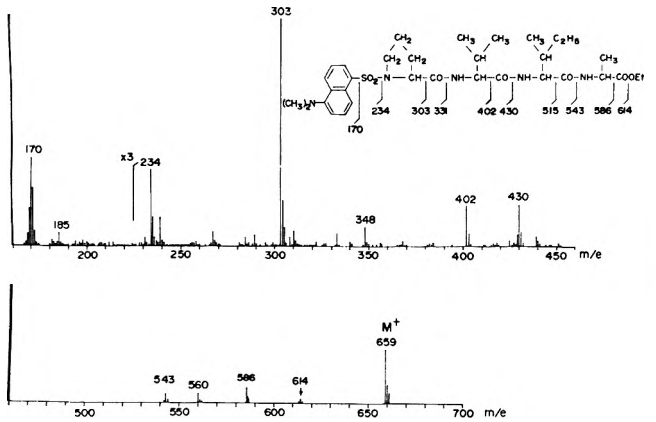


Figure 3.—Spectrum of DNS-Pro-Val-Ile-Ala-OC_2H_5; inlet temperature 380°.

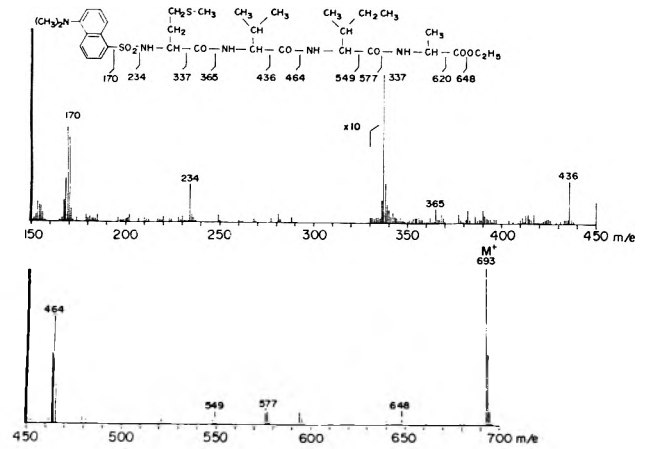


Figure 4.—Mass spectrum of DNS-Met-Val-Ile-Ala-OC_2H_5; inlet temperature 420°.

prominent ions include N-terminal fragment and molecular ions.

The tetrapeptide derivative, DMN-Gly-Pro-Gly-Gly-OEt (not shown), displays the molecular ion and some sequence ions in its spectrum. In addition there

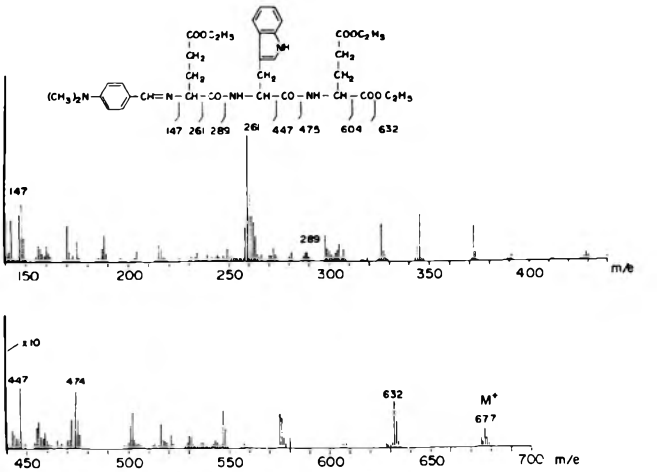


Figure 5.—Mass spectrum of DMB-Glu-Try-Glu-$(OCH_3)_3$; inlet temperature 400°.

are prominent ions at m/e 114 and 154 having the m/e of glycylglycyl and glycylprolyl or prolylglycyl, or the corresponding diketopiperazines. Also, m/e 211 is observed, corresponding to Gly_2-Pro. Additional fragments corresponding to these but plus or minus CO or NH are seen.

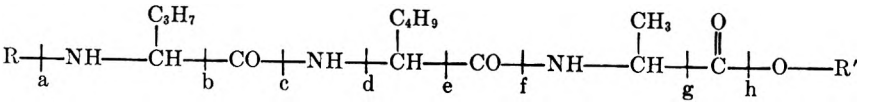
Figure 7 shows the spectrum of the DMB derivative of the C-terminal gastrin fragment, DMB-Try-Met-Asp-(OC_2H_5)-Phe-NH_2. The observed spectrum contains few N-terminal sequence ions. Many of the prominent peaks can be rationalized as arising from two single bond cleavages.[8]

In Figure 8 is shown the mass spectrum of DMB-Val-Ile-Ala-Val-Ile-Ala-OC_2H_5 which may be rationalized in terms of the peptide sequence. The spectrum contains a prominent molecular ion and many of the N-terminal sequence ions are prominent. A McLafferty rearrangement of the Ile side chain may contribute to the observed, low intensity m/e 687.

Figure 9 shows the mass spectrum of DMB-Val-Ile-Ala-Met-Phe-Gly-OC_2H_5, which contains a prom-

TABLE I

RELATIVE INTENSITIES OF SEQUENCE IONS[a] FOR DERIVATIVES OF VALYLISOLEUCYLALANINE ESTERS



Registry no.	Amino blocking group	Ester[b]	a	b	c	d	e	f	g	h	M − 56	M	Source of data[c]
37580-54-4	None	M		100			3.9	1.6	0.5	0.3	0.13	0.3	a
37580-55-5	Phthalyl	M		100	15		48	3		0.4	2.3	0.15	a
	Phthalyl	M		100	33		100	7.2		1.9	10	1.3	b
37580-56-6	Phthalyl	E		100	70		100	19	1	5.3	22	2.1	b
37580-57-7	Cyclohexanecarboxyl	M	11	42	100		10	4	0.07	0.5	2.8	0.5	a
37580-58-8	Benzoyl	M	100	39	27	na[e]	5	2	0.04	0.2	na[e]	0.1	a
37580-59-9	Pentafluorobenzoyl	M	100	54	5	na	10	6	0.3	0.5	na	0.04	a
37580-60-2	*p*-Chlorobenzoyl	M	100	39	13		2.5	2.5	0.04	0.1	1.6	0.1	a
37580-61-3	Acetyl	M	21	100	36		26	12	0.3	0.5	9.8	0.3	a
37580-62-4	Trifluoroacetyl	M		31			100	7	1.5	0.8	33	0.1	a
37580-63-5	Formyl	M	20	100	10	na	89	19	1.4	1.3	na	0.4	a
37580-64-6	*n*-Decanoyl	M	8.4	54	100		9	7	0.09	0.9	4.5	0.5	a
37580-65-7	*n*-Stearoyl	M	8.1	41	100	na	1.4	6	0.2	0.7	na	0.2	a
37580-66-8	Chlorodifluoroacetyl	M		55	5	na	100	11	1.1	0.4	na	0.1	a
6686-82-4	Carbobenzoxy	M		28	100	na	67	10	0.2	1.4	na	1.3	a
37580-68-0	2,4-Dinitrophenyl	M		100		na	3	0.9		0.4	na	0.8	a
37580-69-1	1-Naphthoyl	M	100	65	93		20	9		2	10	8	b
37580-70-4	1-Naphthoyl	E	99	90	100		11	14	<1	2	10	5	b
37580-71-5	2-Naphthoyl	M	100	33	61		4.5	3		1	2	3.1	b
28415-47-6	Adamantoyl	M	19	35	100		3	2		0.4	10	0.6	c
37580-73-7	Naphthalene-1,8-dicarboxyl	M		46	100		8	4					b
37580-74-8	Naphthalene-2,3-dimethylene	M		100									b
37580-75-9	Benzenesulfonyl	M	45	100			85	5		0.4	4.1	0.2	a
37580-76-0	Dansyl	M	100	30	<1	1	5	2				24	b
37580-77-1	1-Naphthalenesulfonyl	M	68	100			54				16	3.2	b
37580-78-2	Benzylidene	E		100		37	37	5		3.7	1.0	0.5	b
37495-93-5	Salicylidene	E		100	21.3	73	35	13		7.8		23.0	b
37580-24-8	β-Indolylmethylidene	E	9.5	100		37	64	2.8	0.74	3.2	0.7	3.2	b
37580-25-9	*p*-Nitrobenzylidene	E	32	37		25	29	15		4	4.4	0.4	b
	p-Nitrobenzylidene[d]	E	27	100		27	9	4	1.7	2.9		0.9	b
37580-26-0	*p*-Cyanobenzylidene	E		94		44	100	47		7.0	1.34	1.07	b
37580-27-1	α-Phenyl-*p*-dimethylaminobenzylidene	E		100								7.3	b
37580-28-2	*p*-Dimethylaminocinnamylidene	E	77	100		37	3			9.2		24	b
37580-29-3	*p*-Diethylaminocinnamylidene	E		100		68	18		3.2	6.8		40	b
37580-30-6	*p*-Methoxybenzylidene	E	12	100		83	67	9	1.2	11		1.2	b
37580-31-7	2-Pyridylmethylidene	E	15	79	31	100	11	12	6.7	11		8.0	b
37580-32-8	3-Pyridylmethylidene	E		79		100	12	5		2.3	1.1	1.2	b
37580-33-9	4-Pyridylmethylidene	E		100		59	98	11	2.2	5.4	1.7	1.1	b
37580-34-0	Acetylacetonyl	E		100	12			4.6	1.0	2.9		6.0	b
37580-35-1	*p*-Dimethylaminobenzylidene	E	29	100	8	44	6	6	22	6		29	b
37580-36-2	4-Dimethylamino-1-naphthylidene	M	77	92		72	9.4		6.0	8.5		100	b
37580-37-3	2-Hydroxy-1-naphthylidene	E		100	3.8	5.7	3.6	2.1	1.2	3.4		29	b

[a] The values were obtained from spectra obtained on an RMU-7 mass spectrometer or from literature cited. Cleavage "a" is between N^{α} and C^{α} of valyl residue for many of the Schiff bases and cyclic imides; R is amino blocking group and may be bonded to the valyl nitrogen by one single bond, one double bond, or two single bonds; R′ is methyl or ethyl. [b] M = methyl, E = ethyl. [c] (a) From an AEI MS-9 mass spectrometer, Prox and Sun;[7] (b) from a Hitachi Perkin-Elmer RMU-7 mass spectrometer in this laboratory; (c) from a Hitachi Perkin-Elmer RMU-6D mass spectrometer, Lengyel, *et al.*[9] [d] Peaks corresponding to *m/e* for cleavage indicated in column heading accompanied by a loss of NO. [e] The term "na" means not available from reference cited.

inent molecular ion and ions whose *m/e* correspond to sequence ions, some of relatively high intensity. The spectrum contains many prominent ions which were not rationalized as N-terminal fragments. The prominent *m/e* 643 can be rationalized as side-chain cleavage of both C_7H_7 and C_2H_5S from the molecular ion. DMN-Gly_6-OCH_3 (spectrum not shown) gave an M − 31 and a small M^+ ion; in addition, it displayed peaks having the nominal masses of Gly_2 and Gly_3 and some sequence ions.

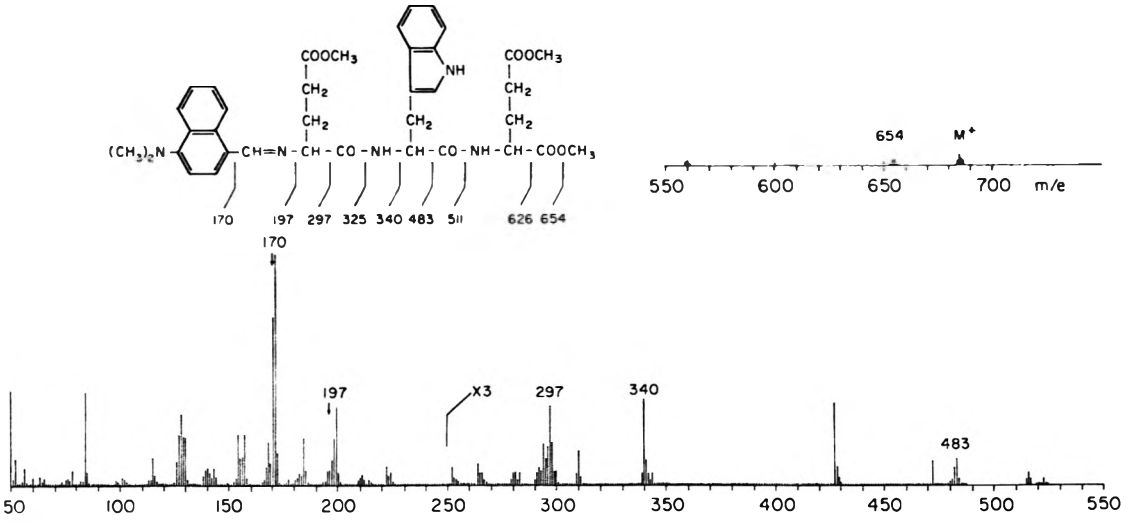


Figure 6.—Mass spectrum of DMN-Glu-(γ-OCH_3)-Try-Glu-$(OCH_3)_2$; inlet temperature 140°.

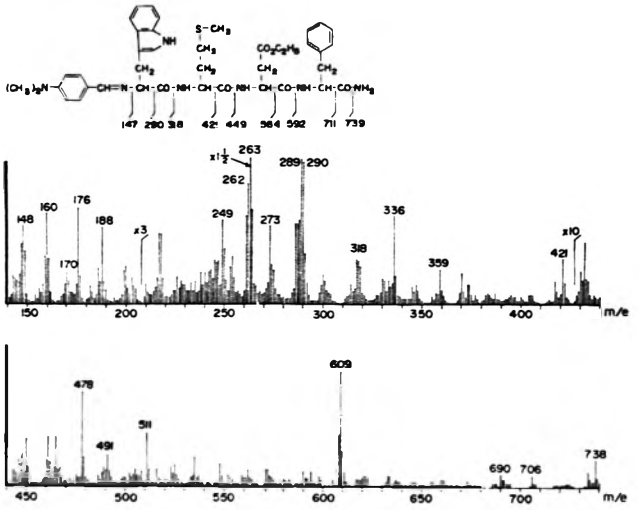


Figure 7.—Mass spectrum of DMB-Try-Met-Asp-(β-OC_2H_5)-Phe-NH_2; inlet temperature 450°.

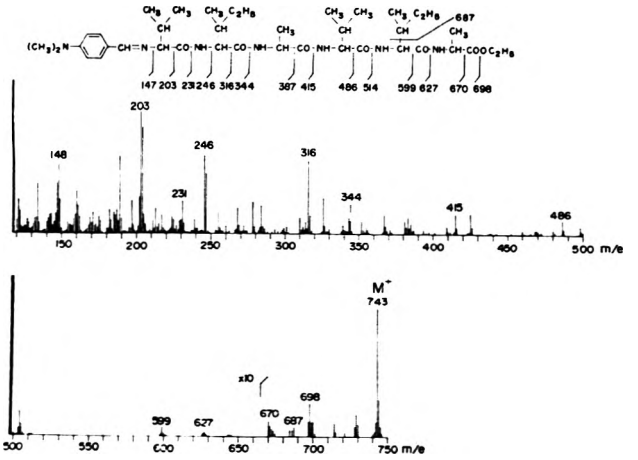


Figure 8.—Mass spectrum of DMB-Val-Ile-Ala-Val-Ile-Ala-OC_2H_5; inlet temperature 400°.

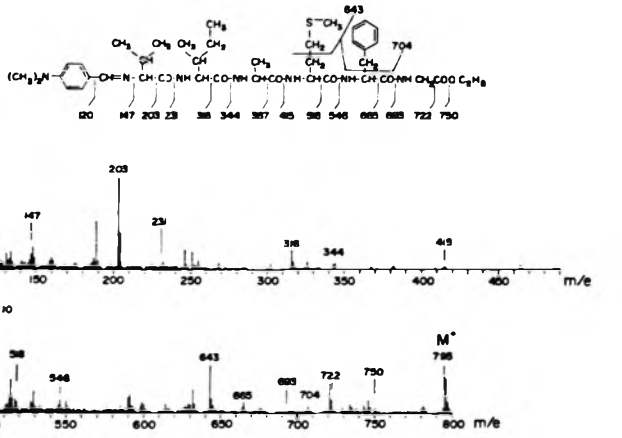


Figure 9.—Mass spectrum of DMB-Val-Ile-Ala-Met-Phe-Gly-OC_2H_5; inlet temperature 175°.

Discussion

It is apparent from the preceding data that some of the peptide derivatives reported here for the first time have important properties relative to the application of mass spectrometry to peptide sequencing. This study, in part an extension of the work of Prox and Sun[7] using **1** as a reference peptide, reveals that certain peptide derivatives give EI mass spectra with relatively more intense molecular and sequence ions than any derivatives reported thus far. DMB-Val-Ile-Ala-OC_2H_5 gave a spectrum containing all of the sequence ions with none less than 6% of the intensity of the base peak of the spectrum. The spectrum of DMN-Val-Ile-Ala-OCH_3 contained the most intense molecular ion of any derivative of **1** reported thus far. Similarly, the DNS derivative of **1**, and its permethylated form, and the naphthoyl derivatives of **1** all give significantly more intense sequence and molecular ions relative to derivatives reported earlier.

The mass spectra of the DNS, DMB, and DMN peptide esters of **1** are dominated by molecular and sequence ions. More complex peptides gave spectra with varying ease of interpretation. The two DNS tetrapeptide derivatives (Figures 3 and 4) both gave relatively intense molecular ions, 15 and 5.2%, respectively, compared to the base peaks of the spectra. McLafferty product ions arising from rearrangement of the Val or Ile side chains were not found in either instance, nor was cleavage of the Met side chain of the latter observed; the sequence and molecular ions dominate the mass spectra of both. Similar results were obtained for DNS-Gly-Val-Ile-Ala-OC_2H_5 (not shown). The low-resolution mass spectra discussed

above are suitable for the assignment of the sequences of the respective peptides without prior knowledge of the amino acid compositions. The DNS pentapeptide ester of Leu-Ala-Val-Ile-Ala (not shown) gave a mass spectrum containing all of the sequence ions but no molecular ion. This derivative required a very high inlet temperature to obtain the observed spectrum, and it can be suspected that the derivative's vapor pressure was insufficient and that the observed spectrum was that of pyrolysis products. Other DMB and DMN peptide esters gave mass spectra which required knowledge of the amino acid composition in order to assign the amino acid sequences, or they gave spectra which could not be unambiguously interpreted with respect to amino acid sequence on the basis of N-terminal fragments, even with knowledge of the composition of the peptide.[8]

The mass spectrum of DMB-Glu-Try-Glu-$(OC_2H_5)_3$ (Figure 5) would be difficult to interpret on the basis of its N-terminal fragments alone without the knowledge that the amino acid composition was Glu_2-Try. With this knowledge, *m/e* 677 is identified as the molecular ion and *m/e* 632 as the M − OC_2H_5 ion. The expected N-terminal sequence ions for all possible sequences of the composition Glu_2-Try are tabulated as follows: DMB-Glu-Try-Glu-$(OC_2H_5)_3$ 147, 261, 289, 447, 475, 604, 632; DMB-Try-Glu-Glu-$(OC_2H_5)_3$ 147, 290, 318, 447, 475, 604, 632; DMB-Glu-Glu-Try-$(OC_2H_5)_3$ 147, 261, 289, 418, 446, 604, 632. Intense ions corresponding to the expected sequence ions are found only for one of the possible sequences, Glu-Try-Glu. This spectrum illustrates some of the difficulties to be encountered in attempting to assign composition and sequence of peptides on the basis of expected N-terminal cleavages in their low-resolution EI mass spectra. If the amino acid composition of the peptide were unknown, it would be necessary to assign the molecular weight on the basis of the *m/e* 677 and 632 (M − OC_2H_5) ions. The molecular weight in this and parallel cases would be uncertain due to the presence of side-chain carboxyl groups. A detailed analysis of all possible fragment ions which could give rise to *m/e* 677 in conjunction with the observed ions would be necessary if one were to unambiguously assign the composition and sequence of the peptide on the basis of the observed mass spectrum. In addition, the plethora of fragment ions below the highest *m/e* of 677 such as *m/e* 577 (M − $CH_2CHCO_2C_2H_5$) and 547 (M − $C_9H_8N_1$) would render the spectrum more difficult to interpret without prior knowledge of the amino acid composition of the peptide. The sequence assignment is unambiguous if the compositional data and other fragmentation data from the mass spectrum as utilized. In contrast to the spectrum of DMB-Glu-Try-Glu-$(OC_2H_5)_3$ discussed above, the spectrum of DMN-Glu-Try-Glu-$(OCH_3)_3$ (Figure 6) contains fewer ions, and the sequence ions are of greater relative intensity making this spectrum more readily interpreted. We have not observed any significant differences in observed spectra attributable to the choice of either the methyl or ethyl ester derivative in a number of comparative spectra.

The observed mass spectra of the DMN peptide ester derivatives in general contain the sequence and molecular ions in greater relative abundance than do the spectra of the DNS and DMB ester derivatives of the same peptide. The DMN ethyl ester derivative of I (Table I) is a striking example in that the base peak of the observed spectrum (Figure 2) is the molecular ion in contrast to the DMB derivative where the M^+ is 29% of the base peak. Most of the sequence peaks are of relatively high intensity in the spectrum of the DMN derivative of **1** as well. The spectrum of DMN hexaglycine methyl ester (not shown) contained some sequence ions, M^+ and M − 31 ions and fragment ions corresponding to di- and tripeptide fragments of the molecule. This spectrum is notable in that this large high glycine content peptide was not found to be amenable to EI mass spectrometry with other N-terminal blocking groups. The spectra discussed above indicate the potential utility of the DMN derivative in peptide sequencing studies by mass spectrometry.

The spectrum of the DMB derivative of the gastrin fragment (Figure 7) reveals that for this tetrapeptide amide no total sequence assignment can be made on the basis of N-terminal sequence peaks with or without knowledge of the amino acid composition. By applying the "internal fragmentation" concept,[8] the majority of the most prominent peaks can be rationalized and assigned structures. These assignments provide unambiguous data for sequence assignment in this and other peptides from their low-resolution spectra. The spectra shown in Figures 8 and 9 are further representative examples. The spectrum of DMB-Val-Ile-Ala-Val-Ile-Ala-OC_2H_5 (Figure 8) contains a prominent molecular ion and relatively intense sequence ions. Given the amino acid composition, it is possible to assign the amino acid sequence of the peptide unambiguously from the low-resolution spectrum on the basis of the N-terminal fragments. DMB-Val-Ile-Ala-Met-Phe-Gly-OC_2H_5 (Figure 9) gives a strong molecular ion with most of the N-terminal sequence ions. Other prominent ions can be rationalized as C-terminal fragments (*m/e* 550, 591) with an H shift and as arising from two single bond cleavages, *e.g.*, *m/e* 643 from two side chains, *m/e* 514 and 529 from the two ends of the chain.

An important characteristic of the DNS, DMB, and DMN peptide ester derivatives of **1** is the suppression of the McLafferty rearrangement of the Ile and Val side chains. This rearrangement was found operative in all of the other derivatives of **1** examined by Prox and Sun[7] and Lengyel, *et al.*[9] Most of the Schiff base derivatives failed to give the M − 56 peak. Significantly reduced side-chain cleavage of DNS, DMB, and DMN peptide derivatives relative to other derivatives was found for a variety of peptides containing amino acids with readily cleaved side chains such as Met, Phe, Try, and Glu.

Comparison of the spectra of analogous benzene and naphthalene derivatives (Table I) shows that the latter have a more favorable cleavage pattern in general. The 1- and 2-naphthoyl derivatives gave a larger fraction of the total ion current in the sequence and molecular ions than did the benzoyl and several substituted benzoyl derivatives; the McLafferty cleavage manifested as *m/e* M − 56 shows the converse relationship. The naphthalenesulfonyl shows a more intense M^+ than

(9) I. Lengyel, R. A. Salamone, and K. Biemann, *Org. Mass Spectrom.*, **3**, 789 (1970).

the benzenesulfonyl derivative. The DMN derivative displays an M^+ that is the base peak, while the M^+ is 29% of the base peak for the DMB derivative. All of the aromatic Schiff bases examined thus far display a prominent ion corresponding to a cleavage of the N^{α}–C^{α} bond of the second amino acid residue from the N-terminus (Table I, column d). There is no apparent relationship between the electron-withdrawing properties of the aromatic moiety and the relative intensity of the "d" cleavage. The spectra of the *p*-diethyl- and *p*-dimethylaminocinnamylidene ester derivatives of **1** (Table I) were found to be comparable in their ease of interpretation although differences in the distributions of ion intensities were noted. This suggests that dimethylamino and diethylamino substituents should have about the same effect.

Many of the peptide mass spectra discussed above exhibit two properties which are pertinent to the problem of peptide sequencing by EI mass spectrometry. These features are (1) relatively intense molecular and high *m/e* sequence ions, and (2) suppression or elimination of McLafferty fragmentations and other side-chain cleavages in certain derivatives. It has been well documented that substituent groups within a molecule can have a decided effect on the EI mass spectrum of the molecule.[10,11] Numerous studies have shown that the ionization potential (IP) of a molecule with an aryl amino or dimethyl amino group is significantly lower than that of the unsubstituted molecule or one with another substituent.[12,13] It has been suggested that the fragmentation observed is a function of the difference between the IP of the molecule and the appearance potential (AP) of the fragment(s), *i.e.*, the greater the $\Delta(AP - IP)$, the less likely the fragmentation will be observed.[14,15] The Schiff base ester derivatives of **1** (Table I) examined in this study appear to bear out this contention if the IP's of model compounds are taken as estimates of the IP's of the peptide derivatives.[16] Wachs and McLafferty[17] have shown that an aryl substituent greatly affects the relative amount of McLafferty fragmentation through intervening σ bonds and that an aryl amino group almost completely suppresses the fragmentation in the model compound studied.

Audier[18] has demonstrated the generalization that when a fragmentation takes place in EI mass spectroscopy the positive charge remains on the fragment with the lowest IP. Bursey and McLafferty[19] recorded similar observations for a series of para-substituted aceto- and benzophenones. The EI mass spectra reported here of peptide derivatives containing an aryl dimethyl amino group are in contrast with previously reported chemical ionization mass spectra of peptide derivatives which contain both the C- and N-terminal sequence identifying ions.[20]

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(10) (a) R. G. Cooks, I. Home, and D. H. Williams, *Org. Mass Spectrom.*, **2**, 137 (1969); (b) M. S. Chin and A. G. Harrison, *ibid.*, **2**, 1073 (1969).
(11) F. W. McLafferty, *Chem. Commun.*, 956 (1968).
(12) C. Lageot, *Org. Mass Spectrom.*, **5**, 845 (1971).
(13) M. M. Bursey and F. W. McLafferty, *J. Amer. Chem. Soc.*, **88**, 529 (1966).
(14) M. A. Baldwin and A. G. London, *Org. Mass Spectrom.*, **2**, 549 (1969).
(15) D. A. Lightner and F. S. Steinberg, *ibid.*, **3**, 1095 (1970).
(16) R. W. Kiser, "Introduction to Mass Spectrometry and Its Application," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 301 ff, Appendix IV.
(17) T. Wachs and F. W. McLafferty, *J. Amer. Chem. Soc.*, **89**, 5044 (1967).
(18) H. E. Audier, *Org. Mass Spectrom.*, **2**, 283 (1969).
(19) M. M. Bursey and F. W. McLafferty, *J. Amer. Chem. Soc.*, **88**, 529 (1966).
(20) A. A. Kiryushkin, H. M. Fales, T. Axenrod, E. J. Gilbert, and G. W. A. Milne, *Org. Mass Spectrom.*, **5**, 19 (1971).

An Electrochemical and Spectrophotometric Study of Fluorene and the Fluorene Carbanion in Dimethylformamide, Dimethyl Sulfoxide, and Acetonitrile[1]

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The reduction behavior of the nonalternant aromatic hydrocarbon fluorene is investigated in DMF, DMSO, and acetonitrile, and compared and contrasted to that of alternant hydrocarbons. It is concluded that the normal electrochemical sequence does not occur on formation of the fluorene anion radical at the electrode in protic media, or when self-protonation occurs in aprotic media. Polarographic and coulometric data indicate that, rather than the usual reduction of a double bond, with a two-electron change, three electrons per molecule of fluorene are transferred under protic conditions, and reactive intermediates are formed which yield colored products on addition of oxygen. These products are unstable and decay rapidly to fluorenone under uv light. Spectrophotometric data of the colored intermediates are given, along with that of the fluorene anion radical.

It has been known for several years that chemical and electrochemical reduction of alternant aromatic hydrocarbons in aprotic solvents yields relatively stable anion radicals, which degrade by reaction with solvent and/or impurities. In the presence of electroinert proton donors such as phenol and resorcinol the anion radical abstracts a proton from the donor, and the resultant neutral radical is further reduced and protonated.[3] This sequence is the so-called electrochemical–chemical–

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(2) To whom all correspondence should be addressed.
(3) (a) N. H. Velthorst and G. J. Hoijtink, *J. Amer. Chem. Soc.*, **87**, 4529 (1965); (b) *ibid.*, **89**, 209 (1967).

electrochemical (ECE) mechanism. It is of considerable interest to determine whether nonalternant benzenoid hydrocarbons act in a similar manner. Certain nonalternant aromatic compounds which have undergone substantial study in this regard are those in which a methylene group acts as a bridge between two parts of a benzenoid system. As the bridge methylene contributes to the aromaticity of the molecule through hyperconjugative effects, these compounds can be considered nonalternant. The methylene hydrogens of such systems are somewhat acidic (pK_a = 20–25),[4-6] and it has been shown in an electrochemical study of a molecule of this type, 4,5-methylenephenanthrene, that even in aprotic media the usual ECE process takes place, to a small degree, *via* self-protonation, yielding the carbanion in addition to the unstable neutral radical.[6] It was demonstrated that 9,10-dihydro-4,5-methylenephenanthrene was a final reduction product in both protic (this is the exclusive product in protic solution) and aprotic media; *i.e.*, the most reactive double bond is reduced, in the manner of alternant hydrocarbons.[6] However, the reduction mechanism for the similar nonalternant hydrocarbon fluorene has not been clarified despite considerable study. It has previously been suggested that its reduction with alkali metal yields the carbanion, not *via* the ECE sequence, but by a loss of a hydrogen atom from the anion radical.[7] Janzen and Gerlock[8a] and Casson and Tabner[8b] also appear to favor this decomposition route of the initially formed anion radical (to the carbanion) rather than the ECE sequence, while Eisch and Kaska do propose an ECE mechanism involving the parent, RH_2, acting as a proton donor.[9]

In order to add to the understanding of the electrochemistry of nonalternant hydrocarbons and to attempt a resolution of the above differences it was decided to study the reduction of fluorene in several aprotic solvents, dimethylformamide (DMF), acetonitrile (MeCN), and dimethyl sulfoxide (DMSO), under both aprotic and protic conditions. It was also desired to determine whether dihydrofluorene is a final product of reduction, both in aprotic and protic media, as would be expected if the usual ECE sequence is followed in the case of fluorene.

All of the reduction reactions were carried out electrochemically, as changes in reactant and product concentration could be easily followed polarographically and spectrophotometrically, and reaction conditions could be controlled more exactly than with an active metal reductant.

Experimental Section

Instrumental.—Polarographic and constant-potential coulometric electrolyses were carried out using a three-electrode system, the details of which have been reported elsewhere.[6,10] The constant potential coulometry experiments were carried out in a flow cell which allowed the macroscopic electrolysis at a mercury pool to continue while the instantaneous polarographic diffusion current was measured at a dropping-mercury electrode. This cell system has been described previously.[11] The reference electrode in all cases was an anodized silver wire immersed in a 0.01 *M* $AgClO_4$–0.1 *M* *tert*-butylammonium perchlorate (TBAP) solution of the particular solvent being studied. Details of the construction of the reference and salt-bridge compartments are found elsewhere.[10]

Solutions were deoxygenated by bubbling with nitrogen which had been passed through a gas train consisting of a tube of hot copper wool to remove traces of oxygen, a magnesium perchlorate tube to remove water, and a presaturator containing the solvent system under study. Solutions to be electrolyzed in the flow cell were deaerated for at least 1 hr.

Simultaneous electrochemical–spectrophotometric experiments were performed utilizing the above-mentioned flow cell in the Cary 14 recording spectrophotometer. Polarographic determination of n (apparent) values was carried out at 25.0 ± 0.1°. Certain experiments carried out to produce the fluorene anion radical in high concentration were effected at a mercury pool in both DMF and MeCN at reduced temperatures in a 1-cm quartz spectrophotometer cell. The mercury electrode was frozen with liquid nitrogen while the electrolysis was proceeding. Electrolyses performed at these lower temperatures in the sample compartment of the Cary 14 spectrophotometer enabled the visible spectrum of the anion radical to be obtained.

Fluorenone concentrations, as massive electrolysis products, were determined, in aprotic media, *via* the limiting current of the two one-electron reduction waves, −1.71 and −2.45 V in DMF, −1.53 and −2.64 V in DMSO, and −1.63 and −2.16 V in MeCN. In protic media the fluorenone was separated from other products and reactants by passing the electrolyzed solution through a column of neutral alumina. The resulting yellow product was still heavily contaminated with TBAP, which was then removed by adding toluene to the mixture. Several treatments precipitated virtually all of the TBAP.

Infrared analyses of electrolysis products were performed with the Perkin-Elmer 337 spectrophotometer using the usual KBr pellet technique.

Chemicals and Solutions.—All solvents used were Matheson Coleman and Bell Spectroquality grade. The DMF was purified according to the method of Moe.[12] It was found that fresh solvent had to be prepared weekly, as some deterioration occurred. DMSO and MeCN were used as received, but all three solvents were stored over Linde Type 4A Molecular Sieves, and as used, had very small (<0.2 μA) polarographic background currents prior to breakdown. The fluorene (Baker photosensitizer grade) was used as received. The resorcinol (Matheson Coleman and Bell) was recrystallized several times from ethanol, the final product being large, colorless crystals. The TBAP (Southwestern Analytical Chemicals, Inc., Austin, Texas) was dried *in vacuo* at 60° for several hours, or over silica gel for over 1 week. All chemicals were stored over silica gel prior to use.

Fluorene electrolysis solutions were generally 1.00 m*M* except for the massive protic electrolysis experiments, which utilized 0.05 *M* solutions of both fluorene and resorcinol.

Results and Discussion

Aprotic Conditions.—Under certain conditions, using DMF which was rigorously dried and deoxygenated, the blue-green anion radical of fluorene could be seen at room temperature on the surface of the mercury pool electrode during exhaustive electrolysis. This was somewhat unexpected, even though Van Duyne and Reilley indicate that DMF is an excellent solvent for the study of radical anions.[13a] Normally, however, no color was seen, nor was this color ever seen at room temperature in MeCN or DMSO regardless of experimental conditions. At temperatures reduced to the

(4) C. D. Ritchie and R. E. Uschold, *J. Amer. Chem. Soc.*, **89**, 1721 (1967).
(5) A. Streitwieser, Jr., "Molecular Orbital Theory," Wiley, New York, N. Y., 1962, pp 414–415.
(6) J. Janata, J. Gendell, R. C. Lawton, and H. B. Mark, Jr., *J. Amer. Chem. Soc.*, **90**, 5226 (1968).
(7) G. W. H. Scherf and R. K. Brown, *Can. J. Chem.*, **38**, 2450 (1960).
(8) (a) E. G. Janzen and J. L. Gerlock, *J. Organometal. Chem.*, **8**, 354 (1967); (b) D. Casson and B. J. Tabner, *J. Chem. Soc. B*, 887 (1969).
(9) J. J. Eisch and W. C. Kaska, *J. Org. Chem.*, **27**, 3745 (1962).
(10) J. R. Jezorek and H. B. Mark, Jr., *J. Phys. Chem.*, **74**, 1627 (1970).
(11) J. Janata and H. B. Mark, Jr., *Anal. Chem.*, **39**, 1876 (1967).
(12) N. S. Moe, *Acta Chem. Scand.*, **21**, 1389 (1967).
(13) (a) R. P. VanDuyne and C. N. Reilley, *Anal. Chem.*, **44**, 142 (1972). (b) Because of the severe reaction conditions employed, the spectra actually obtained were quite noisy, and a smoothed, average curve is shown. The position of λ_{max} is probably ±5 nm.

TABLE I

POLAROGRAPHIC AND SPECTRAL DATA FOR FLUORENE, FLUORENE ANION RADICAL, FLUORENE CARBANION, AND FLUORENONE ANION RADICAL IN MeCN, DMF, AND DMSO

Solvent	$E_{1/2}$ of RH_2 redn,[a] V	λ of RH^-,[b] nm	RH^- oxidation wave max	$t_{1/2}$ of RH^-, min	λ of $RH^- + O_2$ reaction,[c] nm	λ of protic electrolyzed intermediate,[d] nm	λ of $RH_2\cdot^-$, nm	λ of $R{=}O\cdot^-$,[e] nm
MeCN	−3.0₃	368	−1.13	13	422	448	693 ± 5	545
		425 (sh)			533			
		453			642			
		481						
		514						
DMF	−3.130	371	−1.17	30	557	510	708 ± 5	553
		425 (sh)			648			
		456						
		485						
		520						
DMSO	−2.910	362, 371	−1.00	100		507		
		430 (sh)						
		~455						
		482						
		~515						

[a] *Vs.* $Ag/AgClO_4$ (0.01 *M*); RH_2 = fluorene. [b] The short-wavelength band is about ten times as intense as the quartet. [c] Products of oxygen addition to electrolyzed fluorene in aprotic media; each band is a different species. [d] Products of oxygen addition to electrolyzed fluorene in protic media. [e] $R{=}O\cdot^-$ = fluorenone anion radical.

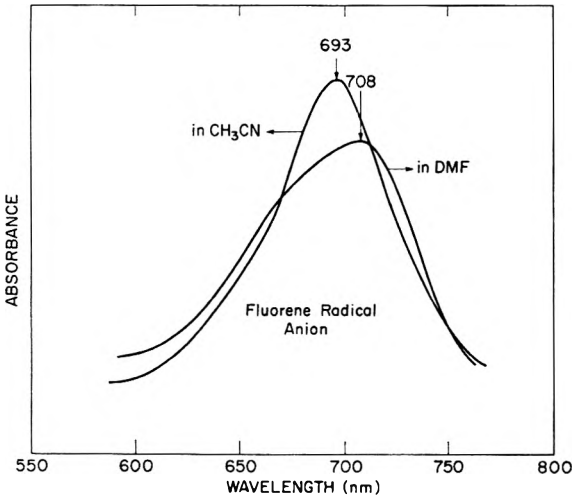


Figure 1.—Visible spectrum of the fluorene anion radical in DMF and MeCN. The actual spectra were much noisier than shown.[13] $T = <-20°$.

point that the mercury pool electrode was frozen, the radical anion was sufficiently stable and formed in high enough concentration so that a spectrum (Figure 1)[13b] could be obtained. Our spectral results in DMF and MeCN are in good agreement with those of Casson and Tabner in ethereal solvents.[8b]

Polarographically, fluorene exhibited essentially reversible one-electron reduction waves in both aprotic DMF and DMSO, Plots of $E_{1/2}$ *vs.* log $i/i_d - i$ (where i_d = the diffusion limited current) yielded slopes of 58–61 mV/decade, in good agreement with the theoretical Nernstian behavior. In aprotic MeCN, however, the polarographic limiting current is much larger than expected for a one-electron change, and constant-potential electrolysis yielded an n value around 2.0. The background breakdown of the MeCN–0.1 *M* TBAP solvent system begins around −3.10 V, which is near the fluorene half-wave potential. It appears that electron transfer, near the electrode, from fluorene to solvent and/or direct solvent system reduction is occurring. Either of these processes would account for the high n values.

Coulometric reduction at a Hg pool yielded an electron change value, n, only slightly greater than 1.0 over the first 20–30% of the electrolysis in DMF and DMSO. In MeCN, the proximity of background breakdown caused n to be erratic and much higher than 1.0.

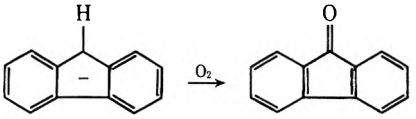
In all three aprotic solvents, electrolysis at or near the current limiting plateau potentials (−3.20 to −3.35 V in DMF, −3.05 V in DMSO, and −3.05 V in MeCN under aprotic conditions) of the fluorene reduction wave yields as one product the fluorene carbanion, as evidenced by a change of the solution from colorless to yellow-orange. This species has a very sharp and intense band around 370 nm, and a quartet of less intense bands farther out in the visible region (Table I) in all three solvents.[14,15] The build-up of this product could

(14) (a) A. Streitwieser, Jr., and J. I. Brauman, *J. Amer. Chem. Soc.*, **85**, 2633 (1963). (b) G. Hafelinger and A. Streitwieser, Jr., *Chem. Ber.*, **101**, 657 (1968). (c) Qualitatively, the stability of the carbanion (in the absence of air) varies considerably in the three solvents, as shown in Table I. The order of the anion stability, DMSO > DMF > MeCN, is explainable in terms of the solvating ability of the three solvents. MeCN solvates anions very weakly, DMSO very strongly, while DMF is intermediate in strength. Degradation of the anion in these experiments probably occurs by reaction with traces of oxygen and/or carbon dioxide, or with water or other impurities. In basic solvents carbanion stability is greatly enhanced.[14a] Indeed, if the anion is formed with potassium *tert*-butoxide in DMF, so that an excess of base is present, the half-life is over 6 hr.

(15) Hogen-Esch and Smid [T. E. Hogen-Esch and J. Smid, *J. Amer. Chem. Soc.*, **88**, 307 (1966)] have postulated the existence of both contact and solvent-separated ion pairs of the fluorene anion in several solvents. Where solvent separation occurs, for strongly solvating conditions, the position of the short-wavelength band is said to be fixed at 373 nm, while contact ion pairing shifts the band anywhere from 368 to 346 nm. In both MeCN (λ_{max} 368 nm) and DMF (λ_{max} 371 nm) only one band was observed in the present study. It is likely that this indicates rather poor solvation of the anion by MeCN, yielding only the "free" ion. This is reasonable, as MeCN does not solvate anions particularly strongly. For DMF, however, strong solvation of the anion is indicated. In DMSO two short-wavelength bands are observed. At low carbanion concentrations λ_{max} is 362 nm, while at higher concentrations a band at 372 nm becomes predominant. Hogen-Esch and Smid also report these two peaks in DMSO, and attribute the shorter wavelength band to the free ion. However, this explanation does not seem reasonable; first, dilution would be expected to cause even more extensive solvation; and, second, no free ion would be expected in the extremely strongly solvating DMSO medium. Anion–anion interaction at higher concentrations may be responsible for the shift in wavelength.

be followed spectrophotometrically during the course of the electrolysis. Streitwieser has discussed this spectrum in some detail.[14a,b] Anion build-up can also be followed polarographically, as the carbanion possesses a characteristic oxidation wave with a very distinctive maximum (Table I) in all three solvents. It is of interest to note that no other product was detected in measurable quantities by either of these methods.[14c]

If air is admitted to an aprotic DMF, DMSO, or MeCN solution containing the fluorene carbanion, immediate decay of the carbanion is observed, as evidenced by the simultaneous disappearance of both the fluorene carbanion polarographic oxidative wave and its visible absorption spectrum. Russell and coworkers[16] have shown that oxygen reacts rapidly with the fluorene anion; so this result was not unexpected. However, a



result that was unexpected is that when air was admitted to the electrolyzed DMF or DMSO solution containing the carbanion the fluorene remaining unelectrolyzed was considerably reduced in concentration. In fact, if the electrolysis was carried out to about 40 or 50% (*i.e.*, judging from the size of the fluorene polarographic wave, 40 or 50% of the original RH_2 had been reduced), and then terminated, and oxygen admitted to this solution of RH_2 and RH^-, the RH_2 remaining unelectrolyzed *completely* disappeared. In addition, the amount of fluorenone which resulted was much larger than expected, appearing in approximately equimolar amounts to the *original* RH_2 concentration. Dehl and Fraenkel also observed the formation of a yellow species, presumably the anion of fluorene, during electrolysis in DMF, but, because of molecular oxygen impurity, obtained the ketone directly during the course of the electrolysis.[17] In MeCN at least three intermediates are observed on addition of air to the carbanion solution,[18] but the degradation (uv light) product of all three is also the ketone. No other major product was found in any of the three solvents. Therefore, it would appear that, while self-protonation does indeed occur to some extent for aprotic reduction of fluorene, yielding the carbanion, RH^-, and neutral protonated radical, $RH_3\cdot$ (these are the electrochemical and chemical steps of the ECE sequence), this sequence is not stoichiometric and does not go to completion in the usual manner. We suggest a possible, nonspecific reaction pathway below, based on approximately 50% electrolysis of the RH_2, which is consistent with the above observations.

(electrochemical) $RH_2 + e^- \rightleftharpoons RH_2\cdot^-$ (1)

(chemical) $RH_2\cdot^- + RH_2 \longrightarrow RH^- + RH_3\cdot$ (self-protonation) (2a)

or $RH_2\cdot^- + SH \longrightarrow S^- + RH_3\cdot$ (SH = solvent and/or impurities) (2b)

(electrochemical) $RH_3\cdot + e^- \not\longrightarrow RH_3^- \xrightarrow{H^+} RH_4$ (final steps of usual ECE sequence) (3)

$RH_3\cdot \xrightarrow{\text{solvent}} Q^*$ (4)

$Q^* + RH_3 + O_2 \longrightarrow 2R{=}O + 2H\cdot$ or $2H^+$ (5)

$RH^- + O_2 \longrightarrow R{=}O + OH^-$ (6)

The ratio of fluorenone produced to RH_2 originally present should have a maximum value of about 0.5 if all $RH_2\cdot^-$ species react with neutral RH_2 (an unlikely occurrence) and the usual ECE pathway occurs, and 1.0 for the alternate route indicated above. Experimentally a ratio near 1.0 was obtained, indicating that nearly all of the RH_2 originally present was converted to the ketone although only one-half of it was reduced at the electrode. The above very generalized sequence of reactions is consistent with this fact, as well as with an n value of 1.0. The experimental evidence also indicates that the second electrochemical step, which normally leads to the second protonation and the RH_4 species, does not occur. Rather, it appears as if the $RH_3\cdot$ somehow reacts with solvent or impurities to form an anaerobically stable species, Q*, which, in the presence of unreacted RH_2 and O_2, yields the ketone. This conclusion is strongly indicated by the fact that the 50% RH_2 unelectrolyzed also yields fluorenone. Of course, that RH^- formed *via* the self-protonation (2a) also forms the ketone.

Protic Conditions in DMF and DMSO.—From the reaction pathway shown above it is seen that the species RH_3^-, if formed under protic conditions, ought to favor the usual ECE mechanism; in fact reduction in the presence of a large excess of proton donor should yield no carbanion, as self-protonation should be swamped out, and, therefore, no fluorenone if the usual ECE sequence is followed. Carrying out the reduction under protic conditions was expected to answer the

(16) (a) G. A. Russell, A. J. Bemis, E. J. Geels, E. G. Janzen, and A. J. Moye in "Oxidation of Organic Compounds," Vol. I, Advances in Chemistry Series, No. 75, American Chemical Society, Washington, D. C., 1968, pp 174–202. (b) G. A. Russell in "Free Radicals in Solution," IUPAC, Division of Organic Chemistry, International Symposium, Ann Arbor, Mich., 1966, Butterworths, London, 1967, pp 185–206.

(17) R. Dehl and G. R. Fraenkel, *J. Chem. Phys.*, **39**, 1793 (1963).

(18) In most cases exhaustive electrolysis of fluorene in MeCN produced (besides the fluorene anion) a pink species as reduction progressed. When air was admitted *slowly* to a solution of fluorene anion in MeCN the same pink species was obtained. This is not the fluorenone ketyl radical, as λ_{max} for the ketyl does not quite match that for the pink species (Table I). A short while after the pink species begins to form, a very large band appears at 422 nm. A band with the same characteristics is observed when fluorenone itself is electrolyzed at a mercury pool. This yellow species may be the fluorene pinacol discussed by Korsun and Nekrasov [A. D. Korsun and L. N. Nekrasov, *Elektrokhimiya*, **4**, 1501 (1968)] which forms during the electrolysis of fluorenone.

If air is admitted *rapidly* to a solution of the fluorene anion in MeCN, a blue species, λ_{max} 642 nm, forms immediately, to the exclusion of the pink species. Under these conditions the band at 422 nm does not form.

When air is admitted at intermediate rates, both the blue and the pink species are observed, as is the yellow (422 nm). In most cases fluorenone is not formed concurrently with these species. That the formation of these "intermediates" results from reaction of oxygen with the carbanion is indicated by the fact that the anion formed by the reaction of potassium *tert*-butoxide with fluorene yields the same species with oxygen.

Sunlight degrades the pink species to fluorenone in under 1 min, while the blue takes several minutes to degrade to the same product. In the dark the blue lasts for days, while the pink decomposes in several hours. All efforts to isolate and characterize these products (pink, blue) failed as rapid degradation to the ketone resulted.

In DMF both slow and rapid admission of air to an anion solution resulted in immediate formation of fluorenone in nearly all cases. Occasionally, however, the intermediate red and blue species were obtained (Table I). In DMSO, no product other than fluorenone was ever obtained.

As the blue product formed in excess oxygen, some form of peroxy structure is likely, although Sprinzak [Y. Sprinzak, *J. Amer. Chem. Soc.*, **80**, 5449 (1958)] claims that no peroxide intermediate forms in the oxidation of fluorene anion to ketone in pyridine. In addition Hock, *et al.* [H. Hock, S. Lang, and G. Knauel, *Chem. Ber.*, **83**, 227 (1950)], claim that the fluorene hydroperoxide is colorless.

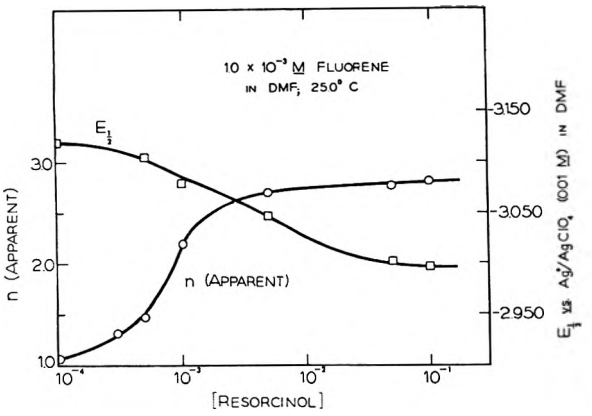


Figure 2.—Plots of n(apparent), the ratio of the polarographic limiting current of the fluorene reduction wave in resorcinol media to that in aprotic solvent, and the polarographic reduction half-wave potential of fluorene *vs.* resorcinol concentration in the DMF–resorcinol–TBAP solvent system.

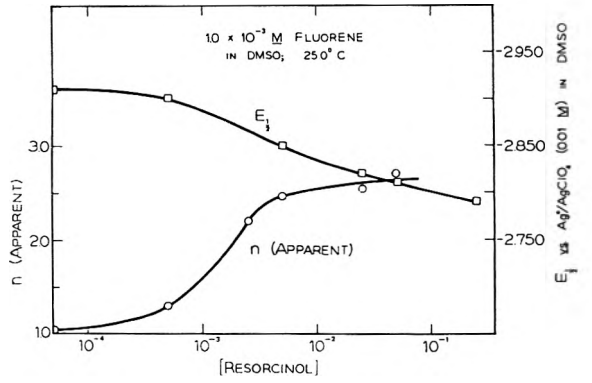


Figure 3.—Plots of n(apparent), the ratio of the polarographic limiting current of the fluorene reduction wave in resorcinol media to that in aprotic solvent, and the polarographic reduction half-wave potential of fluorene *vs.* resorcinol concentration in the DMSO–resorcinol–TBAP solvent system.

questions of whether RH_3^- formed at all in protic media, whether a pathway to fluorenone exists other than *via* the carbanion, RH^-, as does appear to be the case under aprotic conditions, and whether the twice-protonated species RH_4, dihydrofluorene, is the major product. (This is the usual ECE product and is the situation found for 4,5-methylenephenanthrene.) To test this hypothesis and to see if fluorene deviates from the usual sequence in protic, as in aprotic conditions, the reduction of fluorene was carried out in the presence of a large excess of resorcinol as an electroinert proton donor in all three solvents.

In Figures 2 and 3 there are plotted the n(apparent) values [n(apparent) = i/i_d, where i is the polarographic limiting current in the various protic media, and i_d is the diffusion limited current, in aprotic conditions, obtained in DMF and DMSO] *vs.* resorcinol concentration. The polarographic half wave potential is also shown as a function of resorcinol concentration. It can be seen that n(apparent) reaches a maximum value of about 2.8 in DMF and 2.7 in DMSO, indicating an electron change in protic media approaching a value of 3.0. In order to confirm this result, exhaustive electrolyses (at −3.10 V in DMF, and at −2.9 to −3.0 V in DMSO) of 1 mM fluorene solutions were carried out at a mercury pool in 0.01 M resorcinol medium. According to the modified Faraday expression the polarographic

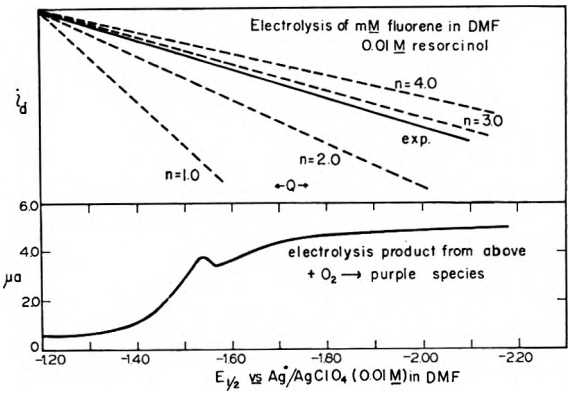


Figure 4.—The fluorene polarographic diffusion current, i_d, as a function of Q, the total amount of charge passed in the electrolysis of 1.0 mM fluorene in 0.01 M resorcinol–0.1 M TBAP–DMF. Shown below is the polarographic reduction wave of the purple solution resulting from addition of oxygen to the above electrolyzed solution.

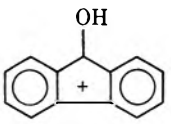
diffusion current, i_d, is expected to yield a straight line when plotted *vs.* Q, the total charge passed in the electrolysis.[6] That is,

$$i_d = i_{d_0}\left(1 - \frac{Q}{nFVC_0}\right) \quad (7)$$

where Q = total charge passed in the electrolysis, recorded *vs.* i_d, the polargraphic diffusion current at time $= t$; i_{d_0} = polarographic diffusion limited current at $t = 0$; V = volume of solution; C_0 = original concentration of fluorene in molarity; n and F have their usual meaning.

Figure 4 shows the observed results as well as the theoretical results to be expected for n values from 1 to 4. Experimentally, an n value of just under 3.0 was observed over the entire span of the exhaustive electrolysis. As expected, no indication of any measurable fluorene carbanion concentration was found spectrophotometrically, nor was any observed polarographically. The electron change of 3.0 indicates that a reactive species is formed, as reduction of a double bond in the usual ECE sense requires but two electrons and yields a stable dihydro product. Addition of air to the system after electrolysis in protic DMF and DMSO results in the gradual formation of a purple species, likewise indicating that a reactive intermediate is present. However, as the electrolyzed solution is colorless before admission of air, the reactive species is most likely not a radical or radical ion. Formation of the purple species takes several hours to complete, also indicating that the electrolysis product is not a radical. In order to confirm this, the esr spectra of both the colorless electrolysis solution and the purple solution resulting on admission of air were examined. In neither case was any evidence for a radical species obtained. The polarographic wave associated with the purple species (in protic media) is shown in Figure 4. The relatively low cathodic reduction potential suggests that some type of oxygenated species (which is easily reduced) has been formed. The purple solution, formed in both DMF and DMSO, exhibited an unusually broad visible spectrum, extending from 450 nm to 650 nm (Figure 5). Extensive attempts to isolate this species met with failure, as decoloration occurred for all separation methods tried. It was observed that in sunlight this purple solution was converted to a bright yellow after a few hours. In

order to obtain sufficient material for investigation, exhaustive electrolyses were carried out, in DMF, on more concentrated solutions (0.05 *M* fluorene, 0.05 *M* resorcinol). Again no anion is formed during electrolysis and, again, the dark brown-purple solution formed with admission of air. This solution, which exhibited an absorbance peak with similar maximum and shape to the purple compound formed under more dilute conditions, was warmed slightly, and was converted completely to the purple. When exposed to uv light it also turned yellow, yielding *fluorenone* as the major product. This purple species can be identified as being the cation



of the ketone. The spectrum is virtually identical with that normally obtained when fluorenone is dissolved in concentrated sulfuric acid.[19] It is interesting to note that this protonated species cannot be formed by approaching from the opposite direction (addition of fluorenone to a nonaqueous solution containing excess proton donor). It is not stable and can only be obtained during the decay of the colorless electrolysis product, or under the forcing conditions of very high proton activity. In addition, several other products were observed, as minor constituents, during separation; none of these could be isolated and identified. It should be mentioned, however, that *none of these minor products resembled* (even remotely) *a dihydro* or higher reduced form of fluorene, which would result from the usual ECE process.

Therefore, under protic, just as under aprotic conditions, it appears as if the normal ECE sequence is not followed. Instead of a dihydrofluorene, the product, after oxidation with air, is a protonated form of fluorenone (perhaps ion pair stabilized) which is degraded to fluorenone on uv light treatment. The intermediate species formed on electrolysis in protic media appears to be more stable than those formed under aprotic conditions, as the purple product (protic conditions) takes several hours to form completely after oxygen is admitted, while the red and blue intermediate species in MeCN,[18] and fluorenone itself in DMF and DMSO (aprotic conditions), form immediately in the presence of air. One might conclude that under protic conditions, in view of the three-electron change, a dimeric species is formed, accounting for the fact that the colorless species is not a radical. These dimers might then react with oxygen and be further degradable to fluorenone under uv light. The spectral changes of both 9,9′-bifluorene and bifluoronylidene with excess proton donor present were studied as these compounds were exposed to uv light in the presence of oxygen. Although the bifluoronylidene did convert to fluorenone, there

(19) (a) J. Michl, R. Zahranik, and P. Hochman, *J. Phys. Chem.*, **70**, 1732 (1966). (b) The structural characteristics of the spectrum of the purple species are identical with those of fluorenone in concentrated H_2SO_4. There is a slight difference in the peak maximum: 510 nm in DMF and 540 nm in concentrated H_2SO_4. However, this is not surprising for such different solvent systems. It is assumed that the species formed in concentrated H_2SO_4 is the simple protonated form of fluorenone, as dilution of the acid with H_2O results in complete recovery of the fluorenone. It is interesting that this protonated species is formed in the protic nonaqueous media under these conditions as the effective acid strength of these nonaqueous solution is certainly much less than that of concentrated H_2SO_4.

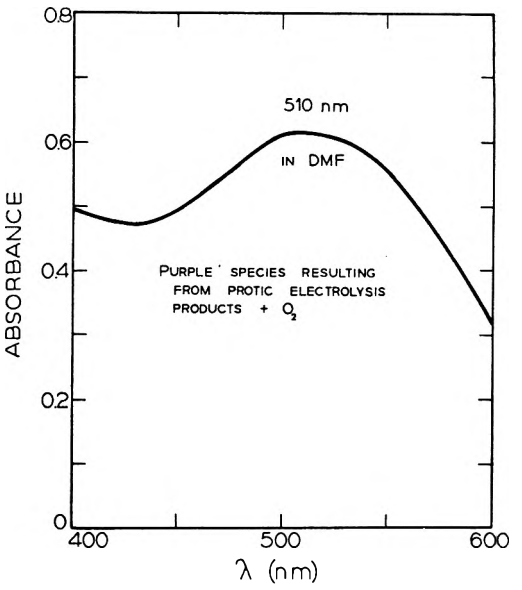
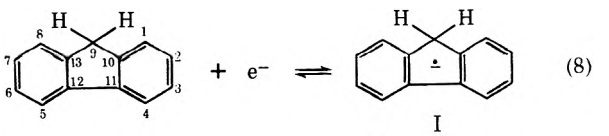


Figure 5.—Visible adsorption spectrum of the purple solution resulting from addition of O_2 to electrolyzed 1.0 m*M* fluorene–0.01 *M* resorcinol–0.1 *M* TBAP–DMF.

was no spectral evidence of the purple intermediate or any of the intermediates described above. Likewise, none of the spectral data obtained on the electrolysis solutions gave any evidence of bifluoronylidene or any oxygenated intermediate of it. Also, because of the dilute nature of the electrolysis solutions, it is unlikely that reactive radical intermediates would form the coupled dimer in quantitative yield; one would expect numerous decay paths for a radical of fluorene, especially in view of the excess proton donor. Consistent with the experimental observation that the intermediate product reacts with oxygen to form a protonated fluorenone cation species and this oxidized intermediate can be degraded (with uv light) to fluorenone is the proposition that the point of attack in the oxidation of the colorless reduction product is at the 9 (bridging) position. Also, the fact that an apparent n value of 3 is observed with no evidence of dimerization or higher order polymerization on reduction permits one to speculate on a possible mechanism for the electroreduction of fluorene in protic media (which can be either a large excess of the parent hydrocarbon or an added acidic organic species). As Casson and Tabner[8b] have determined the spin density of the fluorene radical anion (I) to be greatest at the 2 position, and, as the proton donor obviously causes a follow-up chemical reaction, the first two steps in the reaction are probably[9] eq 8 and



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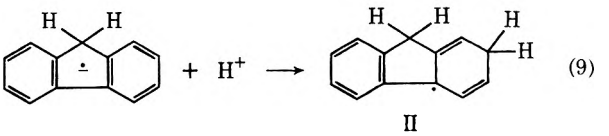
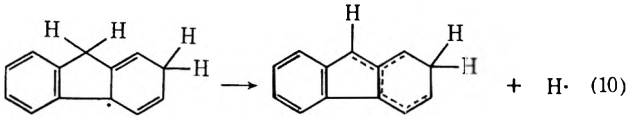


(9)

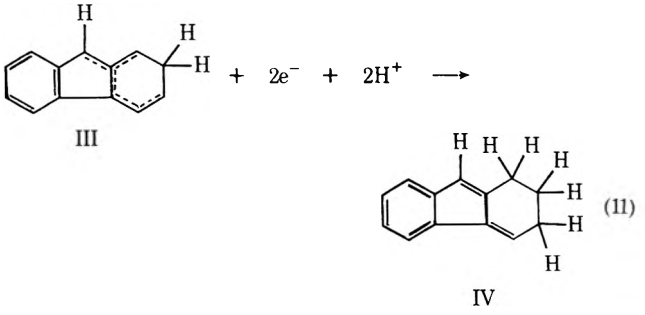
9, which are the same as the first two steps in a typical aromatic hydrocarbon reduction in the presence of a proton donor. Fessenden and Schuler have determined the spin density of the cyclohexadienyl radical

system to be greatest at the para position, *i.e.*, at the sp^2-hybridized carbon opposite the sp^3 carbon atom.[20] By analogy, then, we speculate that the electron in the fluorene radical is localized in the π orbital on the number 11 carbon as indicated by structure II in reaction 9, and we argue *post facto* that the normal ECE second electron transfer is either kinetically or thermodynamically unfavorable. We simply do not find any evidence of tetrahydrofluorene, the product expected if a second electron transfer occurs. Apparently, the electrode potentials applied are not large enough to force a second electron into species II, although the more negative potentials of lithium metal reduction will accomplish this.[9] As we have identified hydrogen gas being evolved on electrochemical reduction under these conditions and other investigators[8,21] have suggested that hydrogen is a product of the metal mirror reduction of fluorene, we suggest that species II then undergoes an elimination of H· to form III.



II III (10)

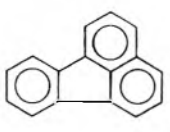
Species III would be expected to be easily reduced at the potentials employed in the electrolysis to form IV.



III IV (11)

This mechanism accounts for the $n_{app} = 3$ and a product which does not exhibit an esr spectrum. We suggest that species IV is the colorless electrolysis product that we obtain under protic conditions. As partially reduced fluorene compounds such as the tetrahydro and hexahydro species are known to oxidize under relatively mild conditions,[22] it is certainly possible that species IV would oxidize in the presence of O_2 to form the cation I and eventually yield fluorenone.

Although we have no direct evidence for the proposed intermediates and product, II, III, and IV, respectively, an indirect test of this sequence is possible. This mechanism predicts that, if the loss of H· from the 9 carbon is prevented or not possible (reaction 10), the subsequent further reduction of a double bond to give an $n_{app} = 3$ cannot occur. We have, therefore, examined the reduction of fluoranthene (V) (which has no proton at the analogous 9 position of fluorene) under identical conditions of solvent and proton donor concentration. We find that the limiting current of the first one-electron wave for fluoranthene does *not* increase with increasing concentration of proton donor. However, the value of the $E_{1/2}$ does shift positive as a function of added proton donor, indicating that the proton donor does bring on a follow-up chemical reaction of some kind. This is exactly as would be expected if the loss of a 9-position hydrogen was a determining step in the mechanism of the three-electron ECE mechanism for fluorene.



V

Protic Conditions in MeCN.—Because of the proximity of the fluorene reduction wave to background breakdown in MeCN, definitive protic electrolysis data was more difficult to obtain than in DMF or DMSO. Nevertheless, exhaustive electrolysis (at −3.05 V) of fluorene in resorcinol medium was performed in MeCN. No evidence of fluorene carbanion was found, similar to the situation in DMF and DMSO. An i_d *vs.* Q slope equivalent to an n value of about 2.5 was obtained. It seems, therefore, as if a three-electron transfer path may also occur in MeCN.

When air is admitted to the electrolyzed fluorene solution in MeCN (0.01 *M* in resorcinol) a yellowish coloration gradually appears, which becomes somewhat brownish on standing. The visible spectrum exhibits one broad band, similar to that observed for the purple solution in DMF and DMSO, but λ_{max} is 448 nm rather than about 500 nm. Ultraviolet light causes this "intermediate" to break down into several components, one of which appears to be fluorenone. Therefore, a reactive intermediate also seems to form in the protic electrolysis of fluorene in MeCN, as in DMF and DMSO. While this oxygenated intermediate has a different color than formed in DMF and DMSO (yellow *vs.* purple), it is possible that it is the same or a closely similar species, and merely shifted toward shorter wavelengths. Admittedly, though, this shift is larger than one would expect merely from solvent effects.

Conclusions

Several statements can be made, in conclusion, about the fluorene system. First, it appears as if the anion radical, $RH_2\cdot^-$, is somewhat more stable in dipolar, aprotic solvents than had been thought previously,[8a] as it could rather easily be seen at lowered temperatures in DMF and MeCN, and in carefully prepared DMF at room temperature. Presumably, if extensive care (such as drybox conditions) were taken to remove oxygen and impurities, the anion radical produced in dilute fluorene solutions should be even more stable in these solvents.

Secondly, of the three solvents studied, the one most suited for the study of the fluorene anion appears to be DMSO. This is no doubt related to its strong solvating tendency. The relatively acidic acyl proton of the DMF molecule probably results in lowered carbanion stability in that solvent,[23] while MeCN is just not a good solvating agent toward anions.

Finally, it appears that the fluorene anion radical does not degrade *via* the usual ECE reaction sequence of alternant hydrocarbons, but, rather than the second

(20) R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **38**, 773 (1963).
(21) B. J. Bitman and I. Skorokhodov, *Teor. Eksp. Khim.*, **6**, 418 (1970); N. L. Bauld and J. H. Zoller, *Tetrahedron Lett.*, **No. 10**, 885 (1967).
(22) W. Treibs and E. Heyner, *Chem. Ber.*, **90**, 2285 (1957).
(23) M. D. Malbin and H. B. Mark, Jr., *J. Phys. Chem.*, **75**, 2992 (1969).

electrochemical step, forms anaerobically stable reaction intermediates under both protic and aprotic reduction conditions. Whereas normally under protic conditions a two-electron change and addition of two protons to a double bond to form a dihydro product is found for alternant hydrocarbons, fluorene reduction under the same conditions does not lead to a dihydro or any other stable reduction product.

As was pointed out earlier, fluorenone is also formed as a major product of the electrochemical reduction of fluorene under aprotic conditions, as expected, but in greater amounts than the ECE mechanism would allow; unexpectedly, no dihydrofluorene is found here either. It appears as if one of the reaction intermediates, possibly the product of $RH_3\cdot$ reaction with solvent, in the presence of oxygen, reacts very readily with unelectrolyzed fluorene, in a second pathway to the ketone besides that through the carbanion. A significant solvent effect is observed in that addition of oxygen to the electrolyzed aprotic fluorene solution leads to different colored intermediates in MeCN than in DMF and DMSO. The major and final product in all three solvents is, however, fluorenone.

As different intermediates are observed depending on whether protic or aprotic conditions obtain, it is clear that different pathways to the ketone exist. One fact seems consistent, however, that the second electrochemical step ($RH_3\cdot + e^- \rightarrow RH_3^-$) does not occur in either case, and up to reaction 10 the sequences are probably the same.

Further study is necessary to establish the nature of the differences in the reaction pathways and intermediate stabilities (the inability to isolate the purple cation species is puzzling, and further investigation is in progress) and to define the nature of the reaction products formed in both protic and aprotic conditions. Nevertheless, it seems clear from this work that fluorene does not follow the normal ECE sequence. It would be of interest to study other nonalternant hydrocarbons to determine if the above behavior is common with nonalternant species or peculiar to the fluorene-type structure.[24]

Registry No.—Fluorene, 86-73-7; dimethylformamide, 68-12-2; dimethyl sulfoxide, 67-68-5; acetonitrile 75-05-8; fluorene anion radical, 34484-03-2; fluorene carbanion, 35782-20-8; fluorenone anion radical, 37439-74-0.

Acknowledgment.—The authors wish to express their thanks to David B. Knight and Philip J. Hamrick, Jr., for helpful discussions concerning this investigation. Professor Hamrick was also kind enough to provide us with some 9-substituted fluorene compounds used in this study.

(24) We have some evidence that 9,10-dihydrophenanthrene also exhibits an n value of about 3.0 under protic conditions in DMF, but further study of this system is necessary. It should be noted that this species is also a cross-conjugated, biphenyl-related compound.

Reduction with Trichlorosilane. II. Mechanistic Study of Reduction of Methyl Acetate to Ethyl Methyl Ether

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The kinetics of the previously reported reduction of alkyl aliphatic carboxylates with trichlorosilane under γ and photoirradiations was studied by using methyl acetate as a starting material. Initially the stoichiometry corresponded to $CH_3COOCH_3 + 3Cl_3SiH \rightarrow C_2H_5OCH_3 + SiCl_4 + HSiCl_2OSiCl_3$. However, since trichlorosiloxydichlorosilane behaved similarly to trichlorosilane, the amount of trichlorosilane consumed at the later stage of the reaction was smaller than 3 mol and the amount of trichlorosiloxydichlorosilane produced was less than 1 mol. Acetaldehyde was detected together with ethyl methyl ether by glpc analysis. The formations of intermediates, acetal type and α-chloroethyl methyl ether, were supported by several results. These intermediates gave acetaldehyde during glpc analysis, and were converted to ethyl methyl ether under irradiations with trichlorosilane. A free-radical chain mechanism *via* these intermediates was proposed. The rate of methyl acetate consumption is derived as $-d[\text{methyl acetate}]/dt = k(\text{dose rate})^{1/2} \times [\text{trichlorosilane}]$ by assuming that recombination of $CH_3\dot{C}(OSiCl_3)OCH_3$ radicals predominates over other termination steps. This rate equation is consistent with the results obtained by kinetic determinations. A small amount of benzene added to the reaction system was found to strongly retard the reaction, suggesting that benzene acts as a scavenger of trichlorosilyl radical.

In paper I of this series,[1] we reported that trichlorosilane can reduce alkyl aliphatic carboxylates, in some cases quantitatively, to dialkyl ethers under γ irradiation, and proposed that the reaction may proceed by a free-radical chain mechanism. However, the detailed mechanism has remained unsettled.

$$RCOOR' \xrightarrow[Cl_3SiH]{\gamma \text{ ray}} RCH_2OR'$$

Also, one could not explain why carboxylic esters containing an aryl group in either R or R′ of RCOOR′ could not be reduced by this reaction. In the present paper we have established the reaction mechanism of methyl acetate with trichlorosilane under γ and photoirradiations. In addition, we found that addition of a catalytic amount of benzene to the reaction system greatly retarded the reaction. This retarding effect is interpreted by assuming that benzene acts as a scavenger of trichlorosilyl radical. This effect explains why carboxylic esters containing an aryl group cannot be reduced.

(1) J. Tsurugi, R. Nakao, and T. Fukumoto, *J. Amer. Chem. Soc.*, **91**, 4587 (1969).

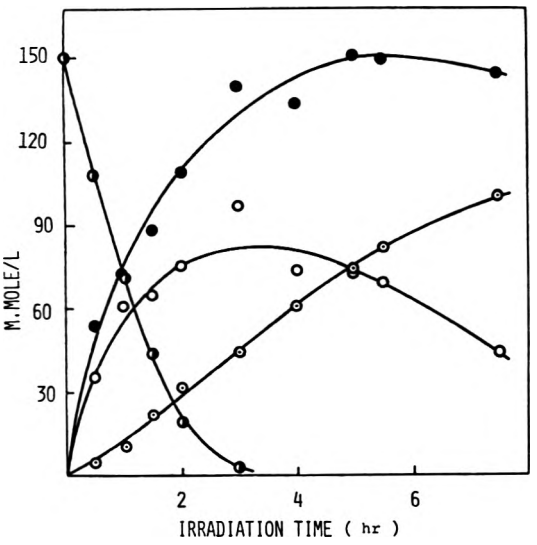


Figure 1.—Time plot of γ-irradiated mixture in cyclohexane: $[CH_3COOCH_3]_0$ = 0.150 and $[Cl_3SiH]_0$ = 0.600 mol/l., dose rate, 1.85×10^5 R/hr; ○, CH_3CHO; ⊙, $C_2H_5OCH_3$; ●, CH_3CHO + $C_2H_5OCH_3$; ◑, CH_3COOCH_3. As seen in text, the amount of acetaldehyde actually corresponds to the amount of intermediate. This also holds for all the succeeding figures.

Results and Discussion

The reaction in cyclohexane indicates that a prominent amount of acetaldehyde together with ethyl methyl ether was produced as compared with the result in neat reaction (Figure 5). Figure 1 shows the amounts of the products and methyl acetate remaining *vs.* γ-irradiation time. The products and methyl acetate remaining were determined by glpc. Figure 1 seems, at first glance, to support the assumption that acetaldehyde is the intermediate of the reaction because the sum total of acetaldehyde and ethyl methyl ether corresponds to the consumption of methyl acetate. However, this assumption is contradicted by subsequent experiments.

The cyclohexane solution of the same mixture sealed in a photoabsorption cell was photoirradiated. Determination of uv-absorption spectra of the irradiated mixture indicates a decrease of absorption of methyl acetate, but no absorption of acetaldehyde. This result indicates no production of acetaldehyde during the irradiation. However, glpc identified acetaldehyde from this irradiated mixture. Addition of a small amount of water to the same irradiated mixture in the same photocell was found to cause the formation of acetaldehyde. Assuming that the same mechanism prevails both in γ and photoirradiations, these results support the formation of an intermediate other than acetaldehyde and the decomposition of this intermediate to acetaldehyde during glpc separation process.

In another experiment acetaldehyde was added to the reaction system prior to the irradiation. After uv irradiation, this mixture indicated a decrease of acetaldehyde but no decrease of methyl acetate nor formation of ethyl methyl ether. This result suggests that the reaction of acetaldehyde with trichlorosilane[2] predominates over that of methyl acetate with trichlorosilane. If acetaldehyde was an intermediate in the reaction system, the reaction of methyl acetate

(2) R. Calas, *Pure Appl. Chem.*, **13** (1–2), 61 (1966).

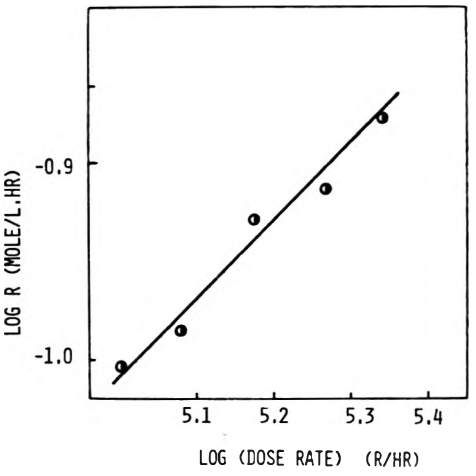


Figure 2.—Dependence of rate of methyl acetate consumption on dose rate (from 0.98 to 2.20×10^6 R/hr).

with trichlorosilane would not proceed. All these results clearly indicate that acetaldehyde determined by glpc is a decomposition product from the intermediate other than acetaldehyde.

In our previous communications, the acetal type intermediate $RCH(OSiCl_3)OR'$ was assumed by analogy to the reaction of ketones with trichlorosilane.[1] Also acetals were found to be converted to α-chloro ethers through the reaction with trichlorosilane.[3] To confirm the structure of the intermediate, a mixture of methyl acetate and trichlorosilane (CH_3COOCH_3/Cl_3SiH, 1:4 molar ratio) in cyclohexane-d_{12} sealed in a nmr tube was irradiated with γ rays at room temperature. After the irradiation, nmr spectra indicated the presence of a methyne proton coupled with an adjacent methyl proton which was identical with the methyne proton of α-chloroethyl methyl ether (II). When the irradiation and nmr analysis were carried out at low temperatures (−20°), the resulting spectrum indicated the presence of a methyne proton which was also coupled with an adjacent methyl proton but different from that of II. It was concluded that this methyne proton was derived from acetal type intermediate I,[4] since this spectra changed into that of II[4] on standing at room temperature. From the results cited above we can write the reaction sequence as

$$CH_3COOCH_3 + Cl_3SiH \xrightarrow{\gamma} \underset{\text{I}}{CH_3CH(OSiCl_3)OCH_3}$$

$$I + Cl_3SiH \longrightarrow \underset{\text{II}}{CH_3CHClOCH_3} + HSiCl_2OSiCl_3$$

$$II + Cl_3SiH \xrightarrow{\gamma} CH_3CH_2OCH_3 + SiCl_4$$

In the presence of water, *e.g.*, by glpc process,

$$II \text{ (or I)} + H_2O \longrightarrow CH_3CHO + CH_3OH + HCl \text{ (or } Cl_3SiOH)$$

Although methanol, the counterpart of acetaldehyde, has not been identified by glpc, methanol should further react with excess trichlorosilane to yield poorly characterized products. The equimolar relation between the intermediates and acetaldehyde is clear from the results in Figure 1. The sum total of acetaldehyde

(3) R. Nakao, T. Fukumoto, and J. Tsurugi, *J. Org. Chem.*, in press.

(4) Nmr spectra for $CH_3CH(OSiCl_3)OCH_3$ δ 1.45 (d, 3, J = 5 Hz, CCH_3), 5.20 (q, 1, J = 5 Hz, CH), 3.38 (s, 3, OCH_3); for $CH_3CHClOCH_3$ δ 1.70 (d, 3, J = 5 Hz, CCH_3), 5.50 (q, 1, J = 5 Hz, CH), 3.40 (s, 3, OCH_3).

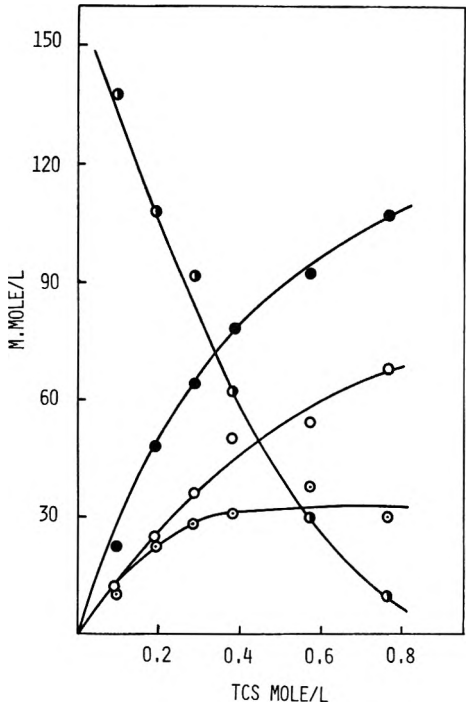


Figure 3.—Dependence on initial trichlorosilane concentration at a given dose of 3.7×10^5 R: $[CH_3COOCH_3]_0 = 0.156$ mol/l. in cyclohexane; ○, CH_3CHO; ⊙, $C_2H_5OCH_3$; ◑, CH_3COOCH_3; and ●, $CH_3CHO + C_2H_5OCH_3$.

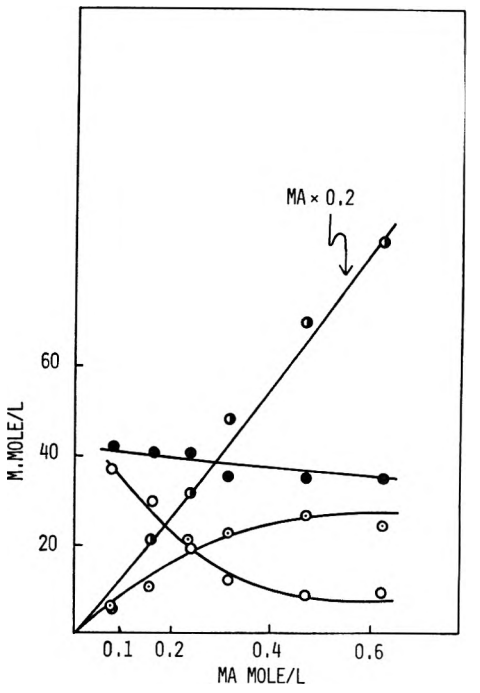


Figure 4.—Dependence of initial methyl acetate concentration: dose 3.7×10^5 R; $[Cl_3SiH]_0 = 0.156$ mol/l. in cyclohexane; ○, CH_3CHO; ⊙, $C_2H_5OCH_3$; ◑, CH_3COOCH_3; and ●, $CH_3CHO + C_2H_5OCH_3$.

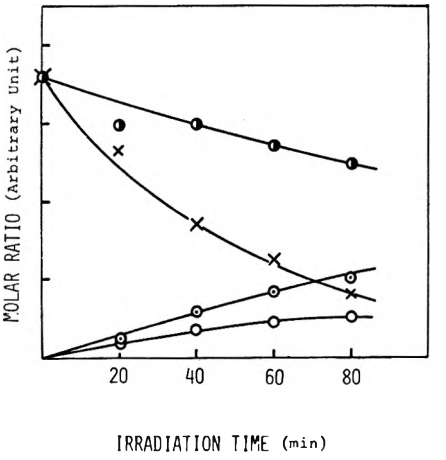


Figure 5.—Time plot of the irradiated mixture in neat reaction: ◑, CH_3COOCH_3; ⊙, $C_2H_5OCH_3$; ○, $HSiCl_2OSiCl_3$; and ×, Cl_3SiH; determined by nmr, dose rate 2.5×10^6 R/hr.

and ethyl methyl ether in Figure 1 and all the figures cited hereafter corresponds to the amount of methyl acetate consumed.

Figure 2 shows a logarithmic plot of methyl acetate consumption rate $-d[CH_3COOCH_3]/dt$ *vs.* dose rate and gives

$$-d[CH_3COOCH_3]/dt = k(\text{dose rate})^{0.40}$$

The exponent value of this equation suggests that the termination process consists predominantly of recombination of the propagating species, this value (0.40) being near to 0.5.

Kinetic orders were determined (in Figures 3 and 4) by varying the concentration of the starting materials in cyclohexane under the γ irradiations at a constant dose. The rate of consumption of methyl acetate was proportional to $[Cl_3SiH]$ in a range where $[Cl_3SiH]/[CH_3COOCH_3]$ is small, and almost independent of $[CH_3COOCH_3]$.

This reaction proceeds under γ and photoirradiations. Taking into consideration the free-radical chain mechanism suggested by the observed high G value (400–500), and the structures of the intermediates mentioned in the present paper, we propose the following mechanism.

$$\text{initiator} \longrightarrow R\cdot \quad (1)$$

$$R\cdot + Cl_3SiH \longrightarrow RH + Cl_3Si\cdot \quad (2)$$

$$Cl_3Si\cdot + CH_3COOCH_3 \longrightarrow CH_3\dot{C}(OSiCl_3)OCH_3 \quad (3)$$

$$CH_3\dot{C}(OSiCl_3)OCH_3 + Cl_3SiH \longrightarrow I + Cl_3Si\cdot \quad (4)$$

$$I + Cl_3SiH \longrightarrow II + HSiCl_2OSiCl_3 \quad (5)$$

$$II + Cl_3Si\cdot \longrightarrow CH_3\dot{C}HOCH_3 + SiCl_4 \quad (6)$$

$$CH_3\dot{C}HOCH_3 + Cl_3SiH \longrightarrow CH_3CH_2OCH_3 + Cl_3Si\cdot \quad (7)$$

$$2CH_3\dot{C}(OSiCl_3)OCH_3 \longrightarrow \text{nonradical product(s)} \quad (8)$$

If we assume that the termination step (8) predominates over the other possible steps, by the standard steady-state treatment the rate of methyl acetate consumption is derived as

$$-d[CH_3COOCH_3]/dt = k_4k_8^{-1/2}I_a^{1/2}[Cl_3SiH]$$

where I_a is the rate of absorption of energy and is proportional to the dose rate. This equation is consistent with the results (Figures 2–4).

Figure 5 shows amounts of the products and the starting materials *vs.* γ-irradiation time in a neat reaction. In contrast to the reaction in cyclohexane, only a trace amount of the intermediates was formed. Figure 5 shows formation of 1 mol of ethyl methyl ether and less than 1 mol of trichlorosiloxydichlorosilane and the consumption of 1 mol of methyl acetate and 2–3 mol of trichlorosilane. Furthermore, Figure 5 indicates that the relationship $a - b = 2c$ holds, where

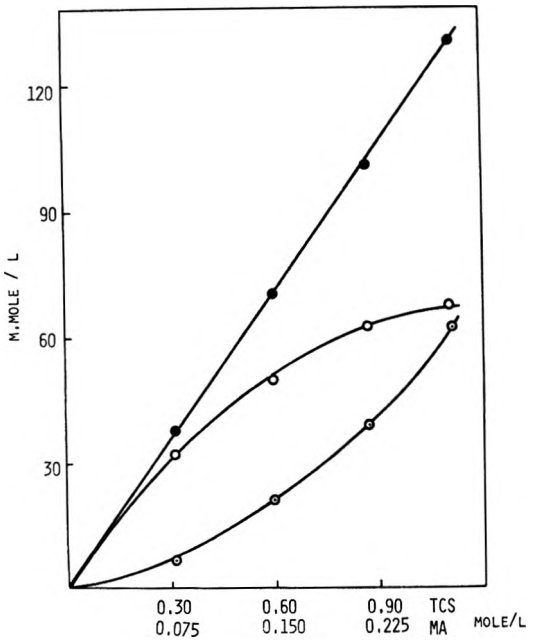


Figure 6.—Effect of the concentration of reactants in cyclohexane on the intermediate formation at a constant molar ratio of $[CH_3COOCH_3]_0/[Cl_3SiH]_0$ = 1:4; dose, 1.85×10^5 *R*; ○, CH_3CHO; ⊙, $C_2H_5OCH_3$; and ●, $CH_3CHO + C_2H_5OCH_3$.

a signifies the amount of trichlorosilane consumed, *b* the amount of trichlorosiloxydichlorosilane formed, and *c* the amount of ethyl methyl ether formed. This relationship suggests that trichlorosiloxydichlorosilane produced *via* eq 5 reacts almost identically to trichlorosilane.

Figure 6 shows the effect of the concentration of the reactants at a constant molar ratio on the amount of the intermediates formed at a given γ-irradiation dose. Figure 6 indicates the tendency of an increasing amount of cyclohexane to increase the ratio of the intermediates to ethyl methyl ether. To find a reason for the intermediates[3] formation in cyclohexane, we utilized *n*-hexane and tetrahydrofuran as alternant solvents[5] and ran the reaction under the same conditions as those in Figure 1. Using *n*-hexane, we observed similar results to that of cyclohexane. However, while the use of tetrahydrofuran resulted in the same reaction rate, it gave only a small amount of acetaldehyde[6] as compared with the reaction in cyclohexane. The above results suggests that, while eq 4 and 6 are not dependent on solvent, eq 5 is. This results because the dielectric constant of tetrahydrofuran (7.4) is near that of methyl acetate (7.03) and greater than those of cyclohexane (2.02) and *n*-hexane (1.89).

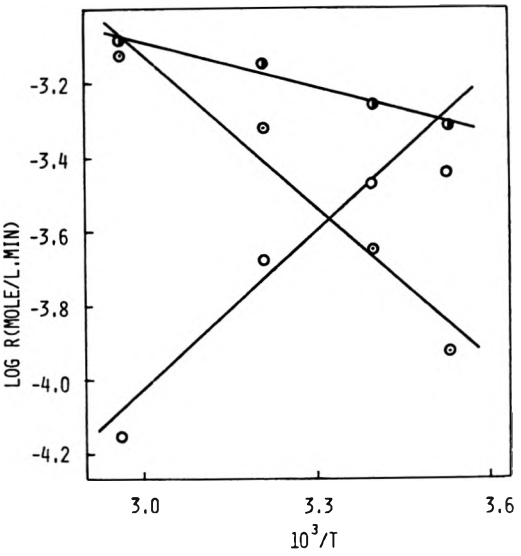


Figure 7.—Arrhenius plot of R($-CH_3COOCH_3$), ◑; R(CH_3CHO), ○; and R($C_2H_5OCH_3$), ⊙; under 3.70×10^6 *R*; $[CH_3COOCH_3]_0$ = 0.156 and $[Cl_3SiH]_0$ = 0.312 mol/l. in cyclohexane.

Arrhenius plots of R (−methyl acetate), R (intermediate), and R (ethyl methyl ether) are shown in Figure 7, where R (X) denotes initial rate of the formation of X. From the results in Figure 7, the apparent activation energies of ethyl methyl ether formation, intermediate formation, and methyl acetate consumption are calculated as 8.2, −6.5, and 1.9 kcal/mol, respectively.

As stated above, the present reaction mechanism consists of three sequences; the first is the radical formation of acetal type intermediate I (eq 3 and 4), the second is ionic transformation of the intermediate I to II (eq 5), and the third is radical formation of ethyl methyl ether from the intermediate II (eq 6 and 7). The rate of the first radical sequence is considered much slower than the rate of the third radical sequence.[7] Therefore, the amount of acetaldehyde derived from the intermediate II and/or I depends on the rate of eq 5. Equation 5 is faster in neat reaction (as in tetrahydrofuran) than in nonpolar solvents. Hence, in neat reaction the amount of acetaldehyde derived from II and/or I becomes smaller than in nonpolar solvents. On the contrary, in nonpolar solvent the concentration of I in the reaction system becomes higher during the irradiation, and hence acetaldehyde derived from II and/or I becomes larger than in the neat reaction. For the same reason the reaction at higher temperatures favors a decreased amount of acetaldehyde because the activation energy of eq 5 is much larger than those of the other steps.

The effect of adding benzene to this reaction system is shown in Figure 8 for a mixture of methyl acetate and trichlorosilane (1:2) in cyclohexane irradiated with a fixed dose. In order to interpret the result in Figure 8, we assume that benzene acts as a scavenger

(5) Alcohols,[5a] amines,[5b] amides,[5c] and nitriles[5d] are known to react with trichlorosilane. Ketones,[5e] aldehydes,[5e] haloalkanes,[5f] and alkenes[5g] react with trichlorosilane under free-radical conditions. Compounds containing *S*-oxide[5h] and *P*-oxide[5i] functions are easily deoxygenated. Aromatic hydrocarbons retard the present reaction as described in this paper. Therefore, solvents available are restricted only to alkanes and ethers. (a) B. Helferich and J. Hausen, *Ber.*, **57**, 795 (1924); (b) H. J. Campbell-Ferguson and E. A. V. Ebsworth, *J. Chem. Soc.*, 705 (1967); (c) Y. Nagata, T. Dohmaru, and J. Tsurugi, *Chem. Lett.*, 989 (1972); (d) R. Calas and N. Duffaut, *C. R. Acad. Sci.*, 906 (1957); *Rev. Fse. Corps. Gras.*, **2**, 1 (1959); (e) R. Calas, E. Frainnet, and A. Bazouin, *C. R. Acad. Sci.*, **252**, 420 (1961); (f) J. A. Kerr, B. J. A. Smith, A. F. Trotman-Dickenson, and J. C. Young, *Chem. Commun.*, 157 (1966); (g) L. H. Sommer, E. W. Pietrusza, and F. C. Whitmore, *J. Amer. Chem. Soc.*, **69**, 188 (1947); (h) T. H. Chan, A. Milnyk, and D. N. Harpp, *Tetrahedron Lett.*, 201 (1969); (i) L. Horner and W. D. Balzer, *ibid.*, 1157 (1965).

(6) Under the same conditions as those in Figure 1, molar ratios of (acetaldehyde)/(ethyl methyl ether) obtained from the reduction in tetrahydrofuran were 0.03 and 0.07 for 2.5- and 4-hr irradiations, respectively.

(7) In part IV of this series (ref 3) the *G* value (number of molecules formed per 100 eV energy absorbed) of the reduction of α-chloro ether to ether was reported as 500. Compare this value with 400–500 in the present paper.

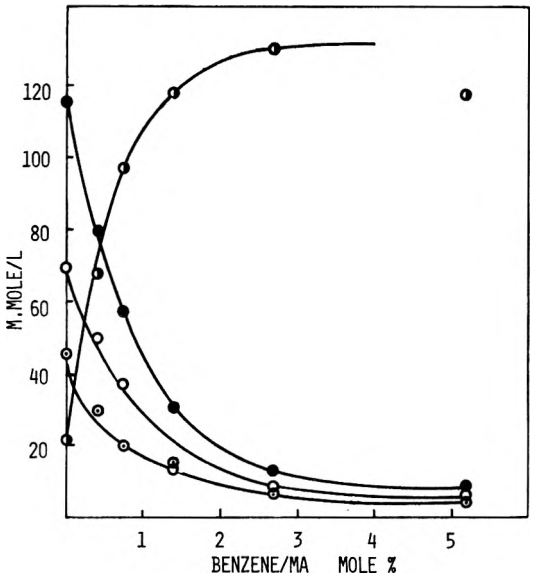


Figure 8.—Effect of benzene concentration; dose, 6.62 × 10^5 R; $[CH_3COOCH_3]_0$ = 0.156 mol/l; $[Cl_3SiH]_0$ = 0.312 mol/l. in cyclohexane; ○, CH_3CHO; ⊙, $C_2H_5OCH_3$; ●, CH_3CHO + $C_2H_5OCH_3$, and ◑, CH_3COOCH_3.

of trichlorosilyl radical and competes with methyl acetate for trichlorosilyl radical.

$$\text{benzene} + Cl_3Si\cdot \xrightarrow{k_b} \quad (9)$$

$$\text{methyl acetate} + Cl_3Si\cdot \xrightarrow{k_m} \quad (10)$$

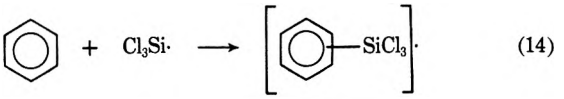
$$R = k_b[\text{benzene}][Cl_3Si\cdot] + k_m[\text{methyl acetate}][Cl_3Si\cdot] \quad (11)$$

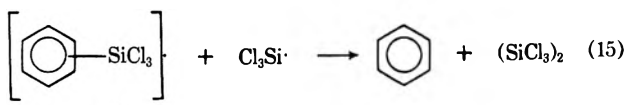
$$\Delta R = k_b[\text{benzene}][Cl_3Si\cdot] \quad (12)$$

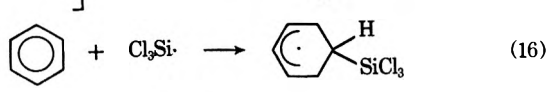
Here R signifies the rate of the methyl acetate consumed in the absence of benzene, and ΔR the decreased rate due to the presence of benzene. Equations 11 and 12 lead to

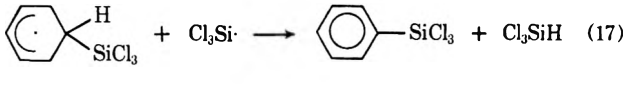
$$\Delta R^{-1} = R^{-1}\{1 + (k_m/k_b)[CH_3COOCH_3][\text{benzene}]\} \quad (13)$$

Figure 9 shows a plot of ΔR^{-1} *vs.* $[CH_3COOCH_3]/[\text{benzene}]$ and satisfies eq 13 in a range of lower concentrations of benzene. The value of k_m/k_b was calculated as 7.8×10^{-3}. The scavenging effect of benzene can be interpreted in two ways, eq 14 and 15 or eq 16 and 17.









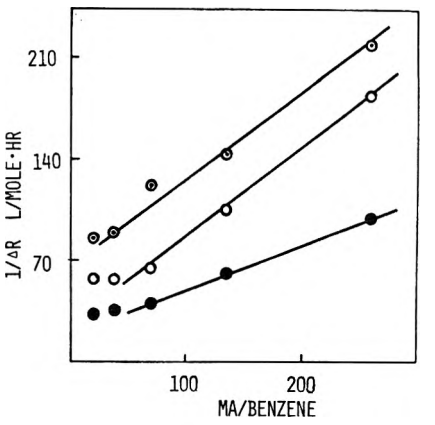


Figure 9.—Dependence of ΔR^{-1} values on CH_3COOCH_3/benzene: ○, CH_3CHO; ⊙, $C_2H_5OCH_3$; and ●, CH_3CHO + $C_2H_5OCH_3$.

The first results in the formation of hexachlorodisilane *via* the complex between benzene and trichlorosilyl radical (eq 14 and 15). The second describes the substitution of benzene with trichlorosilyl group. Which sequence is operative is not clear at the present time. The effect of adding some substituted benzenes is now under investigation at our laboratory.

Experimental Section

Trichlorosilane was treated with quinoline to remove hydrogen chloride and was distilled under atmospheric pressure. The distillate (boiling range 31.8–32.2°) was further purified by vacuum distillation. Methyl acetate was washed twice with saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and distilled twice through a 50-cm fractionation column packed with glass Raschig rings. The fraction boiling at 56.0–56.5° was further distilled under vacuum from a trap at −60° to a trap at −196°. Cyclohexane, *n*-hexane, tetrahydrofuran, and benzene, all Spectrograde, were refluxed with lithium aluminum hydride and distilled under vacuum. All the materials thoroughly degassed were stored at −78°.

Sample preparations for γ and photoirradiations were performed on a vacuum line by bulb to bulb distillations, and irradiation tubes were sealed under vacuum. The pressure of each materials was measured on a mercury manometer. The γ irradiations were performed at constant temperature (22°) in a Pyrex tube (10 mm φ) or a nmr tube using ^{60}Co–10,000 Ci. Dose rates were determined by the standard Fricke method using $G(Fe^{3+})$ = 15.6. Irradiation was carried out at the dose rate of 1.85×10^5 R/hr unless otherwise stated.

The photochemical reactions were carried out in a 1-cm path length absorption cell using a 100-W medium-pressure mercury lamp (Toshiba SHL-100 uv). A Hitachi 063 glpc (equipped with FID using a 1-m column of Porapak-q at 200°), a JEOL JNM 3H-60 nmr spectrometer, and a Shimazu RS-27 spectrophotometer were used for analyses. Uv absorption spectra of methyl acetate (at λ 240 nm) and acetaldehyde (at λ 285 nm) contributed to the qualitative analyses.

Registry No.—I, 37676-11-2; II, 1538-87-0; trichlorosilane, 10025-78-2; methyl acetate, 79-20-9; ethyl methyl ether, 540-67-0.

Kinetics and Mechanism of Iodolactonization of γ,δ-Unsaturated Acids[1]

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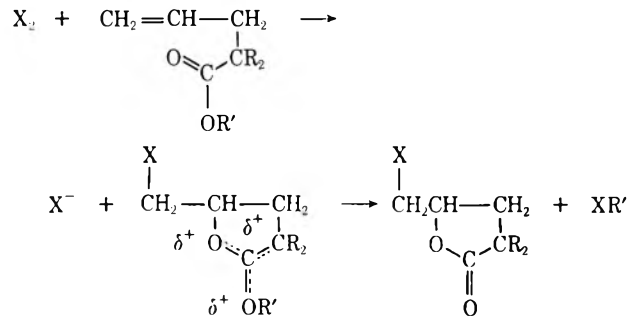
The kinetics of iodolactonization of 4-pentenoic acid (I), 2-phenyl-4-pentenoic acid (II), and 2,2-diphenyl-4-pentenoic acid (III) in chloroform have been studied at several temperatures using ^{131}I-labeled iodine. The rate law is given by the expression rate = $k_3(\text{acid})(I_2)^2$. Activation parameters which have been obtained are (acid, $\Delta H^{\pm}$, $\Delta S^{\pm}$, $\Delta G^{\pm}$): I, 3.3, −59, 21; II, 5.8, −51, 21; III, 9.0, −28, 17. A mechanism is postulated and discussed.

The iodolactonization of γ,δ-unsaturated acids has been studied by Bougault,[3] Linstead,[4] and Van Tamelen.[5] Arnold, *et al.*,[6] proposed a general mechanism for the reaction of electrophilic reagents and γ,δ-unsaturated acids and esters.



Later, it was shown in a qualitative way that an increase of electron density on the carbonyl group[7] and/or the presence of substituents at the α position of the carboxylic acids[8,9] increases the rate of the iodolactonization.

Our kinetic investigations were undertaken in order to obtain quantitative rate information pertinent to the iodolactonization of γ,δ-unsaturated acids referring specifically to the effects caused by substituents on the α position of the acids.

Experimental Section

Materials.—4-Pentenoic acid was obtained from the Chemical Procurement Laboratories; 2-phenyl-4-pentenoic acid and 2,2-diphenyl-4-pentenoic acid were synthesized according to known procedures.[10,11] All the other chemicals were reagent grade and were used without further purification.

Radioactive iodine was used in the experiments. Solutions of the tagged iodine were prepared by air oxidation of aqueous solutions of $Na^{131}I$ (specific activity 5 mCi ml^{-1}) to which a few drops of 0.1 *M* hydrochloric acid had been added. The iodine formed was immediately extracted into a solution of nonactive iodine in chloroform. The solution was treated with sodium sulfate and the concentration of iodine was determined by titration with thiosulfate. The solution was diluted with chloroform to the desired concentration of iodine. The final specific activity of the solution was determined (approximately 0.02 mCi ml^{-1}).

Product Analysis.—The products of the reaction of 4-pentenoic acid, 2-phenyl-4-pentenoic acid, and 2,2-diphenyl-4-pentenoic acid with iodine were prepared according to known procedures[9] with the exception that a 1:2 mole ratio of acid to iodine was used. The products were identified by means of a carbon and hydrogen analysis. The yields obtained were, respectively, valeric acid 4-hydroxy-5-iodo-γ-lactone, 77%; valeric acid 4-hydroxy-5-iodo-2-phenyl-γ-lactone, 79%; valeric acid 4-hydroxy-2,2-diphenyl-γ-lactone, 88%. Although the yields of these products were not determined in the solutions used in the kinetic experiments, the experimental conditions were close to those used in the product determinations. The products are stable in chloroform solution for several weeks.

Product Separation and Identification.—A 0.050 *M* solution (5 ml) of the tagged iodine in chloroform was mixed with 5 ml of a 0.025 *M* solution of the 4-pentenoic acid in chloroform. Meanwhile a chromatographic plate was wetted with a buffer solution of pH 7 and 2 drops of a 10% thiosulfate solution was applied at the origin. After 2 hr, a 0.1-μl aliquot of the reaction mixture was withdrawn and applied to the plate at the origin over the thiosulfate solution so that iodine was reduced to iodide and the reaction was quenched. The chromatographic plate was placed in an electrophoresis cell with the application point turned to the cathode. A force field of 12.5 V cm^{-1} was maintained for 10 min. By radiometric determination and by autoradiography it was possible to determine the composition of the radioiodide-containing products. One fraction was identified as iodolactone by treatment with hydroxylamine (transformation into hydroxamic acid) and ferric chloride, and the second fraction was identified as iodide, employing lead acetate.

Kinetic Experiments.—The kinetic runs were performed at constant temperature and in the absence of light. Individual kinetic runs were started by mixing a known volume of tagged iodine in chloroform with a known volume of the γ,δ-unsaturated acid in chloroform at the same temperature. After mixing (zero time) 0.1-μl aliquots were withdrawn at regular intervals of time and immediately applied to the chromatographic plate. Separation of the two fractions was performed as above.

The radioactivity of the two fractions (iodolactone and iodide) was determined with the aid of a geiger gas flow detector chromatograph (Nuclear Chicago, Model Actigraph III). The percentage of the radioiodolactone over the total of the radioiodine was calculated.

Isotopic Exchange.—A 0.035 *M* chloroform solution (5 ml) of the δ-iodo-γ-valerolactones prepared with nonactive iodine, and 5 ml of a 0.035 *M* chloroform solution of the tagged iodine were mixed (zero time) at several temperatures (0.0, 10.0, 20.0, and 32.0°); 0.1-μl aliquots were withdrawn at regular intervals of time; and the formation of radioiodolactone was followed as above. At 0.0, 10.0, and 20.0° there was no formation of radioiodolactone within 300 hr. At 32° the formation of 1% of the radioiodolactone was observed after 75 hr. Thus it was established that the isotopic exchange between the δ-iodo-γ-lactone and ^{131}I is a very slow reaction, and that the radioiodolactone must be formed in the direct reaction.

Results

It was shown in this work that, in chloroform solution, 1 mol of the γ,δ-unsaturated acid reacts with 2 mol of iodine, giving rise to 1 mol of iodolactone and 1 mol of hydrogen triiodide. This explains why the reac-

(1) Supported in part by the Fund for Overseas Research Grants and Education.

(2) Abstracted from M.S. Thesis of S. C. M.

(3) J. Bougault, *Ann. Chim. Phys.*, **14**, 145 (1908); **15**, 296 (1908).

(4) R. P. Linstead and C. May, *J. Chem. Soc.*, 2565 (1927).

(5) E. E. Van Tamelen and M. Shamma, *J. Amer. Chem. Soc.*, **76**, 2315 (1954).

(6) R. T. Arnold, M. Moura Campos, and K. L. Lindsay, *J. Amer. Chem. Soc.*, **75**, 1044 (1953).

(7) M. Moura Campos, *An. Acad. Brasil. Ciênc.*, **27**, 405 (1955).

(8) M. Moura Campos, *Chem. Ber.*, **93**, 1075 (1960).

(9) M. Moura Campos and L. do Amaral, *Arch. Pharm. (Weinheim)*, **298**, 92 (1965).

(10) H. Veldstra and C. Van Westeringh, *Recl. Trav. Chim. Pays-Bas*, **70**, 1113 (1951).

(11) R. T. Arnold, W. E. Parham, and R. M. Dodson, Jr., *J. Amer. Chem. Soc.*, **71**, 2439 (1949).

tion, when performed with 1 mol of the acid and 1 mol of iodine in chloroform solution, gives a maximum yield of 50% of iodolactone.[9]

The reaction of 4-pentenoic acid, 2-phenyl-4-pentenoic acid, and 2,2-diphenyl-4-pentenoic acid with iodine in chloroform solution, was studied at several temperatures.

For each acid at the various temperatures several kinetic runs were made in which the concentration of iodine or the concentration of the acid was varied and the initial velocity of the reaction as function of the concentration was determined. The calculated per cent of iodolactone formed was plotted against time, and the tangent at zero time was determined graphically. The slopes of the tangents gave the initial velocity of the reaction expressed in per cent of the iodolactone formed per unit of time. With those values and the initial concentration of the acids the slopes could be expressed in moles of iodolactone formed per unit of time (Table I). One notices from the values of

TABLE I

INITIAL RATES[a] OF THE REACTION OF 4-PENTENOIC ACID (I), 2-PHENYL-4-PENTENOIC ACID (II), 2,2-DIPHENYL-4-PENTENOIC ACID (III) AND IODINE, AND RATE CONSTANTS, IN CHLOROFORM SOLUTION AT 32°, AS A FUNCTION OF THE CONCENTRATIONS OF THE REAGENTS

C_0 I, M	C_0 iodine, M	Iodolactone, M min^{-1}	k_3, M^{-2} min^{-1}
0.140	0.0250	5.8×10^{-5}	6.6×10^{-1}
0.070	0.0250	2.5×10^{-5}	6.4×10^{-1}
0.070	0.0125	7.5×10^{-6}	6.8×10^{-1}
0.0350	0.0350	2.9×10^{-5}	6.6×10^{-1}
C_0 II, M	C_0 iodine, M	Iodolactone, M min^{-1}	k_3, M^{-2} min^{-1}
0.100	0.0250	5.5×10^{-5}	8.8×10^{-1}
0.0500	0.0250	2.7×10^{-5}	8.8×10^{-1}
0.0250	0.0250	1.3×10^{-5}	8.6×10^{-1}
0.0500	0.0125	8.0×10^{-6}	1.0×10^{0}
C_0 III, M	C_0 iodine, M	Iodolactone, M min^{-1}	k_3, M^{-2} min^{-1}
0.00750	0.00750	1.5×10^{-4}	3.7×10^{2}
0.00750	0.00375	4.0×10^{-5}	3.8×10^{2}
0.00750	0.001875	9.4×10^{-6}	3.6×10^{2}
0.001875	0.00750	3.8×10^{-5}	3.8×10^{2}

[a] In moles of δ-iodo-γ-lactone formed per minute.

Table I that the rate of the reaction is first order in the acid concentration and second order in iodine concentration. The rate law is

$$\text{rate} = k_3(A)(I_2)^2$$

From the values of the initial velocity, the initial concentration of the acids, and the initial concentration of iodine the values of k_3 were calculated (Table II).

TABLE II

RATE CONSTANTS[a] FOR THE REACTION OF 4-PENTENOIC ACID (I), 2-PHENYL-4-PENTENOIC ACID (II), AND 2,2-DIPHENYL-4-PENTENOIC ACID (III) AND IODINE, IN CHLOROFORM SOLUTION, AT SEVERAL TEMPERATURES

	0.0°	5.0°	10.0°	15.0°	20.0°	25.0°	32.0°	40.0°
I	0.35		0.41		0.51		0.66	
II	0.27		0.40		0.60		0.90	
III		69	77	98	200	340	370	480

[a] The constants are expressed in M^{-2} min^{-1}.

Arrhenius plots of log k_3 *vs.* $1/T$ for the reaction of 4-pentenoic acid, 2-phenyl-4-pentenoic acid, and 2,2-diphenyl-4-pentenoic acid with iodine gave reasonably straight lines from which the activation energy, E_a, was determined by least squares analysis (Table III). The

TABLE III

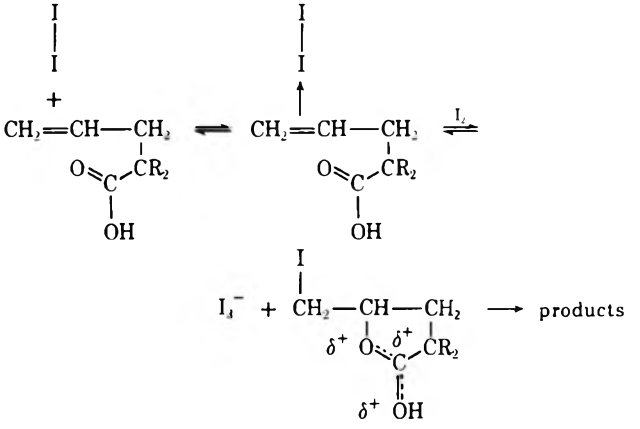
ACTIVATION PARAMETERS FOR THE REACTION OF 4-PENTENOIC ACID (I), 2-PHENYL-4-PENTENOIC ACID (II), AND 2,2-DIPHENYL-4-PENTENOIC ACID (III) AND IODINE IN CHLOROFORM SOLUTION

	E_a, kcal mol^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu	$\Delta G^{\ddagger}$, kcal mol^{-1}
I	3.9	3.3	−59	21
II	6.4	5.8	−51	21
III	9.6	9.0	−28	17

enthalpy of activation, $\Delta H^{\ddagger}$, was obtained by subtracting RT from E_a. The entropy of activation, $\Delta S^{\ddagger}$, was calculated from the formula given by Schaleger and Long.[12] The activation parameters are shown in Table III.

Discussion

From the data obtained in this work it is possible to propose a more detailed mechanism for the iodolactonization of γ,δ-unsaturated acids than that proposed by Arnold, *et al.*[6]



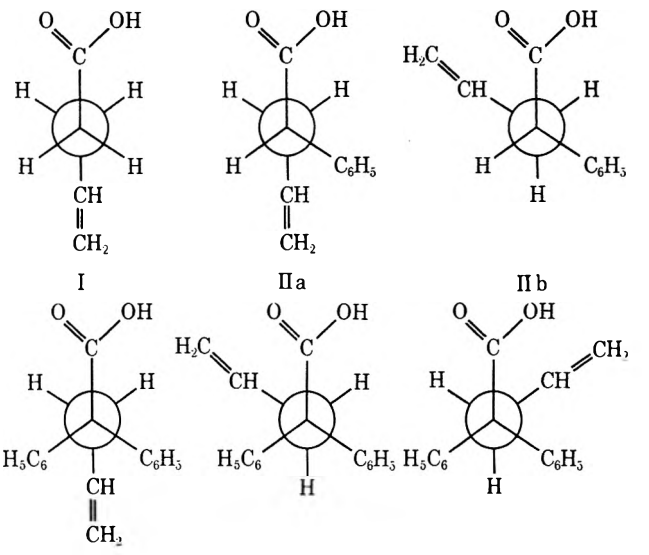
In accordance with the general mechanism of the addition reaction of halogens to alkenes in poorly ionizing solvents,[13,14] the iodolactonization of γ,δ-unsaturated acids starts by the formation of a complex between iodine and the double bond of the acids. In poorly ionizing media, as in chloroform solution, the formation of the intermediate ion, a reaction that requires charge separation, is aided by a second molecule of iodine, which helps to disperse the negative charge by formation of the triiodide ion I_3^-. The reaction is aided also by the formation of a cation whose positive charge is dispersed by resonance. The formation of the intermediate cation may occur in a prequilibrium step in which an iodine–carbonium, or iodonium ion,[15] is formed, followed by cyclization. It may also occur by a concerted reaction.

(12) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 7 (1963).
(13) E. P. White and P. W. Robertson, *J. Chem. Soc.*, 1509 (1939).
(14) K. Yates and W. V. Wright, *Can. J. Chem.*, **45**, 167 (1967).
(15) A. Hassner and C. C. Heathcock, *Tetrahedron Lett.*, **No. 19**, 1125 (1964).

The values of the entropy of activation become more negative from the reaction of iodine with 2,2-diphenyl-4-pentenoic acid to the reaction of iodine with 4-pentenoic acid, while the values of the enthalpy of activation increase from the reaction of iodine with 4-pentenoic acid to the reaction of iodine with 2,2-diphenyl-4-pentenoic acid (Table III).

The formation of the complex between iodine and the acid probably occurs as a fast step in each of the systems studied.[12] The very high negative values of the entropy of activation indicate a high degree of order in the activated complex with respect to the reactants, which is as expected for a third-order electrophilic addition process.

The increase in the measured entropy of activation from the reaction of iodine with 2,2-diphenyl-4-pentenoic acid (−28 eu) to the reaction with 4-pentenoic acid (−59 eu) is at least partly explained by a conformation analysis of the acids. For the 4-pentenoic acid the more stable conformation should be the anti (I); for the 2-phenyl-4-pentenoic acid there are two stable conformations (IIa and IIb); for the 2,2-diphenyl-4-pentenoic acid there are three stable conformations (IIIa, IIIb, and IIIc). As the conformations IIb of the 2-phenyl-4-pentenoic acid, and IIIb and IIIc for the 2,2-diphenyl-4-pentenoic acid, are appropriate to the formation of the intermediate cyclic cations, there is an increase of the population of the appropriate conformation for the reaction from the 4-pentenoic acid to the 2,2-diphenyl-4-pentenoic acid.



I IIa IIb

IIIa IIIb IIIc

The increasing values of the enthalpy of activation from 4-pentenoic acid to 2,2-diphenyl-4-pentenoic acid are consistent with the eclipsed conformation of the cyclic transition state, since repulsion between phenyl hydrogens and those β to the carbonyl group is expected to contribute to the energy of activation.

Registry No.—I, 591-80-0; II, 1575-70-8; III, 6966-03-6; iodine, 7553-56-2.

Acknowledgment.—The author is indebted to Dr. John M. Malin for helpful comments concerning this work.

Notes

Syntheses of Several 1,3-Thiazine Derivatives with Polyphosphate Ester

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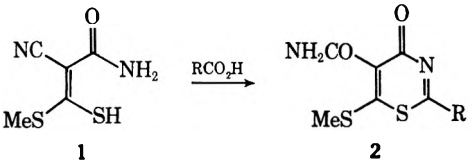
Received February 22, 1972

In previous work,[1] 3-alkylthio-2-cyano-3-mercaptoacrylamide (**1a**) and 3-alkylthio-2-cyano-3-mercaptothioacrylamide (**1b**) promised to be useful intermediates for synthesizing 4-keto-1,3-thiazine derivatives and 4-thioketo-1,3-thiazine derivatives, respectively.

It has been shown recently by Kanaoka and coworkers[2] that benzothiazoles can be obtained by condensation of *o*-mercaptoanilines and free carboxylic acids in the presence of polyphosphate ester (PPE). This suggested that a similar condensation of the mercaptoamides with acids and PPE might provide a good route to 1,3-thiazine derivatives.

Pursuing this possibility, we have found that reaction of the cyanoamide **1** with an aromatic acid and PPE in refluxing chloroform gives the 5-carbamoyl-6-methylthio-1,3-thiazin-4-ones (**2**) in 27–90% yield. The cyano thiazines could not be detected.



1 **2**

The structure **2** is consistent with analyses and spectral data. Mass spectral data for **2** show a P − 47 ion characteristic for the SCH_3 group.[3] The nmr spectrum (DMSO-d_6) of **2a** gives a singlet methyl signal at δ 2.65, a multiplet phenyl signal at 7.70, and a broad amino signal at 8.20, which disappears on deuterium exchange. Ir spectral data of **2a** show a very strong peak of the

(1) (a) M. Yokoyama, *Bull. Chem. Soc. Jap.*, **44**, 1610 (1971); (b) M. Yokoyama, *J. Org. Chem.*, **36**, 2009 (1971).

(2) Y. Kanaoka, T. Hamada, and O. Yonemitsu, *Chem. Pharm. Bull.*, **18**, 587 (1970).

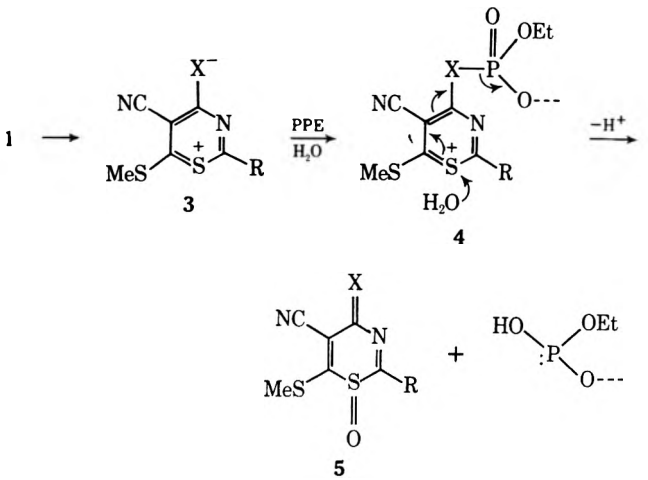
(3) Mass spectral data for 6-methylthio-2,3-dihydro-1,3-thiazin-4-one (thione) derivatives showed a P − 47 ion which was considered to be a fragment of the P − SCH_3 ion (see ref 1).

TABLE I

1	Carboxylic acid	Product	Time, min	Mp, °C	Yield, %
1a (X = O)	Benzoic acid	2a	60	222–223	90
	p-Hydroxybenzoic acid	2b	30	252–254	48
	p-Chlorobenzoic acid	2c	180	213–214	27
	β-Naphthoic acid	2d	60	211–212	67
	Furan-2-carboxylic acid	2e	180	279–280 dec	37
	Phenylacetic acid	5f	15	198–199	35
	Acetic acid	5g	30	195–196 dec	35
	Propionic acid	5h	60	155–156 dec	13
1b (X = S)	Benzoic acid	5i	10	232–233	53
	Furan-2-carboxylic acid	5j	20	134–135	56
	Acetic acid	5k	50	238–239	12

amide group and two characteristic peaks of the phenyl group at 1600 and 1510 cm^{-1}. The features of the uv spectrum of 2 are similar to those of 2-amino-6-methoxycarbonyl-1,3-thiazin-4-one and 2-acetylamino-6-methoxycarbonyl-1,3-thiazin-4-one.[4] These spectroscopic data show the presence of methylthio, carbamoyl, and phenyl groups. Their positions on the 1,3-thiazin-4-one ring are determined according to a possible cyclization reaction reported by Kanaoka, *et al.*[2]

In contrast to the reaction 1 → 2, the reaction of 1 with aliphatic acids gave in low yields the 5-cyano-6-methylthio-1-oxo-1,3-thiazin-4-ones (5, X = O). These



structures are supported by the appearance of an S=O stretching band at 1002–1010 cm^{-1} and a CN band at 2200–2230 cm^{-1}. The presence of an $SOCH_3$ group was ruled out by the absence of P − $SOCH_3$ and $SOCH_3$ ions (mass spectra).

Analogous 5-cyano-1-oxo products (5, X = S) were obtained from the thioamide (1, S replacing O) and either aromatic or aliphatic acids. These sulfoxides were obtained when the reaction were carried out in an inert atmosphere, suggesting that the S=O group arises by nucleophilic attack of water, resulting from the dehydration step, on the intermediate (3). The competition between attack of water on sulfur (4) or at the cyano group of 3 to give 2 appears to depend on both the group X and the electronic nature of R.

The thiazinium structure (3) makes a more important contribution with X = S because of poor 2p–3pπ overlap, and the reaction 4 → 5 is favored. When X = O, reaction 3 → 4 is important only when R is an electron-releasing group such as alkyl. When R is an electron-attracting group such as aryl, which cannot stabilize the thiazinium structure (3), hydration of the cyano thiazine intermediate occurred to give 2 instead of the reaction 3 → 4.

Our attempt to isolate the cyano thiazine intermediate from the reaction mixture failed. Hydration of the cyano thiazine intermediate in the formation of 2 presumably involves coordination of PPE at the cyano group and attack of water to the nitrilium center instead of at sulfur. The 1-oxo-5-cyano compounds (5) were unaffected by heating with PPE in chloroform, but hydration to the amide occurred on heating in polyphosphoric acid.

Table I summarizes the results obtained by this method. The reaction rate for the formation of 5 generally exceeded the rate for 2. In this experiment, two reactions to give 2 and 5 did not occur simultaneously.

Experimental Section[5]

Compounds 1a and 1b were prepared by our method.[1a,6] PPE was prepared by refluxing a mixture of 150 g of phosphorus pentoxide, 150 ml of diethyl ether, and 300 ml of chloroform until the solution was clear.[7] All other carboxylic acids, pure grade of Wako Chemicals, were used without further purification.

Preparation of 5-Carbamoyl-6-methylthio-2-phenyl-1,3-thiazin-4-one (2a).—A mixture of 1a (3.5 g, 20 mmol), benzoic acid (2.5 g, 20 mmol), PPE (12 g), and chloroform (80 ml) was refluxed for 60 min. After evaporation of the solvent *in vacuo*, the red oily residue was treated with ice–water and neutralized with $NaHCO_3$. The red oil which was separated from the solution was crystallized from acetic acid–H_2O. The resulting orange powder (5 g) was recrystallized twice from acetic acid to give orange plates. Compounds 2b–5k were prepared in the same method as mentioned above. Compounds 2 were generally isolated as yellow plates or needles and 5 as an orange powder.

(4) E. Winterfeldt and J. M. Nelke, *Chem. Ber.*, **100**, 3671 (1967).

(5) Elemental analyses, uv, ir, nmr, and mass spectral data of compounds synthesized by this method will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-73-802. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(6) T. Takeshima, M. Yokoyama, N. Fukada, and M. Akano, *J. Org. Chem.*, **35**, 2438 (1970).

(7) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 892.

In this reaction, the refluxing was allowed to continue until red oil appeared on the reaction mixture (the reaction had been completed at this point). Compound **5i** was synthesized by refluxing **1b** and benzoic acid in the dehydrated chloroform under nitrogen which was deoxygenated by using alkali pyrogallol and by crystallization of the resulting red oil with the absolute alcohol. Compound **2a** was also prepared in the same method as above. By employing the mild reaction conditions such as decreasing the amount of PPE, shortening the refluxing time, and increasing the amount of chloroform solvent, a small amount of **2** or **5** was collected together with the unreacted compound **1**, and the expected cyano thiazine derivatives could not be detected.

Nitrile Hydrolysis of 5-Cyano-6-methylthio-2-phenyl-1-oxo-1,3-thiazine-4-thione (5i).—A mixture of **5i** (1 g, 3.5 mmol) and polyphosphoric acid (PPA, 61 g) was heated at 80° for 3 hr. The reaction mixture was cooled and decomposed by adding ice–water (*ca.* 200 ml) and neutralized with KOH. The resulting brown crystals (0.8 g) were recrystallized from acetic acid to give brown plates: mp 223–224°; ir (KBr) 3440, 3400 (NH_2), 2920 (CH_3), 1640 (CO), 1580 (benzene ring), 1533 (hetero ring), 1444, 1415 (CH_3), 1119 (CS), 1002 cm^{-1} (SO); uv $\lambda_{max}^{99\%EtOH}$ 225 nm (log ϵ 4.14), 268 (4.29), 329 (3.78), 370 (4.48).

Anal. Calcd. for $C_{12}H_{10}N_2S_3O_2$: C, 46.43; H, 3.25; N, 9.03; mol wt, 310.42. Found: C, 46.51; H, 3.18; N, 8.98; mol wt, 310 (mass spectrum).

Registry No.—**1a**, 37614-61-2; **1b**, 29082-78-8; **2a**, 37614-62-3; **2b**, 37614-63-4; **2c**, 37614-64-5; **2d**, 37614-65-6; **2e**, 37614-66-7; **5f**, 37614-67-8; **5g**, 37614-68-9; **5h**, 37614-69-0; **5i**, 37614-70-3; **5j**, 37614-71-4; **5k**, 37614-72-5; benzoic acid, 65-85-0; *p*-hydroxybenzoic acid, 99-96-7; *p*-chlorobenzoic acid, 74-11-3; *β*-naphthoic acid, 93-09-4; furan-2-carboxylic acid, 88-14-2; phenylacetic acid, 103-82-2; acetic acid, 64-19-7; propionic acid, 79-09-4.

Transmission of Electronic Effects through the Cyclopropane Ring in Some Arylcyclopropanes

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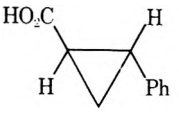
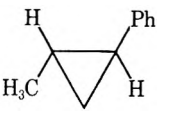
The possibility of electronic interaction between the cyclopropane ring and unsaturated groups has been of interest to several workers.[1-5] Some theoretical predictions[1] of Walsh for special geometric requirements for such interactions were tested[6] through the study of the ultraviolet spectra of a series of rigid arylcyclopropanes, but it was concluded that the steric relationship between a cyclopropane and benzene ring is of little consequence on the ultraviolet spectra.[6]

However, nmr evidence has been presented[7] showing that a conformation with the phenyl ring bisecting the three-membered ring is preferred in phenylcyclopropane. These results seem to imply that ultraviolet spectra are not sensitive to the relatively small conjugative effects in arylcyclopropanes.

This conclusion received indirect support by the recent report[8] that the ultraviolet and circular dichroism (CD) spectra of compounds I and II are very similar. In fact, this evidence was interpreted[8] as



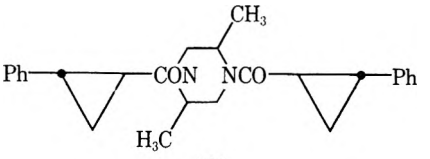
I



II

indicating that the carboxyl chromophore did not contribute significantly to the absorption, the latter being attributed exclusively to the benzene chromophore.

We report here additional evidence on the uv and CD spectra of compound I, which indicates some electronic interaction between the benzene and carboxyl chromophores in this molecule. This result suggests some transmission of electronic effects through the cyclopropane ring in arylcyclopropanes. These effects are also present in the diamide III, derived from the acid I.

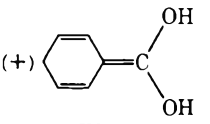


III

Results and Discussion

Relevant data on the uv, ORD, and CD spectra of compound I in tetramethylenesulfone (TMS) and methanesulfonic acid (MSA) are reported in Table I. The CD spectrum in TMS shows the typical vibrational structure of the ^1L_b benzene band in the 250–275-mμ region as well as a peak of higher intensity at 225 mμ which has been assigned[8] to the ^1L_a benzene transition. Although the TMS curve shows essentially the same features of the methanol spectrum previously reported,[8] a red shift is observed (Table I) in the MSA spectrum, with regard to the 225-mμ band.

This suggests that the 225-mμ band reflects an electronic interaction between the ^1L_a benzene transition and the carboxyl group, *via* the cyclopropane ring. In fact, red shifts of uv bands are known[9] to occur in aromatic carboxylic acids by addition of strong acids capable of protonating the carboxyl group, generating quinoid species such as IV absorbing at lower energy.[9]



IV

If the band at 225 mμ was entirely due to the ^1L_a benzene transition, it should not be drastically affected by the MSA addition. We have ascertained that phenylacetic acid shows a moderate blue shift in the corresponding uv absorption band in going from TMS (210 mμ) to MSA (204 mμ). However, the 280-mμ absorption of *trans*-cinnamic acid in TMS is shifted to about 325 mμ in MSA.

(1) A. D. Walsh, *Trans. Faraday Soc.*, **45**, 179 (1949).
(2) L. S. Bartell, B. L. Carroll, and J. P. Guillory, *Tetrahedron Lett.*, 705 (1964); L. S. Bartell and J. P. Guillory, *J. Chem. Phys.*, **43**, 647 (1965).
(3) G. J. Karabatsos and N. Hsi, *J. Amer. Chem. Soc.*, **87**, 2864 (1965).
(4) R. Hoffmann, *Tetrahedron Lett.*, 3819 (1965), and references cited therein.
(5) M. Pelissier, A. Serafini, J. Devanneaux, J. F. Labarre, and J.-F. Tocanne, *Tetrahedron*, **27**, 3271 (1971), and references cited therein.
(6) A. L. Goodman and R. H. Eastman, *J. Amer. Chem. Soc.*, **86**, 908 (1964).
(7) G. L. Closs and R. A. Moss, *ibid.*, **86**, 4042 (1964); G. L. Closs and H. B. Klinger, *ibid.*, **87**, 3265 (1965).
(8) L. Verbit and Y. Inouye, *ibid.*, **89**, 5717 (1967).
(9) R. Stewart and K. Yates, *ibid.*, **82**, 4059 (1960).

TABLE I
OPTICAL DATA OF (−)-(*R*)-*trans*-2-PHENYLCYCLOPROPANECARBOXYLIC ACID (I)

Solvent	ORD λ, mμ	ORD *m*	CD λ, mμ	CD θ	Uv λ, mμ	Uv ε
TMS	274	−9,700 (t)[b]	273	−4,000 (M)[b]	273	350
	271	−9,500 (p)	269	−3,500 (m)		
	267	−10,500 (t)	265	−4,500 (M)	266	500
	264	−10,000 (p)	262	−3,500 (m)		
	259	−11,000 (s)	260	−4,000 (M)	260	500
	234	−37,500 (t)	254	−3,500 (m)		
	224	0	225	−61,000 (M)	223	13,000
	215	+27,500 (p)				
	207	0	211	−23,500 (m)		
	(200)	(−)	(205)	(−40,000)		
MSA	271[a]	−11,500 (t)				
	241	0	240[a]	−41,000	240	7,500
	217	+37,500 (p)	216	0		
			214	+3,500		
	205	+19,500 (t)	212	0		
	(200)	(+25,000)	(205)	(−14,000)		

[a] Very broad. [b] t, trough; p, peak; s, shoulder; M, + or − maximum; m, + or − minimum.

TABLE II
OPTICAL DATA OF (−)-(*R*)-Ph-C3·DMPIP DIAMIDE (III)

Solvent	ORD λ, mμ	ORD *m*	CD λ, mμ	CD θ	Uv λ, mμ	Uv ε
TMS	275	−10,500 (t)[b]	274	−5,500 (M)[b]	274	350
	272	−9,000 (p)	271	−2,500 (m)		
	268	−10,000 (t)	267	−6,000 (M)	267	500
	264	−9,000 (p)	264	−3,500 (m)		
	260	−10,500 (s)	261	−4,000 (M)	259	500
	237	−37,000 (t)	257	−3,000 (m)		
	229	0	230	−92,000 (M)		
	218	+72,000 (p)	218	0	221	23,000
			215	+12,000 (M)		
			212			
	(210)	(+33,000)	(210)	(−10,000)		
MSA	275	−16,500 (t)	272	−13,500 (s)		
	269	−15,000 (s)	265	−18,500 (s)		
	262	−11,500 (s)				
	248	0	247[a]	−30,000 (M)	242	9,000
	222	+39,500 (p)	225	0		
	213	0	217	+28,000 (M)		
	210	−6,500 (t)	211	0	207	26,000
	206	0				
	(200)	(+17,000)	(200)	(−38,000)		

[a] Very broad. [b] t, trough; p, peak; s, shoulder; M, + or − maximum; m, + or − minimum.

It seems reasonable to conclude that the 225-mμ band in compound I arises from the ^1L_a benzene transition modified by the electronic interaction with the cyclopropane ring. Accordingly, the fact that the methyl derivative II is isospectral to I does not necessarily imply the absence of interaction between phenyl and carboxyl, but rather indicates the presence of electronic interaction between benzene and cyclopropane rings in both compounds I and II.

A behavior similar to that observed for compound I is shown by the uv, ORD, and CD spectra of the diamide III, reported in Table II. The CD spectrum in TMS shows the typical vibrational structure of the ^1L_b benzene band in the 250–280-mμ region, and this fine structure is still detectable in MSA, superimposed by a long wavelength "tail" of the red-shifted (conjugation) band (Table II). We interpret this red shift as due to the protonation of the amide linkage by MSA. Thus benzamide is reported to be completely protonated in 59% H_2SO_4,[10] and its absorption maximum is considerably red shifted.[11] Aliphatic amides do not show this behavior; thus only minor changes in the intensity of these bands are observed.[11] The data suggest an electronic interaction from the benzene ring to the amide unit through the "conducting" cyclopropane bridge.

The presence of this electronic interaction poses the question of the identity of the preferred conformation for this system. It has been proposed[12] that the cyclopropylthioamides exist in a preferred conformation where the endo orbitals of the cyclopropane rings overlap with the adjacent π orbital of the thiocarbonyl group in the thioamide unit, so that the latter bisects exactly the cyclopropane ring. Since there are no appreciable differences in going from thioamides to amides, the above conformation should be also preferred in the case of cyclopropylamides.

(10) K. N. Bascombe and R. P. Bell, *J. Chem. Soc.*, **82**, 1096 (1959).

(11) J. T. Edward, H. S. Chang, K. Yates, and R. Stewart, *Can. J. Chem.*, **38**, 1518 (1960).

(12) Y. Inouye, S. Sawada, M. Ohno, and H. M. Walborsky, *Tetrahedron*, **23**, 3237 (1967).

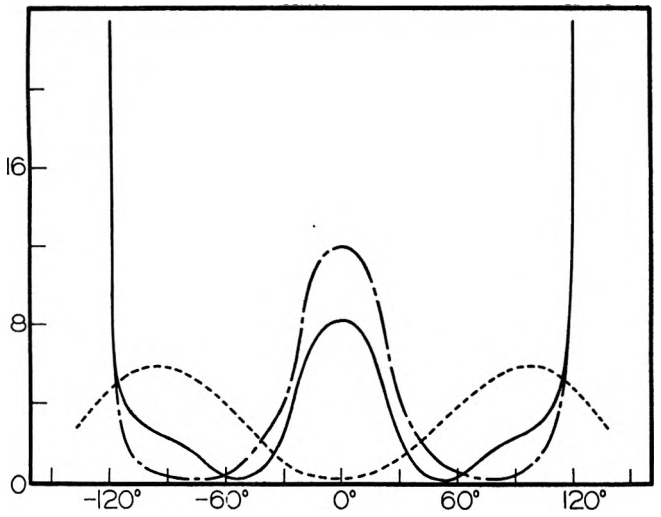


Figure 1.—Energy profiles as a function of the twist angle ϕ, for diamide III (half-molecule): — — — —, nonbonded atoms interactions; – – – – –, conjugative energy; ————, relative conformational energy. The 0° position is that where the carbonyl bisects the cyclopropane ring (maximum orbitals overlap).

However, if it is true that the geometrical arrangement with the amide (or thioamide) unit bisecting the cyclopropane ring meets the Walsh[1] requirements for the maximum overlap of cyclopropyl and carbonyl orbitals, an inspection of molecular models reveals that the nonbonded atom interactions are very unfavorable. As a consequence, a preferred conformation has to be assessed taking into account both conjugative and steric factors.

The conjugative ability of cyclopropane and carbonyl groups at the "maximum overlap" conditions has been estimated[4,5] to be about 6.0 kcal/mol in cyclopropanecarboxaldehyde, a system reasonably free from steric restraints. Assuming[4,5] a cosine^2 dependence of the conjugative energy from the angle of twist ϕ, the latter energy can be calculated for each ϕ value.

In Figure 1 are reported, as a function of the twist angle ϕ, the nonbonded interactions,[13] the conjugative energy, and the resultant relative conformational energy curves, relative to the half-molecule of diamide III.

It is apparent that the conformational minima are removed about 50–60° from the maximum-overlap position; this would still allow more than one-half of the maximum conjugative energy to be present.

This simple analysis appears to provide a more realistic basis to rationalize the transmission of electronic effects observed in the case of diamide III. Thus, it is not necessary to have coincidence between the maximum orbital overlap and the actual preferred conformation in order to get a sizable conjugative interaction and, therefore, the transmission of electronic effects through the cyclopropane ring.

Experimental Section

Spectra were recorded on a Jasco-Durrum ORD/CD/UV-5 spectropolarimeter; concentration 10^{-2}–10^{-3} M, cell length 0.1–1.0 mm, temperature 20–25°. All ORD/CD data are given in deg cm^2/dmole of substrate.

Tetramethylenesulfone (Aldrich Chemical Co.) and methanesulfonic acid (Eastman Kodak Co.) were used without further purification.

(−)-(1*R*,2*R*)-*trans*-2-Phenylcyclopropanecarboxylic Acid (I).—(−)-(1*R*,2*R*)-*trans*-2-Phenylcyclopropanecarboxylic acid (I) was prepared as previously described:[15] mp 48.5–49.5° [petroleum ether (bp 30–60°)]; $[\alpha]^{20}D$ −410° ($CHCl_3$, 1.0 g/dl) [lit.[14a] mp 51–52°; $[\alpha]^{24}D$ −368° ($CHCl_3$, 0.931 g/dl)].

Bis-1,4-[(−)-(1*R*,2*R*)-2-phenylcyclopropanecarbonyl]-2,5-dimethylpiperazine (III).—(−)-(*R*)-*trans*-2-Phenylcyclopropanecarboxylic acid and a catalytic amount of anhydrous zinc chloride were added to thionyl chloride (120% excess relative to carboxyl groups) at room temperature. The mixture was stirred at 40° for 3 hr. The excess thionyl chloride was then removed under reduced pressure and the residue was fractionated to afford an 85% yield of the acid chloride, bp 80° (0.25 mm).

A mixture of 0.193 g (1.69 mmol) of *trans*-2,5-dimethylpiperazine (DMPIP), 9.32 ml (3.63 mmol) of 0.4 N aqueous NaOH solution, and 35.5 ml of methylene chloride was precooled to 0° in a Waring semimicro blender. This mixture was cooled in ice and vigorously stirred during the addition of 0.641 g of acid chloride and for an additional 10 min. The reaction mixture was filtered through a medium sintered glass funnel and the methylene chloride phase was separated and evaporated to dryness to afford 0.68 g (~100% based on DMPIP) of crude III which was purified by column chromatography (Florisil 60–100 mesh and 160 ml, MeOH 60 ml/hr, room temperature, retention volume 140–200 ml) and two recrystallizations from *n*-hexane, mp 120–121°.

Anal. Calcd for $(C_{10}H_9O_2)_2(C_6H_{12}N_2)$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.76; H, 7.64; N, 6.84.

Registry No.—I, 3471-10-1; I (acid chloride), 37107-48-5; III, 37107-49-6.

Acknowledgments.—The authors wish to thank Dr. Y. Shimokawa for his help in the preparation of compounds I and II and are grateful for financial support by the Department of the Army, Research Office (Durham), under Grant DAHCO-4-69-C-0050.

(13) The nonbonded atoms interactions were estimated using pertinent literature data on interatomic distances and bond angles.[5] Coefficients for the pair-wise Lennord–Jones potential functions and for angular deformations were taken from Scott and Scheraga.[14]

(14) R. A. Scott and H. A. Scheraga, *J. Chem. Phys.*, **45**, 2091 (1966); T. Ooi, R. Scott, G. Vanderkooi, and H. A. Scheraga, *ibid.*, **46**, 4410 (1967).

(15) (a) H. M. Walborsky and L. Plonsker, *J. Amer. Chem. Soc.*, **83**, 2138 (1961); (b) Y. Inouye, T. Sugita, and H. M. Walborsky, *Tetrahedron*, **20**, 1695 (1964).

A Convenient Synthesis of β-Halopyruvaldoximes

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Received August 15, 1972

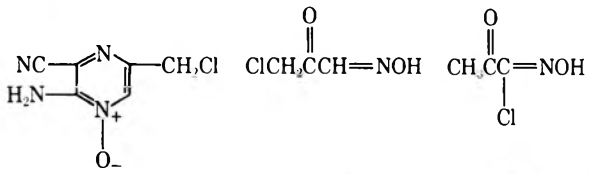
In order to further our recent studies on unequivocal syntheses of 6-substituted pteridines,[1,2] we required large quantities of 2-amino-3-cyano-5-chloromethylpyrazine 1-oxide (**1**), obtained in good yield by condensation of aminomalononitrile with β-chloropyruvaldoxime (**2**). The preparation of **2** had previously been accomplished by chlorination of pyruvaldoxime in dilute chloroform solution,[3] but this proved to be a tedious and unpredictable reaction. Major problems

(1) E. C. Taylor in "Chemistry and Biology of Pteridines," K. Iwai, M. Akino, M. Goto, and Y. Iwanami, Ed., International Academic Printing Co., Ltd., Tokyo, 1970, pp 79–93.

(2) E. C. Taylor, K. L. Perlman, I. P. Sword, M. Séquin-Frey, and P. A. Jacobi, *J. Org. Chem.*, submitted for publication.

(3) J. Armand, J-P. Guette, and F. Valentini, *C. R. Acad. Sci., Ser. C*, **263**, 1388 (1966).

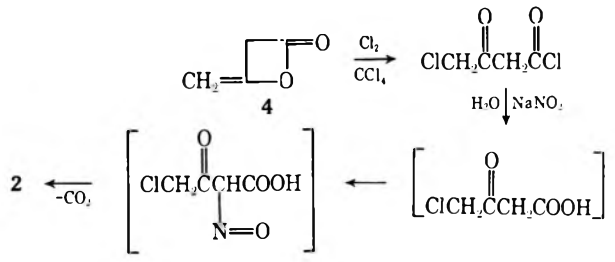
were the consistently poor yields, concomitant formation of the isomeric hydroxamoyl chloride (**3**), the instability of the desired product **2** in the acidic reaction medium, and a mysterious dependence of results on unknown variables in the nature and water content of the solvent.



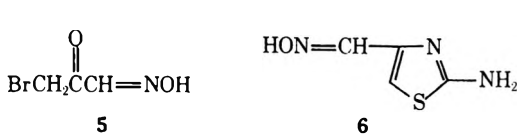
1 **2** **3**

In preference to identifying and standardizing the many variables in the chlorination of pyruvaldoxime, we sought an alternate route to **2**. An attractive possibility was to employ a derivative of γ-chloroacetoacetic acid which could be hydrolyzed, nitrosated, and decarboxylated without jeopardizing the fragile chloromethyl group. Chlorination of diketene (**4**) provided us with γ-chloroacetoacetyl chloride[4] which was converted in one step into **2** in a two-phase system of ether–aqueous sodium nitrite (Scheme I). The desired β-chloropyruvaldoxime was isolated in 60% yield (based on diketene) from the organic layer. Proof of structure was obtained by spectroscopic data, by comparison with an authentic sample,[3] and by conversion into **1** *via* standard procedures.[5]

SCHEME I



Similarly, β-bromopyruvaldoxime[6] (**5**) was prepared in 66% yield by bromination of diketene[7] followed by an analogous hydrolysis–nitrosation–decarboxylation sequence. Proof of structure was obtained for this product from spectral data and microanalysis, and by its facile reaction with thiourea[8] to give 2-amino-5-isonitrosomethylthiazole (**6**).



5 **6**

Both of the β-halopyruvaldoximes prepared by the above method are highly lachrymatory, and the chloro compound (**2**) has been found to produce severe skin irritation in some individuals after sensitization from long exposure. These halo oximes are unstable to storage at room temperature, especially when impure; decomposition is accompanied by the evolution of hydrogen cyanide. Although they are more stable at −20°, it is recommended that they be utilized immediately after preparation.

Experimental Section

β-Chloropyruvaldoxime (**2**).—In a 500-ml, three-neck flask equipped with thermometer, gas inlet tube, drying tube, and magnetic stirring bar was placed a solution of 33.6 g of freshly distilled diketene in 300 ml of dry CCl_4. The flask was weighed and then cooled to 0° (Dry Ice–acetone at −20°). Then 28.4 g of chlorine was bubbled into the solution with efficient stirring (about 1–2 g/min) while the temperature was maintained at −2 to +2°. After the solution had absorbed the required weight of chlorine (checked by intermittent weighing), the solvent was removed on a rotary evaporator and the residue was dissolved in 300 ml of absolute ether.

A solution of 27.6 g of $NaNO_2$ in 300 ml of water was placed in a 1-l., three-neck flask and cooled to 0° (salt–ice bath). Then, with efficient mechanical stirring, the ethereal solution of γ-chloroacetoacetyl chloride (see above) was added dropwise while the temperature was maintained below 5°. After complete addition of the acid chloride, the two-phase mixture was stirred an additional 15 min at room temperature. The layers were separated, and the aqueous layer was extracted with three 50-ml portions of ether. The combined ether layers were dried over Na_2SO_4 and concentrated on a rotary evaporator (less then 25°). The resulting cream-colored waxy solid was recrystallized from carbon tetrachloride and dried *in vacuo* to yield 29.1 g (60%) of white plates, mp 98–100° (lit.[3] mp 98–102°). This material was identical in every way with an authentic sample of **2** prepared by chlorination of pyruvaldoxime,[3] and could be used without further purification for the preparation of **1**: nmr (DMSO-d_6) δ 4.78 (2, s, $-CH_2Cl$), 7.65 (1, s, CH=NOH), 12.75 (1, s, =NOH).

β-Bromopyruvaldoxime (**5**).—In a 100-ml, three-neck flask equipped with dropping funnel, thermometer, and magnetic stirring bar was placed a solution of 4.2 g of freshly distilled diketene in 50 ml of CCl_4. The solution was cooled to −2° (Dry Ice–acetone) and a solution of 8.0 g of bromine in 20 ml of CCl_4 was added slowly with stirring while maintaining the temperature at −2 to +2°. The bromine was added especially slowly near the equivalence point, where bromine decolorization was very slow. After complete addition of the bromine, the solvent was removed on a rotary evaporator, and the residue was dissolved in 50 ml of absolute ether.

β-Bromopyruvaldoxime was prepared from the ethereal solution of the acid bromide by the procedure described above for β-chloropyruvaldoxime. The resulting waxy tan solid was recrystallized from carbon tetrachloride and dried *in vacuo* to yield 5.5 g of white plates (66%): mp 78–79° (lit.[7] mp 89–90°);[9] nmr (DMSO-d_6) δ 4.50 (2, s, $-CH_2Br$), 7.63 (1, s, CH=NOH), 12.75 (1 s, =NOH).

Anal. Calcd for $C_3H_4NO_2Br$: C, 21.71; H, 2.43; N, 8.44. Found: C, 21.68; H, 2.28; N, 8.31.

This compound was identified by conversion into **2-amino-5-isonitrosomethylthiazole** (**6**) as follows: A solution of 0.5 g of β-bromopyruvaldoxime and 0.25 g of thiourea in 10 ml of methanol was allowed to stand overnight at room temperature. The methanol was removed on a rotary evaporator, and the residue was dissolved in 10 ml of water. The solution was made basic with Na_2CO_3, and the resulting light yellow crystals were collected by filtration and recrystallized from ethanol (charcoal). The yield of colorless needles, mp 178–179°, was 0.11 g (39%). The analytical sample was prepared by two further recrystallizations from ethanol without change in the melting point: nmr (DMSO-d_6) δ 6.85 (1, s, C_5–H), 7.10 (2, s, $-NH_2$), 7.91 (1, s, CH=NOH), 11.05 (1, s, =NOH).

(4) C. D. Hurd and J. L. Abernethy, *J. Amer. Chem. Soc.*, **62**, 1147 (1940).

(5) E. C. Taylor and T. Kobayashi, manscript in preparation.

(6) G. C. Singhal and M. M. Bokadin, *J. Indian Chem. Soc.*, **35**, 898 (1958).

(7) N. T. M. Wilsmore and F. Chick, *J. Chem. Soc.*, 1978 (1910).

(8) B. G. Chatterjee and R. F. Abdulla, *Z. Naturforsch. B*, **24**, 1120 (1969).

(9) The melting point of this compound could not be raised above 78–79° even by repeated recrystallizations.

Anal. Calcd for $C_4H_5N_3OS$: C, 33.56; H, 3.52; N, 29.35. Found: C, 33.30; H, 3.55; N, 29.55.

Registry No.—**2**, 14337-41-8; **5**, 37150-52-0; **6**, 37150-53-1.

Acknowledgment.—We are gratful to the FMC Corporation, Princeton, N. J., for a generous gift of diketene.

A Simple Synthesis of the Cis,cis and Trans,trans Isomers of Tetrabenzo[*a*,*c*,*g*,*i*]cyclododecene (*sym*-Tetrabenz[12]annulene)[1]

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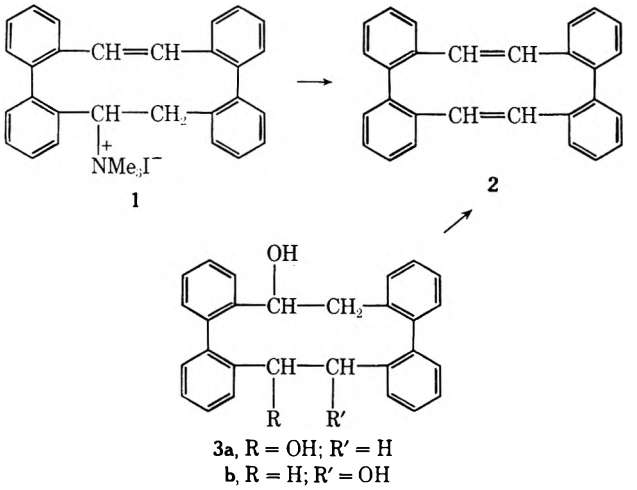
Received August 28, 1972

The stereoisomeric tetrabenzo[*a*,*c*,*g*,*i*]cyclododecenes (*sym*-tetrabenz[12]annulenes) (**2**) are interesting compounds, about which there has been some confusion in the literature. In 1955, Wittig, *et al.*,[3] reported that Hofmann degradation of *cis*-**1** leads to two isomers of **2**, mp 297.5–298 and 163–164°, to which they ascribed the cis,cis and trans,trans stereochemistry, respectively. Very recently, it has been shown by Irngartinger[4] and by Wittig and Skipka[5] that the lower melting isomer in fact has the cis,trans configuration, and we independently came to the same conclusion by repetition of Wittig's synthesis.[3] Moreover, Wittig and Skipka[5] have shown that dehydration of **3a** and **3b** gives rise to



3a, R = OH; R′ = H
b, R = H; R′ = OH

three stereoisomers of **2**, mp (corrected) 306–306.5, 253.5, and 301–301.5°; the first of these proved to be the cis,cis compound obtained previously, the second appears to be another cis,cis isomer, while the third is the trans,trans isomer.

(1) Unsaturated Macrocyclic Compounds. XCVIII. Part XCVII: P. D. Howes and F. Sondheimer, *J. Amer. Chem. Soc.*, **94**, 8261 (1972).

(2) On leave from the University of Connecticut, Storrs, Conn.

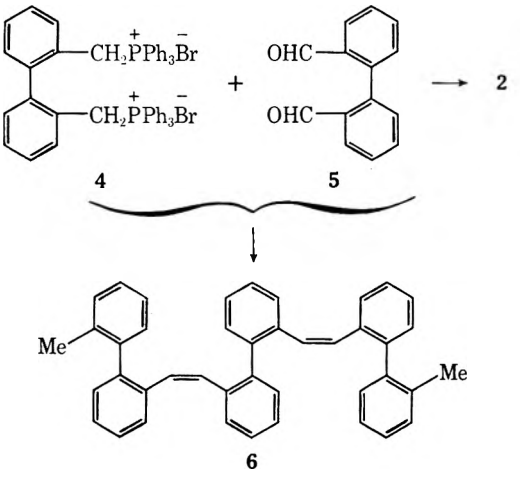
(3) G. Wittig, G. Koenig, and R. Clauss, *Justus Liebigs Ann. Chem.*, **593**, 127 (1955).

(4) H. Irngartinger, *Chem. Ber.* **105**, 2068 (1972).

(5) G. Wittig and G. Skipka, *Justus Liebigs Ann. Chem.*, in press.

Several years ago we required the tetrabenz[12]annulene **2** as a synthetic intermediate, and we devised a simple synthesis through the Wittig reaction between 2,2′-bis(triphenylphosphoniomethyl)biphenyl dibromide (**4**)[6] and 2,2′-biphenyldicarboxaldehyde (**5**).[7] This led in low yield to an isomer of **2**, mp 296–297°, which we considered[8] to be Wittig's cis,cis compound[3] in view of the correspondence of the melting points, ir spectra, and uv spectra.[9] The reaction between **4** and **5** has also been investigated by Bergmann, *et al.*,[5,10] who apparently obtained Wittig's cis,trans and trans,trans isomers of **2**. No details of the reaction between **4** and **5** have been published previously, and Staab, *et al.*,[11] thereby could obtain only traces of **2**.

We now report the details of a reinvestigation of the Wittig reaction between **4** and **5**. When the reaction was carried out with lithium methoxide in methanol under relatively high dilution conditions, both *cis,cis*-**2**, mp 296–297° (1.1%), and *trans,trans*-**2**, mp 302–303° (4.2%), could be isolated by chromatography and fractional crystallization. The structures and stereochemistry of these products are based on their spectral



properties, and are confirmed by the correspondence of the spectra and melting points with those reported by Wittig, *et al.*[3,5] In the case of *cis,cis*-**2**, direct comparison with a sample obtained from *cis*-**1** confirmed their identity.

The reaction between **4** and **5** also gave rise to the all-cis tri(biphenyl) derivative **6**, mp 181–182° (1.5%), the structure of which is based on the spectral data. The all-cis stereochemistry follows from the absence of a strong trans ethylene band at ~960 cm^{-1} in the ir spectrum; it is confirmed by the fact that the olefinic protons resonate as a singlet at τ 3.88 in the nmr spectrum, showing both double bonds to have the same

(6) D. M. Hall and B. Prakobsantisukh, *J. Chem. Soc.*, 6311 (1965); H. J. Bestmann, H. Häberlein, H. Wagner, and O. Kratzer, *Chem. Ber.*, **99**, 2848 (1966); E. D. Bergmann, P. Bracha, I. Agranat, and M. A. Kraus, *J. Chem. Soc. C*, 328 (1967).

(7) P. S. Bailey and R. E. Erickson, *Org. Syn.*, **41**, 41 (1961).

(8) See R. H. Mitchell and F. Sondheimer, *Tetrahedron Lett.*, 2873 (1968), footnote 6.

(9) Wittig and Skipka (ref 5, footnote 15) state that the uv spectrum of this substance, according to a personal communication from Dr. Grohmann, corresponds to the trans,trans isomer. This is a misunderstanding, since the uv spectral data given by Dr. Grohmann to Professor Wittig were not those of the substance considered by us to be *cis,cis*-**2**, but of another product (now known to be *trans,trans*-**2**).

(10) See E. D. Bergmann, *Bull. Soc. Chim. Fr.*, 2681 (1965); E. D. Bergmann, I. Agranat, and M. Kraus, *Israel J. Chem.*, **3**, 48p (1965).

(11) H. A. Staab, E. Wehringer, and W. Thorwart, *Chem. Ber.*, **105**, 2290 (1972).

stereochemistry and indicating the cis configuration (*cis*-stilbene, τ 3.45; *trans*-stilbene, τ 2.90).[12]

The reaction between **4** and **5** was also carried out with lithium ethoxide in dimethylformamide and ethanol (8:1) under more concentrated conditions than used before. This experiment led to *trans,trans*-**2** in 5.5% yield, although other products were not investigated in this case.

The finding that the reaction between **4** and **5** leads to both *cis,cis*-**2** and *trans,trans*-**2** partly explains the different results reported by Bergmann, *et al.*,[5,10] and by us.[8] However, we have not been able to confirm Bergmann's isolation of *cis,trans*-**2** from this reaction, despite the fact that quite small quantities would have been detected by the typical nmr spectrum.

Experimental Section

Melting points were determined on a Kofler micro hot stage apparatus and are uncorrected. Uv spectra were measured on a Unicam SP 800 and ir spectra on a Unicam SP 200 spectrophotometer. Nmr spectra were determined on a Varian T-60 spectrometer, tetramethylsilane being used as an internal standard. Mass spectra were obtained on an AEI MS-9 spectrometer operating at 70 eV.

Reaction between 2,2′-Bis(triphenylphosphoniomethyl)biphenyl Dibromide (4) and 2,2′-Biphenyldicarboxaldehyde (5). A. With Lithium Methoxide in Methanol.—A solution of **4**[6] (21.0 g, 24.3 mmol) and **5**[7] (5.1 g, 24.3 mmol) in dry methanol (500 ml) was added through one dropping funnel at the same rate as a solution of lithium (700 mg, 100 mmol) in dry methanol (500 ml) was added through a second funnel to dry methanol (4 l.) stirred under nitrogen in a 10-l. three-neck flask, over the course of 12.5 hr. The resulting pale yellow solution was stirred at room temperature under nitrogen for a further 12 hr, and the solvent was then removed under reduced pressure (<30°). Ether (1.5 l.) was added, and the mixture was washed well with dilute hydrochloric acid and then with water. The dried solution was evaporated, and the residue was chromatographed on silica gel (500 g).

Pentane eluted 2,2′-dimethylbiphenyl (650 mg, 15%), the ir spectrum of which was identical with the published one.[13] Pentane–benzene (95:5) then eluted **2** (~500 mg), the nmr spectrum of which showed that it consisted of the cis,cis and trans,trans isomers in a ratio of ~1:4. Further elution with pentane–benzene (95:5 to 90:10) led to **6** (99 mg, 1.5% based on **4**), as colorless crystals from petroleum ether (bp 40–60°): mp 181–182°; λ_{max} (cyclohexane) 290 nm (ϵ 22,900); ir (KBr), only weak band (at 955 cm^{-1}) in 950–1000-cm^{-1} region; nmr (CCl_4) τ 2.4–3.2 (m, 24 H, benzenoid), 3.88 (s, 4 H, olefinic), 7.88 (s, 6 H, methyl); mass spectrum *m/e* 538.267 (calcd 538.266).

Anal. Calcd for $C_{42}H_{34}$: C, 93.63; H, 6.37. Found: C, 93.59; H, 6.45.

Later fractions contained a mixture of stereoisomers of **6** (as determined by the nmr, ir, and mass spectra), but these were not investigated further.

Fractional crystallization of the isomers of **2** from ethyl acetate led to the pure cis,cis isomer (95 mg, 1.1%) and trans,trans isomer (365 mg, 4.2%). *cis,cis*-**2** formed colorless crystals: mp 296–297°; λ_{max} (cyclohexane) 240 nm (ϵ 31,900); ir (KBr) only weak bands (960, 980 cm^{-1}) in 950–1000-cm^{-1} region; nmr (CCl_4) τ 2.35–3.15 (m, 16 H, benzenoid), 4.18 (s, 4 H, olefinic); mass spectrum *m/e* 356.155 (calcd 356.156). The melting point was undepressed on admixture with a sample (mp 295–296°) obtained from *cis*-**1**, and the uv, ir, and nmr spectra were essentially identical. *trans,trans*-**2** formed colorless crystals: mp 302–303° (depressed on admixture with *cis,cis*-**2**); λ_{max} (cyclohexane) 226 nm (ϵ 32,200), 248 sh (24,100), 266 (34,100); ir (KBr) 955 cm^{-1} (s); nmr (CCl_4) τ 2.6–3.0 (m, 16 H, benzenoid), 3.82 (s, 4 H, olefinic); mass spectrum *m/e* 356.155 (calcd 356.156).

Anal. Calcd for $C_{28}H_{20}$: C, 94.34; H, 5.65. Found: C, 94.14; H, 5.55.

(12) "High Resolution NMR Spectra Catalog," Varian Associates, Vol. 1, 1962, Spectra 305, 306.

(13) G. Kortüm and H. Maier, *Z. Phys. Chem.*, **7**, 207 (1956).

B. With Lithium Ethoxide in Dimethylformamide and Ethanol.—A solution of lithium (500 mg, 72 mmol) in dry ethanol (50 ml) was added during 4.5 hr to a stirred solution of **4** (8.65 g, 10 mmol) and **5** (2.1 g, 10 mmol) in dry dimethylformamide (400 ml), at room temperature under nitrogen. The dark brown solution was stirred for 16 hr, and was then poured into ice containing concentrated hydrochloric acid. The organic material was extracted with ether, and the ether extract was washed with water, dried, and evaporated. The residue was chromatographed on a column of silica gel (75 × 3.5 cm). Elution with petroleum ether–benzene (80:20) and crystallization from ethyl acetate gave *trans,trans*-**2** (197 mg, 5.5%), mp 303–304°. The melting point was undepressed on admixture with the previously obtained sample, and the uv, ir, and nmr spectra were identical.

Registry No.—*cis,cis*-**2**, 37445-16-2; *trans,trans*-**2**, 37445-17-3; **4**, 37439-54-6; **5**, 1210-05-5; **6**, 37445-18-4.

Acknowledgment.—We are grateful to Professor G. Wittig for sending us a manuscript of the paper by Wittig and Skipka (ref 5).

Preparation of 11-Substituted 5,6-Dihydro-11*H*-6-oxodibenzo[*b*,*e*]azepines (Morphanthridines) and Their *N*-Dimethylaminoethyl Derivatives[1]

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Enhanced stability of extensively delocalized carbanions, arising from the dispersion interaction[3] with dipolar aprotic solvents, favors the formation of Jackson–Meisenheimer complexes[4] (**1**) by the conjugate addition to 9-nitroanthracene of various nucleophiles.[5] Quenching and acidification of the reaction mixtures permit isolation of the adducts (**2**); the stereochemistry, spectral characteristics, properties, and some chemical transformations of these adducts have been reported.[5] Addition of benzyl halide to solutions of the Jackson–Meisenheimer complexes prior to work-up results in the formation of oximes (**3**)[5] and benzaldehyde, the products of the Hass–Bender reaction.[6]

Beckmann rearrangement of these oximes provides 11-substituted 5,6-dihydro-11*H*-6-oxodibenzo[*b*,*e*]azepines (**5**). Many tricyclic compounds of structures similar to **5** with a dialkylaminoalkyl moiety bonded to an atom of the central ring have pharmacological, and in particular, pyschotropic activity.[7] Most notable among these are the tricyclic antidepressants imipramine and amitriptylene; the structure of dibenzepin.[8]

(1) Grateful acknowledgment is made to the U. S. Army Research Office for partial support of this work (Grants DA-ARO(D)-G679 and G857).

(2) NSF Predoctoral Fellow, 1967–1971.

(3) E. Grunwald and E. Price, *J. Amer. Chem. Soc.*, **86**, 4517 (1964).

(4) M. J. Strauss, *Chem. Rev.*, **70**, 677 (1970); J. A. Orvik and J. F. Bunnett, *J. Amer. Chem. Soc.*, **92**, 2417 (1970).

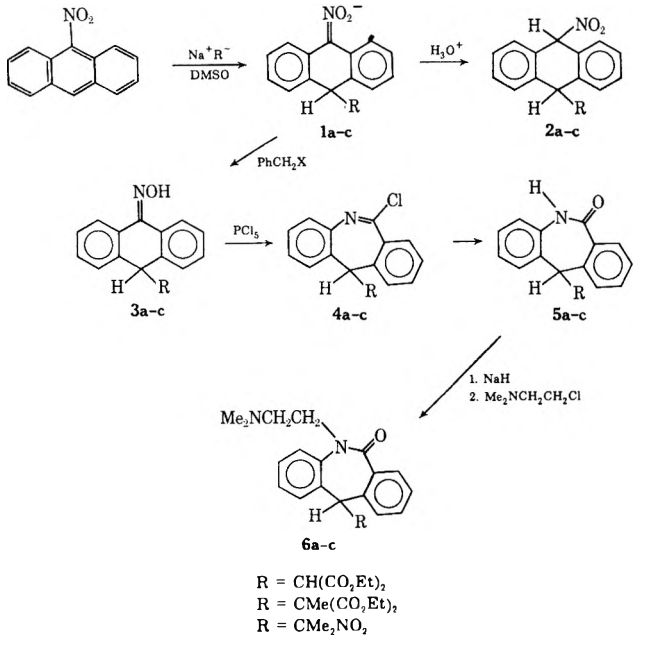
(5) R. H. Williams and H. R. Snyder, *J. Org. Chem.*, **36**, 2327 (1971); R. H. Williams, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1971.

(6) H. B. Hass and M. L. Bender, *J. Amer. Chem. Soc.*, **71**, 1767, 3482 (1949); N. Kornblum and R. A. Brown, *ibid.*, **86**, 2681 (1964).

(7) G. N. Walker, D. Alkalay, A. R. Engle, and R. J. Kempton, *J. Org. Chem.*, **36**, 466 (1971), and references cited therein.

(8) F. Hunziker, H. Lauener, and J. Schmutz, *Arzneim. Forsch.*, **13**, 324 (1963); F. Hunziker, F. Kunzle, and J. Schmutz, *Helv. Chim. Acta*, **49**, 1433 (1966).

another antidepressant, may be obtained by replacing the CHR bridge of **6** with NMe. For this reason, the *N*-(2-dimethylaminoethyl) lactams (**6**) are of interest for pharmacological evaluation.



Beckmann rearrangement of oxime tosylates frequently occurs under very mildly acidic conditions, if not spontaneously;[9] the tosylate of **3c** was recovered unchanged after exposure for 12 hr to boiling glacial acetic acid. In many instances polyphosphoric acid (PPA) has been the reagent of choice for effecting the Beckmann rearrangement;[9] attempts to induce rearrangement of oximes **3a** and **3c** by brief heating with PPA resulted in the formation of complex mixtures of products.[10] Treatment of each of the oximes with a twofold excess of PCl_5 in refluxing CCl_4 and subsequent work-up afforded the corresponding lactam **5**. A sample of the intermediate imino chloride **4c** was isolated and purified for evaluation as a potential precursor of **6c**.

Attempted preparation of **6c** by treatment of **4c** with sodium 2-dimethylaminoethoxide produced a complex mixture of products.[12] A more facile synthesis of **6c** (and of **6a**) entails alkylation of the anion of **5**[13] with 2-dimethylaminoethyl chloride (which, conveniently, may be liberated from the commercially available hydrochloride salt *in situ*).

Difficulties were encountered in the purification of **6a**, as the free base or as the hydrobromide, and of the base **6c**. Walker and Alkalay[14] evidently encountered similar difficulties with an analogous *N*-dimethylaminoethyl compound as the free base, the picrate, or the methiodide. The assignments of structures **6a** and **6c** to the products of alkylation of the anions of **5a** and **5c** are fully supported by the nmr, ir,[15] and mass spectra.

(9) L. G. Donaruma and W. Z. Heldt, *Org. React.*, **11**, 1 (1960).

(10) In the case of PPA treatment of **3a**, products other than **5a** may have arisen *via* ester–amide interchange;[11] the number of products formed by similar treatment of **3c** cannot be explained in this manner.

(11) H. A. Lloyd and E. C. Horning, *J. Amer. Chem. Soc.*, **76**, 3654 (1954).

(12) Treatment of the imino chloride with alkoxide would initially produce a lactim. Lactim–lactam interconversion favors the lactam, and should proceed with facility, particularly in this case, in view of the stability of the 2-dimethylaminoethyl cation, a species which is invoked in a plausible mechanism for the migration.

(13) The anion is ambident; alkylation may occur at either heteroatom.[12]

(14) G. N. Walker and D. Alkalay, *J. Org. Chem.*, **36**, 461 (1971).

Experimental Section[16]

11-Dicarbethoxymethyl-5,6-dihydro-11*H*-6-oxodibenzo[*b*,*e*]azepine (5a).—A 2-mmol (734 mg) sample of **3a**[5] was added to a suspension of PCl_5 (4 mmol, 830 mg) in 25 ml of CCl_4, and the mixture was heated to the boiling point and maintained under reflux for 2 hr. Volatile materials were removed *in vacuo*, the resulting oil was dissolved in 50 ml of 50:50 CH_2Cl_2–CCl_4, and the solution was washed with water, dried, and concentrated. The oil was dissolved in a small volume of CH_2Cl_2 and the solution was heated to the boiling point. EtOH was added as the CH_2Cl_2 was boiled off; crystallization occurred upon standing for several hours at −15°, yield 625 mg (85%), mp 196–201°. The analytical sample was obtained by recrystallization from benzene: mp 197–201°; ir (KBr) 1650, 1750, 1380, 1250, 1145, and 1730 cm^{-1}; nmr (DMSO-d_6–CCl_4) δ 1.0 (6 H, t, J = 7 Hz, CH_2CH_3), 3.9 (4 H, q, J = 7 Hz, CH_2CH_3), 4.4 [2 H, AB, J = 11.5 Hz, $\Delta\delta$ 0.46 ppm, $CHCH(CO_2Et)_2$], 7–8 (8 H, m, aromatic), and 10.2 ppm (1 H, s, NH).

Anal. Calcd for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.84; H, 5.83; N, 3.92.

11-(1,1-Dicarbethoxyethyl)-5,6-dihydro-11*H*-6-oxodibenzo[*b*,*e*]azepine (5b).—The reaction of **3b**[5] with PCl_5 was conducted as described above; after hydrolysis, the product was crystallized from EtOH, yield 49%, mp 151.5–153°. The analytical sample was obtained by recrystallization from EtOH: mp 153–154.5°; ir (KBr) 1650, 1720, 1250, 1385, 1590, and 1450 cm^{-1}; nmr (acetone-d_6) δ 1.05 and 1.10 (6 H, two triplets, J = 7 Hz, CH_2CH_3),[17] 1.35 [3 H, s, $C(CH_3)(CO_2Et)_2$], 4.0 (4 H, q, J = 7 Hz, CH_2CH_3),[17] 5.2 [1 H, s, $CHCMe(CO_2Et)_2$], 7–8.2 (8 H, m, aromatic), and 10.2 ppm (1 H, s, NH).

Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.27; H, 6.08; N, 3.67. Found: C, 69.08; H, 6.08; N, 3.71.

11-(2-Nitro-2-propyl)-5,6-dihydro-11*H*-6-oxodibenzo[*b*,*e*]azepine (5c).—The reaction of **3c**[5] with PCl_5, hydrolysis, and work-up were conducted as described for **5a**. The product of crystallization from EtOH melted indistinctly and volatilized at temperatures above 200°; two recrystallizations from THF–CCl_4 afforded a material of mp 225–226° (sublimes), yield 62.5%. The analytical sample was obtained by recrystallization from CH_2Cl_2–EtOH: mp 225–226°; ir (KBr) 1655, 1540, 1375, 1395, 1595, 1575, and 1450 cm^{-1}; nmr (acetone-d_6) δ 1.5 (6 H, s, CH_3), 4.7 (1 H, s, $CHCMe_2NO_2$), 7.1–8.1 (8 H, m, aromatic), and 10.0 ppm (1 H, s, NH).

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 69.08; H, 5.50; N, 9.52.

(15) The ir band corresponding to lactam C=O stretch is, perhaps, the most indicative probe of structure. It is this band which has the greatest intensity in the ir spectrum of each lactam (**5**) and each substituted lactam (**6a** and **6c**). The ir spectrum of imino chloride **4c** does contain a band at 1645 cm^{-1}; however, the intensity of the absorption is considerably weaker than the 1540-cm^{-1} NO_2 band, in direct contrast to the relative intensities of these bands in spectra of both **5c** and **6c**. Although the intensity of their absorption arising from the C=N stretch is variable, it is weaker than that arising from C=O stretch.

(16) Commercially available reagents were used as supplied. Sodium hydride was obtained by washing the oil-dispersed material with several portions of hexane prior to use. Melting points were determined with a Kofler micro stage apparatus and are uncorrected. The ir spectra were obtained by the use of a Perkin-Elmer 521 spectrophotometer. The peaks listed are the most intense peaks in the spectrum of the particular compound, with the exception of the tosylate of **3c**; for this compound the peaks which have been listed are those which indicate that the rearrangement (with migration of the $ArSO_2$ moiety from O to N) has not occurred.[4] Microanalyses were performed by Mr. J. Nemeth and associates. Routine nmr spectra were recorded on a Varian A-56/60 or A-60A spectrometer.

(17) The two carbethoxy groups are diastereotopic; hence potential magnetic nonequivalence is inherent. The complexity of the signal arising from resonance of the methyl protons is in sharp contradistinction with the simplicity of that arising from resonance of the methylene protons. Examination of the 100- or 220-MHz spectrum confirms the assigned multiplicities.[5] The 100- and 220-MHz spectra were recorded by Mr. Robert L. Thrift and associates on Varian HA-100 and HR-220 spectrometers, respectively. We gratefully acknowledge a grant to the School of Chemical Sciences of the University of Illinois at Urbana—Champaign from the National Science Foundation, which helped make purchase of the HR-220 possible.

11-(2-Nitro-2-propyl)-6-chloro-11*H*-dibenzo[*b*,*e*]azepine (4c).—A 10.0-mmol (2.94 g) sample of **3c**[5] was added to a suspension of 20 mmol (4.16 g) of PCl_5 in CCl_4 (50 ml); the mixture was heated to the boiling point and maintained under reflux for 2 hr. Solvent was removed *in vacuo*, and the residual oil was heated at 65° for 2 hr at 0.5 mm to remove other volatile materials. The oil was dissolved in CH_2Cl_2 (10 ml), the solution was filtered, and the filtrate was diluted with 20 ml of CCl_4, heated to the boiling point, and concentrated to a volume of 20 ml. A 10-ml portion of CCl_4 was added and the solution was reconcentrated to 20 ml; this procedure was repeated one additional time. Crystallization was initiated only with considerable difficulty; after 12 hr at room temperature, 2.1 g of crystals had been deposited. A second crystallization afforded 1.29 g (41%) of analytically pure product: mp 124–129°; ir (KBr) 1540, 760, 1645, 940, 1350, 1375, and 1400 cm^{-1}; nmr (CCl_4) δ 1.45 (6 H, s, CH_3), 4.7 (1 H, s, $CHCMe_2NO_2$), and 7–8 ppm (8 H, m, aromatic).

Anal. Calcd for $C_{17}H_{15}N_2O_2Cl$: C, 64.85; H, 4.81; N, 8.90; Cl, 11.27. Found: C, 64.69; H, 4.78; N, 9.01; Cl, 11.37.

Tosylate of 3c.—A 3.0-mmol (889 mg) sample of **3c**[5] was added to a suspension of 3.34 mmol of oil-free NaH in THF (50 ml), and the mixture was warmed briefly at the boiling point prior to the addition of a solution of 3.0 mmol of *p*-toluenesulfonyl chloride in a small volume of THF. The reaction mixture was maintained at the boiling point for 12 hr prior to solvent removal (*in vacuo*). The residue was dissolved in benzene (50 ml) and the solution was washed with two 100-ml portions of water, dried (Na_2SO_4), and concentrated to a residue. The residue was crystallized from CH_2Cl_2–EtOH: yield 870 mg (64%); mp 184–187° dec; ir (KBr) 1375, 1195, and 1180 ($ArSO_3$–) and 1595 cm^{-1} ($Ar_2C{=}N$–); nmr (acetone-d_6) δ 1.2 [6 H, s, $C(CH_3)_2NO_2$], 2.4 (3 H, s, $ArCH_3$), 4.8 (1 H, s, $CHCMe_2NO_2$), and *ca.* 8.5 ppm (12 H, m, aromatic).

Anal. Calcd for $C_{24}H_{22}N_2O_5S$: C, 63.98; H, 4.92; N, 6.22; S, 7.12. Found: C, 63.78; H, 4.91; N, 6.32; S, 7.03.

5-(2-Dimethylaminoethyl)-11-dicarbethoxymethyl-5,6-dihydro-11*H*-6-oxodibenzo[*b*,*e*]azepine (6a).—A 25.0-mmol (9.19 g) sample of **5a** was added to a suspension of 62.5 mmol of oil-free NaH in 125 ml of DMSO, and the mixture was stirred at room temperature for 1 hr prior to the addition of a suspension of 37.5 mmol (3.6 g) of 2-dimethylaminoethyl chloride hydrochloride in 50 ml of DMSO. The reaction mixture was stirred for 3 hr and poured into 600 ml of water. An orange semisolid separated; the supernatant was rendered strongly alkaline by the addition of 10 ml of 10 *N* NaOH, and was extracted with five 70-ml portions of CCl_4. The semisolid was dissolved in the combined extract and the solution was washed, dried (Na_2SO_4), and concentrated *in vacuo;* the resulting oil was purified by chromatography on silica gel. Elution with 10% EtOH–CH_2Cl_2 afforded (after solvent removal) 1.17 g (12.7%) of recovered **5a**. Elution with 25% EtOH–CH_2Cl_2 provided (after solvent removal *in vacuo*) an oil which could be induced to crystallize from toluene with considerable difficulty, yield 2.94 g, mp 134–154°. Two recrystallizations from PhMe afforded 2.06 g (21.5% conversion) of product: mp 142–146°; ir (KBr) 1640, 1730, 1750, 1370, 1290–1330, 1250, and 1445 cm^{-1}; nmr (acetone-d_6) δ 0.98 and 1.03 (6 H, two triplets, J = 7 Hz, CH_2CH_3),[17] 3.0 [6 H, s, $N(CH_3)_2$], 3.6–5.0 [10 H, m, CH_2CH_3, $CHCH(CO_2Et)_2$, and $CH_2CH_2NMe_2$], and 7.0–8.0 ppm (8 H, m, aromatic).

A 4.7-mmol (2.05 g) sample of **6a** was dissolved in EtOH (15 ml), and hydrobromic acid (4.7 mmol, 0.53 ml) was added. Dilution with an equal volume of Et_2O and cooling at −15° for 12 hr caused the crystallization of the HBr salt: yield 1.90 g (78%); mp 162.5–165°; mass spectrum[18] *m/e* 438.2143 (calcd for $C_{25}H_{31}N_2O_5Br$ − HBr: 438.2154).

Anal. Calcd for $C_{25}H_{31}N_2O_5Br$: C, 57.81; H, 6.02; N, 5.39; Br, 15.38. Found: C, 58.36; H, 6.25; N, 5.43; Br, 15.14.

5-(2-Dimethylaminoethyl)-11-(2-nitro-2-propyl)-5,6-dihydro-11*H*-6-oxodibenzo[*b*,*e*]azepine (6c).—A solution of **5c** (6.0 mmol, 1.78 g) in DMSO (15 ml) was added to a suspension of 6.4 mmol of oil-free NaH in 10 ml of DMSO. After 1.5 hr a suspension of 9.9 mmol of oil-free NaH in a solution of 2-dimethylaminoethyl chloride hydrochloride (9.0 mmol, 1.30 g) in 10 ml of DMSO was added, and stirring was continued for an additional 2.5 hr. The mixture was poured into 250 ml of water and the suspension was extracted into CH_2Cl_2 (five 30-ml portions). The extract was washed with a 200-ml portion of water, and basic substances were extracted into 0.15 *N* HCl (three 40-ml portions). The aqueous solution was made strongly alkaline by the addition of concentrated NaOH and the free amine was extracted into CCl_4 (five 30-ml portions). Upon concentration of the CCl_4 extract to a small volume and cooling for several hours at −15°, 1.066 g of product crystallized. Recrystallization from CH_2Cl_2–EtOH afforded 977 mg (44%) of **6c**, mp 157–162°. The analytical sample was obtained by repeated recrystallizations from CH_2Cl_2–EtOH, and melted at 160–162°: ir (KBr) 1630, 1530, 1380, 1455, 1323, and 1400 cm^{-1}; nmr ($CDCl_3$) δ 1.6 [6 H, s, $C(CH_3)_2NO_2$], 2.4 [6 H, s, $N(CH_3)_2$], 2.7–4.4 (4 H, m, $CH_2CH_2NMe_2$), 4.4 (1 H, s, $CHCMe_2NO_2$), and 7.0–8.0 ppm (8 H, m, aromatic); mass spectrum[18] *m/e* 367.1901 (calcd for $C_{21}H_{25}N_3O_3$: 367.1896).

Anal. Calcd for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.14; H, 6.77; N, 11.43.

Registry No.—**3a**, 29925-32-4; **3b**, 29925-33-5; **3c**, 29925-34-6; **3c** tosylate, 37387-62-5; **4c**, 37387-63-6; **5a**, 37387-64-7; **5b**, 37387-65-8; **5c**, 37387-66-9; **6a**, 37387-67-0; **6a**, 37387-67-0; **6a** HBr, 37387-68-1; **6c**, 37387-69-2.

(18) Exact mass measurements were obtained by the peak-matching technique by Mr. J. Carter Cook using a MAT 731 high-resolution mass spectrometer and data-processing equipment provided by NIH grants CA 11388 and GM 16864, from the National Cancer Institute and the National Institute of General Medical Studies, respectively.

4,5,6,7-Tetrafluoroindole

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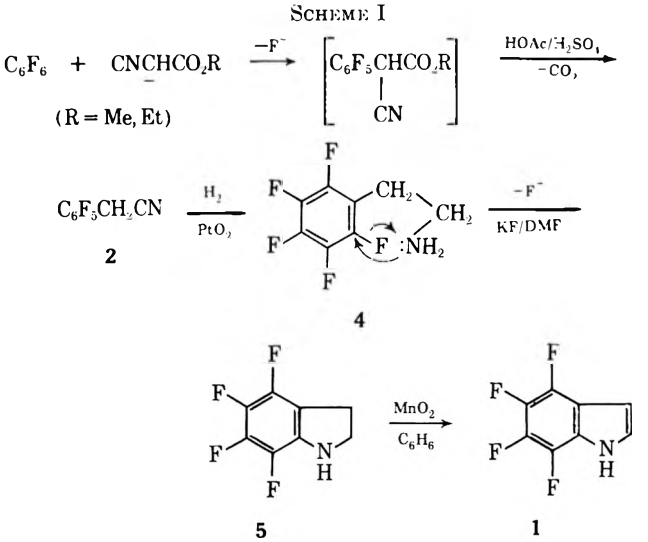
We wish to report a convenient synthesis of 4,5,6,7-tetrafluoroindole (**1**) by a vastly improved five-step sequence starting with hexafluorobenzene (Scheme I).

SCHEME I



Previous routes to **1** have suffered from serious drawbacks, *e.g.*, tedious multistep procedures[3] from readily

(1) Abstracted, in part, from the Ph.D. Thesis of S. M. W., May 1972.
(2) NSF Undergraduate Research Participant, summer 1971.
(3) V. P. Petrov, V. A. Barkhash, G. S. Schegoleva, T. D. Petrova, T. I. Savchenko, and G. G. Yakobson, *Dokl. Akad. Nauk, SSSR*, **178**, 864 (1968).

available starting materials, low and nonreproducible yields of pentafluorophenylacetonitrile (2), and difficulties encountered in the final aromatization step.

The key intermediate in our sequence is the nitrile 2, which is readily prepared in one extended step by nucleophilic reaction of hexafluorobenzene with the anion of methyl (or ethyl) cyanoacetate.[4] While the resulting cyano ester is isolable (80% yield), the crude product may be selectively hydrolyzed *in situ* to the nitrile by heating under reflux with 50% acetic acid containing a small amount of concentrated sulfuric acid.[5] The yield of 2 from hexafluorobenzene is 60–70%.

The previously described[6] route to 2 involves the prior preparation of $C_6F_5CH_2X$ (X = Cl, Br), followed by Sn2 displacement of X^- by cyanide ion. Earlier reports have apparently failed to note that this reaction is *always* accompanied by an undesirable side reaction to yield 15–20% of 2,3-bis(pentafluorophenyl)propionitrile, $C_6F_5CH_2C(CN)HC_6F_5$ (3). Details of the latter reaction will be reported separately.

Compound 2 was catalytically reduced (PtO_2) to 2-pentafluorophenylethylamine (4), which was isolated (81%) as its hydrochloride to obviate the facile intermolecular nucleophilic reaction of the free amine with the pentafluorophenyl ring.[7] Cyclization of the amine 4, which was generated from its hydrochloride as needed, was accomplished by heating with potassium fluoride in dimethylformamide to give a 70% yield of the indoline 5.[3] The indoline was then smoothly aromatized to the indole 1, mp 91–92°, in 82% yield, on treatment with activated manganese dioxide in cold benzene.[8] A host of other reagents, including palladium on charcoal,[3] were found to be much less effective.

The accessibility of 4,5,6,7-tetrafluoroindole has permitted the exploration of the chemical reactivity of this interesting heterocycle. These results will be reported in due course.

Experimental Section

Ethyl α-Cyanopentafluorophenylacetate.—An adaptation of a method employed by Kalir and Pelah[5] was used. A mixture of 650 ml of reagent grade dimethylformamide and 140 g (1.0 mol) of anhydrous potassium carbonate was heated in a 2-l., four-neck flask equipped with a mechanical stirrer, addition funnel, thermometer, and condenser. Water was allowed to flow through the condenser after the temperature of the mixture reached 152–154°, and 113 g (1.0 mol) of ethyl cyanoacetate was added dropwise rapidly without further heating. The temperature of the bright orange mixture was allowed to drop to 110–120° and was maintained within this range while 186 g (1.0 mol) of hexafluorobenzene was added dropwise. The deep brown mixture was stirred for 3 hr after addition was complete, then poured into 3 l. of ice-cold water and acidified with 20% sulfuric acid until all of the potassium carbonate dissolved. A dark brown organic layer settled to the bottom of the beaker. After cooling for 2 hr, the top layer was decanted and discarded. The organic layer was dissolved in ether, washed with water and then with sodium bicarbonate, and dried over anhydrous $MgSO_4$. After removal of the ether on a rotary evaporator, the residue weighed 223 g (80% crude yield). An analytical sample was prepared by dissolving about 2 g of this crude substance in a minimum amount of hot 95% ethanol. Hexane was added until the mixture became turbid. Crystallization occurred when the mixture was cooled in Dry Ice. The solid was filtered on a Büchner funnel and transferred quickly to a sublimator. Triple sublimation at 30° (1.0–0.7 Torr) produced white needles: mp 32° (uncorrected); ir 2920 and 2985 (s, CH_3), 2260 (s, C≡N), 1760 (s, C=O), 1650, 1620, 1570 cm^{-1} (s, aromatic); pmr (CCl_4) δ 5.03 (s, 1, CH) 4.33 (q, 2, CH_2) 1.35 (t, 3, CH_3).

Anal. Calcd for $C_{11}H_6F_5NO_2$: C, 47.27; H, 2.16; N, 5.01. Found: C, 47.06; H, 2.02; N, 4.82.

2,3,4,5,6-Pentafluorophenylacetonitrile (2).—Ethyl α-cyanopentafluorophenylacetate (0.5 mol, 140.5 g) was refluxed for 12 hr with 350 ml of 50% acetic acid containing 12.5 ml of concentrated sulfuric acid. After the mixture was cooled to room temperature, it was diluted with an equal volume of water and stirred, and the viscous, dark organic layer settled to the bottom of the flask. The mixture was chilled in an ice bath, the top layer was decanted until the remaining mixture consisted mostly of the dark organic layer, which was transferred to a separatory funnel, and the remaining water layer was removed. The organic layer was dissolved in ether, washed with water and sodium bicarbonate, and finally dried over anhydrous $MgSO_4$. Distillation through a 10-in. jacketed Vigreux column gave 98.0 g (70%) of a colorless liquid: bp 105–107° (8 Torr); ir 2925 and 2900 (s, CH_2) 2260 (w, C≡N) 1660 (s, aromatic), 1540 (s, C_6F_5), and 1160 (s, CF); pmr δ 3.97 (s, fine structure).

The spectra of this substance were identical with those obtained for an autheutic sample of the nitrile, although the boiling point of the material prepared by the present method was slightly higher than that reported earlier [bp 107–111° (17 Torr[6])].

This compound was reduced over PtO_2[3] and the resulting amine hydrochloride was converted to the free amine, which was cyclized to the indoline, mp 60° (lit.[3] mp 60–61.5°).

Aromatization of 4,5,6,7-Tetrafluoroindoline to 4,5,6,7-Tetrafluoroindole.—A modification of a method described by Jansen, Johnson, and Surtees was employed.[8] To 4.5 g (23.5 mmol) of the tetrafluoroindoline in a round-bottom, one-neck flask was added 190 ml of reagent-grade benzene which was predried over sodium and filtered and chilled to about 10°. Then 4.0 g of Linde Type 4A Molecular Sieves and 22.0 g of activated MnO_2 were added.[9] The mixture was shaken on a wrist-action shaker for 60 hr, during which time the temperature was not allowed to rise above 22°. After the mixture had been filtered on a Büchner funnel using Celite, the solid residue was transferred to a Soxhlet apparatus and extracted with 300 ml of dry benzene for 7 hr. The filtrate and liquid from the extraction were combined and the benzene was removed on a rotary evaporator. The residual brown oil was diluted with about 3 ml of dry benzene and transferred to a 2 ft × 1.2 in. (o.d.) chromatography column packed with 25 g of neutral alumina in practical-grade hexane. The contents of the column were eluted first with 250 ml of hexane, then with 50:50 hexane–diethyl ether, and finally, with 100% ether. The hexane and hexane–diethyl ether fractions were concentrated on the rotary evaporator to yield a material melting at 83–90°. Sublimation at 60° (0.7–1.5 Torr) yielded 3.7 g (82%) of a white solid: mp 91–92.5° (this melting point is identical with that reported for the pure indole[3]); ir 3420 (vs, NH), 3100 (s, CH), 1540, 1600, 1660, and 1490 (aromatic ring), 1500, 1130, and 1000 cm^{-1} (s, CF); pmr δ 8.37 (s, broad, 1, NH), 7.17 (m, 1, CH), 6.57 (m, 1, CH). The solid obtained from the 100% ether eluate contained a mixture of indole, unreacted indoline, and some unidentified materials whose melting points were variable and ranged from 110 to 130°.

Registry No.—1, 16264-67-8; 2, 653-30-5; ethyl α-cyanopentafluorophenylacetate, 2340-87-6.

(4) W. P. Norris, *J. Org. Chem.*, **37**, 147 (1972), has recently reported an analogous reaction with octafluorotoluene.

(5) A. Kalir and Z. Pelah, *Israel J. Chem.*, **4**, 155 (1966).

(6) A. K. Barbour, M. W. Buxton, P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 808 (1961).

(7) W. L. White and R. Filler, *J. Chem. Soc. C*, 2062 (1971).

(8) A. B. A. Jansen, J. M. Johnson, and J. R. Surtees, *J. Chem. Soc., Suppl. 1*, 5573 (1964).

(9) J. Attenburrow, J. H. Cameron, R. M. Evans, A. B. A. Evans, and T. Walker, *J. Chem. Soc.*, 1104 (1952).

2,3-Dimethyl-5,6-bis(methylene)-1,4-benzoquinone. The Active Intermediate of Bioreductive Alkylating Agents

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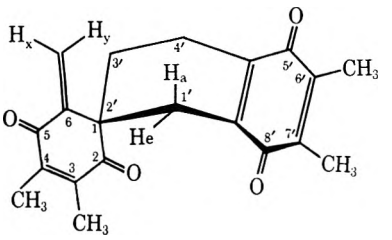
2,3-Dimethyl-5,6-bis(acetoxymethyl)-1,4-benzoquinone (**1**) has been shown by this laboratory to be a potent inhibitor of (a) the biosynthesis of DNA and RNA and (b) the growth of adenocarcinoma 755 ascites cells. It was hypothesized[1] that the action mechanism of this series of benzoquinone derivatives involved bioreduction *in vivo* in a manner analogous to mitomycin C by an NADPH-dependent quinone reductase enzyme[2,3] to corresponding dihydroquinones which generated reactive intermediates, *o*-quinone methides. Further postulation visualized that such active species might function as inhibitors of neoplastic growth by the alkylation of DNA, RNA, or other biological systems. In the present report, chemical evidence is presented to substantiate the formation of intermediate **3** from compound **1** upon sodium borohydride reduction.

Compound **1** was subjected to reduction with 1 molar equiv of $NaBH_4$ in methanol at ice-cold temperature. Two major yellow products were obtained after column chromatography on silica gel. The first compound was identified as duroquinone[4] (**4**) by nmr, ir, and mixture melting point with authentic sample. The second compound (**5**) had a parent ion peak at *m/e* 324 in the mass spectra and good elemental analysis based on the calculation of $(C_{10}H_{10}O_2)_2$, indicating that compound **5** was a dimer of **3** ($C_{10}H_{10}O_2$). Dimerization or trimerization were the most common reactions of *o*-quinone methides in the absence of other trapping reagents.[5] The structures of the dimer and trimer were in general a product of a Diels–Alder reaction of the *o*-quinone methides. There are relatively large numbers of possible dimer adducts which could be derived from the active intermediate **3**; however, only compound **5** (3′,4′-dihydro-3,4,6′,7′-tetramethyl-6-methylenespiro-[3-cyclohexene-1,2′(1′*H*)-naphthalene]-2,5,5′,8′-tetradone) best fits both nmr (Table I) and ir data. Characteristic benzoquinone peaks (KBr) around 1635 cm^{-1} and α,β-unsaturated keto groups at 1665 and 1675 cm^{-1} were observed in the ir spectrum.

In ^1H nmr spectra, the two most downfield signals (5.21 and 6.09 ppm) are assigned to the two olefinic protons. No coupling between these two protons was observed in either 60- or 100-MHz spectra, since the geminal coupling constant of olefinic protons is generally very small. The signal at lower field (6.09 ppm) is assigned to the proton (H_x) cis to the keto group of the ring, and arises from the anisotropic deshielding effect of the carbonyl.[6,7] The most upfield signals (1.87 ppm) appear as a triplet (J = 7.0 Hz) and integrate for two protons. Based on the splitting pattern and the coupling constant, this triplet is apparently part of the spectrum of an A_2B_2 system and therefore is assigned as either the $C_{3'}$ or $C_{4'}$ protons. The other part of the system is complicated by coupling with other protons to give nine peaks centered around 2.37 ppm. The splitting pattern of H_a and H_e indicates a large geminal coupling (J = 19 Hz) between H_a and H_e and a long-range coupling (J = 2.5 Hz) with either $C_{3'}$ or $C_{4'}$ protons. The coupling between the $C_{1'}$ and $C_{3'}$ protons can occur only when the system assumes a ω configuration, with the coupling protons approximately coplanar and linked by a zig-zag path.[8,9] The magnitude of this long-range coupling over four bonds ($^4J_{HH}$) is generally small and is often seen only in the broadening of a proton signal. Since only the H_e proton can assume the required ω configuration with the $C_{3'}$ protons, and long-range coupling is observed with both $C_{1'}$ protons, this coupling is probably derived from the homoallylic[8] long-range coupling between the $C_{1'}$ and $C_{4'}$ protons. Therefore, the triplet signal at 1.87 ppm is unambiguously assigned as $C_{3'}$ and the multiplets at 2.37 ppm assigned as $C_{4'}$. A closely related example of five-bond coupling between the protons of C_2 and C_5 of 1,2,5,6-tetrahydropyridine has been reported.[10] Using high-resolution nmr and decoupling techniques the coupling constant $J_{2,5}$ of 1,2,5,6-tetrahydropyridine was found to be 3 Hz, which is close to the value $J_{1'4'}$ = 2.5 Hz observed for $C_{1'}$ and $C_{4'}$ protons of dimer **5**.

The molecular model of dimer **5** indicated a serious steric interaction between H_y and $C_{1'}$ and $C_{3'}$ protons. Therefore, the most stable conformation of the molecule presumably is the one in which the ethylene group occupies an equatorial position at $C_{2'}$. In this conformation, the H_e proton, which is trans to the ethylene

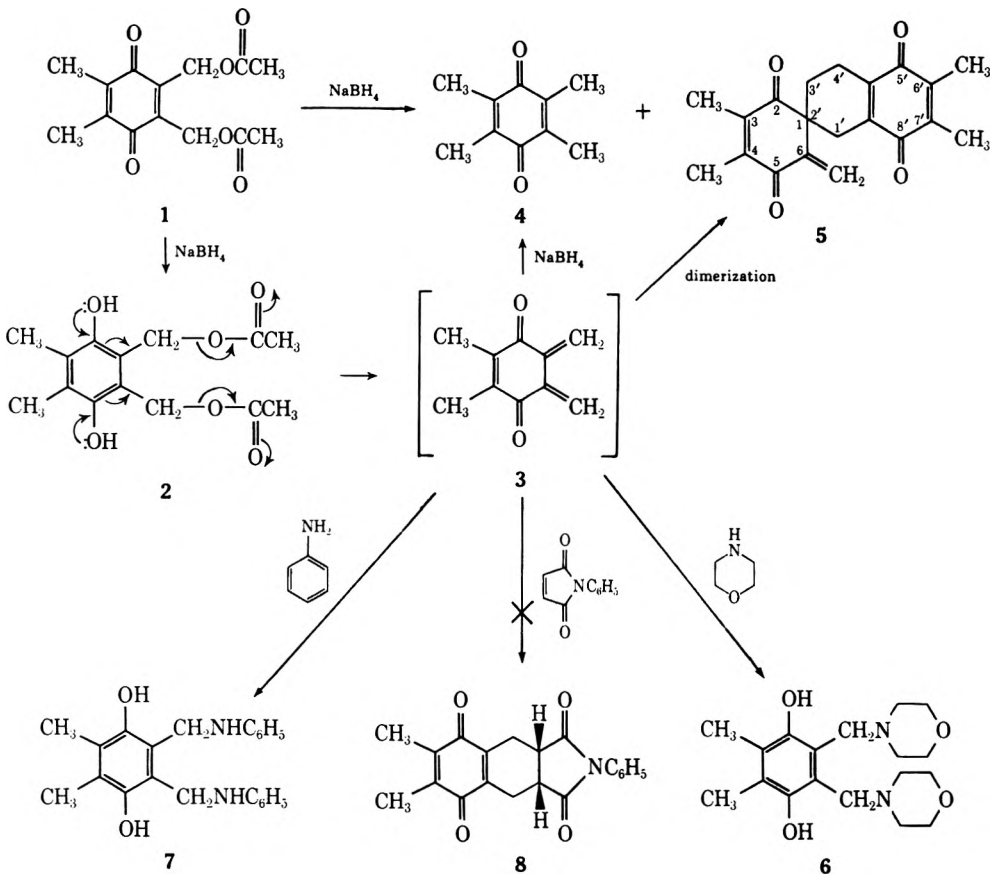
TABLE I[a]



Protons	Chemical shift, ppm	Coupling constants, Hz
$H_{3'}$	1.89 (t, 2)	$J_{3'4'}$ = 7
3,4,6′,7′-Tetramethyl	2.01 (s, 6), 2.06 (s, 6)	
$H_{4'}$	2.37 (m, 2)	$J_{4'3'}$ = 7, $J_{4'1'}$ = 2.5
H_e	2.65 (m, 1)	J_{ea} = 19, $J_{e4'}$ = 2.5
H_a	3.32 (m, 1)	J_{ae} = 19, $J_{a4'}$ = 2.5
H_y	5.21 (s, 1)	
H_x	6.09 (s, 1)	

[a] Chemical shifts and coupling constants from spectra of about 10% solutions in $CDCl_3$.

(1) A. J. Lin, L. A. Cosby, C. W. Shansky, and A. C. Sartorelli, *J. Med. Chem.*, **15**, 1247 (1972).
(2) H. S. Schwartz, J. E. Sodergren, and F. S. Philips, *Science*, **142**, 1181 (1963).
(3) V. N. Iyer and W. Szybalski, *ibid.*, **145**, 55 (1964).
(4) L. I. Smith and F. J. Dobrovolny, *J. Amer. Chem. Soc.*, **48**, 1420 (1926).
(5) A. B. Turner, *Quart. Rev., Chem. Soc.*, **18**, 347 (1964).
(6) J. W. ApSimon, W. G. Craig, P. V. Demarko, D. W. Mathieson, A. K. G. Nasser, L. Saunders, and W. B. Whalley, *Chem. Commun.*, 754 (1966).
(7) G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. J. Fienoglio, *J. Amer. Chem. Soc.*, **89**, 5067 (1967).
(8) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).
(9) S. Sternhell, *Quart. Rev., Chem. Soc.*, **23**, 236 (1969).
(10) J. N. Shoolery, *Discuss. Faraday Soc., No. 34*, 104 (1962).



group, assumes a ω configuration with the equatorial $C_{3'}$ proton required for a four-bond long-range coupling. Consequently the H_e proton appeared as a relatively poorly resolved sextet, which contrasts with the sharply resolved sextet of the H_a proton. The downfield shift of the H_a proton can be explained by a steric compression effect caused by the overcrowding at the axial position.[11]

The mechanism of the formation of the observed products **4** and **5** can best be explained by the initial reduction of compound **1** with $NaBH_4$ to the corresponding dihydrobenzoquinone **2**, which then decomposed to generate **3**. Further reduction or dimerization of **3** produced the observed products **4** and **5**. The formation of a similar dimer, spirodi-*o*-xylylene, from *o*-xylylene has been documented.[12] To provide additional evidence for the existence of **3**, the reduction of **1** with $NaBH_4$ was carried out in the presence of morpholine or aniline. The expected adducts **6** or **7**, respectively, precipitated from the reaction mixture in 5–10 min after the addition of $NaBH_4$. A similar reaction mechanism which involved quinone methide as the intermediate was suggested to account for the formation of 2,5-bis(morpholinomethyl)-1,4-dihydrobenzoquinone by treatment of 2,5-dihydroxy-α,α′-*p*-xylylene bisisothiuronium dihydrochloride with morpholine.[13] However, an alternative mechanism which involves amination of quinone **1** followed by $NaBH_4$ reduction to give adducts **6** or **7** must be considered. Further experiments, therefore, were carried out in which benzoquinone **1** was treated with either morpholine or aniline in the absence of $NaBH_4$ under ice-cold temperature. No appreciable reaction occurred over 2 hr with these reaction conditions, as monitored by thin layer chromatography. This finding tends to eliminate the possibility of an amination–reduction mechanism, and further substantiated a mechanism involving the generation of *o*-quinone methide (**3**) as the active intermediate.

Attempts to trap intermediate **3** in a similar manner with *N*-phenylmaleimide failed to give the desired adduct **8**. Instead, compounds **4** and **5** were isolated. In view of the numerous examples of the susceptibility of imides to $NaBH_4$ reduction,[14] the failure to trap intermediate **3** with *N*-phenylmaleimide may be due to the rapid reductive destruction of the trapping agent. However, identical results were obtained using ω-nitrostyrene, which would be expected to be stable under the reduction conditions employed. These findings do not necessarily disprove the existence of intermediate **3**, but rather that it is a better dienophile than trapping agents in the competitive Diels–Alder reaction.[15]

In summary, evidence was obtained to indicate that the reactive intermediate 2,3-dimethyl-5,6-bis(methylene)-1,4-benzoquinone (**3**) was formed from 2,3-dimethyl-5,6-bis(acetoxymethyl)-1,4-benzoquinone (**1**) upon $NaBH_4$ reduction. To the best of our knowledge, this is the first report of evidence supporting the existence of bis(*o*-quinone methide). The capability of intermediate **3** to alkylate aniline or morpholine suggested a similar potential to alkylate biological materials *in vivo*, if **3** could be generated enzymatically *in vivo*.

(11) T. Sato and K. Uno, *Chem. Commun.*, 579 (1972).
(12) L. A. Errede, *J. Amer. Chem. Soc.*, **83**, 949 (1961).
(13) D. L. Fields, J. B. Miller, and D. D. Reynolds, *J. Org. Chem.*, **30**, 3962 (1965).
(14) Y. Kondo and B. Witkop, *ibid.*, **33**, 206 (1968).
(15) H. L. Holmes, "Organic Reactions," Vol. IV, Wiley, New York, N. Y., 1948, Chapter 2, p 60.

Experimental Section

$NaBH_4$ Reduction of 2,3-Dimethyl-5,6-bis(acetoxymethyl)-1,4-benzoquinone.—Quinone 1 (0.5 g, 1.8 mmol) was suspended in 20 ml of methanol and chilled in an ice bath. $NaBH_4$ (0.065 g, 1.8 mmol) was added in small portions to the suspension with stirring. The clear yellow solution was stirred at ice-cold temperature for another 30 min after the addition of $NaBH_4$. The methanol was evaporated to dryness under reduced pressure and room temperature to give a yellow powder. Water (20 ml) was added and the mixture was extracted three times with ether (30 ml). Ether extracts were combined, dried, and evaporated to dryness. The yellow powder was chromatographed on a column of silica gel (50 g) using EtOAc and petroleum ether (bp 38–47°) (1:4, v/v) as eluent; two major yellow fractions were obtained. The first fraction yielded 50 mg of long needles (from H_2O), mp 110°, and was identified as duroquinone (4) (lit.[4] mp 111°) by ir, nmr, and mixture melting point. The second fraction yielded 75 mg of dimer 5: mp 155.5–157.5°; ir (KBr) 1635, 1665, and 1675 cm^{-1} (-C=O); mass spectrum *m/e* 324 (M^+); uv λ_{max}^{EtOH} 259 nm (ϵ 27,000), 265 (24,000).

Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.07; H, 6.17. Found: C, 73.88; H, 6.31.

$NaBH_4$ Reduction of 2,3-Dimethyl-5,6-bis(acetoxymethyl)-1,4-benzoquinone in the Presence of Morpholine.—Quinone 1 (0.25 g, 0.9 mmol) and morpholine (0.5 ml) were suspended in 10 ml of ice-cold methanol. To the suspension, $NaBH_4$ (0.035 g, 0.9 mmol) was added in small portions with stirring. After the addition, the solution was mixed for an additional 30 min. The white precipitate was collected and washed with ice-cold methanol to give 60 mg of white crystals. The filtrate was evaporated to dryness and the crude product was washed with H_2O followed by cold methanol to give another 50 mg of white crystals. Combination and recrystallization of the product from methanol yielded 100 mg (37%) of white crystals (6): mp 206° dec; ir (KBr) 3450–2700 (broad and weak, -OH···N-) and 1110 cm^{-1} (ether); nmr ($CDCl_3$) 2.71 (s, 6), 2.54 (m, 8), 3.68 (s, 4) and 3.75 ppm (m, 8).

Anal. Calcd for $C_{18}H_{23}N_2O_4$: C, 64.29; H, 8.33; N, 8.33. Found: C, 64.01; H, 8.26; N, 8.28.

$NaBH_4$ Reduction of 2,3-Dimethyl-5,6-bis(acetoxymethyl)-1,4-benzoquinone in the Presence of Aniline.—To quinone 1 (0.15 g, 0.53 mmol) in 20 ml of methanol was added an excess of aniline (0.5 ml). The solution was cooled in an ice bath and $NaBH_4$ (0.02 g, 0.53 mmol) was added in small portions. The clear solution was stirred for 10 min and the formed white precipitate was collected and washed with a small amount of methanol. Recrystallization from ethanol gave white needles of 7 (0.14 g, 76%): mp 171–173° dec; ir (KBr) 3290 (s, NH), 3200–2700 (-OH···N-), 1602, 1500, 747, and 690 cm^{-1} (monosubstituted phenyl); nmr (DMSO-d_6) 2.10 (s, 6), 4.25 (broad singlet, 4), 5.43 (broad singlet, 2), 6.88 (m, 10), 8.13 ppm (broad singlet, 3).

Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.85; H, 6.90; N, 8.05. Found: C, 75.73; H, 7.02; N, 7.79.

Registry No.—**1**, 37439-56-8; **3**, 37439-57-9; **5**, 37439-58-0; **6**, 37439-59-1; **7**, 37439-60-4; $NaBH_4$, 16940-66-2; morpholine, 110-91-8; aniline, 62-53-3.

Acknowledgment.—This study was supported by Grant CA-02817 from the National Cancer Institute, USPHS.

Hydrolysis Products of 4-Acetamido-4-hydroxy-2-butenoic Acid γ-Lactone

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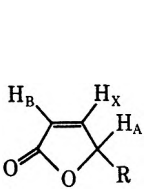
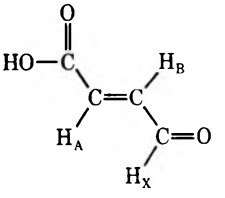
4-Acetamido-4-hydroxy-2-butenoic acid γ-lactone (**1a**) is a mycotoxin produced on laboratory media by a strain of *Fusarium tricinctum* originally isolated from tall fescue hay (*Festuca arundinaceae* Schreb.).[2] Gangrene in tails of cattle receiving **1a** provided circumstantial evidence implicating it in the problem of tall fescue toxicity.[3,4]

Our current interest in the biological activity of **1a** prompted us to examine more closely two earlier reports concerning the hydrolysis products of this mycotoxin. White[5] found that acid hydrolysis of **1a** gave a 23% yield of malealdehydic acid (*cis*-β-formylacrylic acid, **1b**) as the major four-carbon fragment isolated; alkaline hydrolysis also gave **1b**, no yield being reported. Burkhardt, *et al.*,[6] found that alkaline hydrolysis of **1a** yielded a mixture of **1b** and fumaraldehydic acid (*trans*-β-formylacrylic acid, **2**). However, their results were



1a, R = $NHCOCH_3$
b, R = OH
c, R = OCH_2CH_3



2

not unambiguous since the melting point given for cis acid **1b** (127°) is the same as reported by Schroeter, *et al.*,[7] for trans acid **2**. Our investigation shows that, whereas acid hydrolysis of **1a** does indeed give **1b** as the major product, **2** predominates under alkaline conditions. Hydrolysis products were identified by direct comparison with unequivocally characterized samples of **1b** and **2**.

Compound **1b** had been prepared earlier[7] by acid hydrolysis of the corresponding ethyl pseudo ester **1c**, which was obtained by photosensitized oxygenation of furfural in ethanol.[8] We prepared **1b** more directly, albeit in lower yield (25%), by carrying out the photooxygenation of furfural in aqueous ethanol (1:1). The ethanol required to maintain the eosin sensitizer in solution leads to formation of some **1c**. The ir spectrum of **1b** exhibits a pair of carbonyl bands at 1790 and 1760 cm^{-1} characteristic of an α,β-unsaturated lactone of this type.[2] That **1b** exists as the cyclic pseudoacid and not as an open-chain aldehydic acid as its name implies was confirmed by the nmr spectrum (Table I), which shows no aldehyde proton. The three ring protons of **1b** exhibit an ABX pattern with the cis-vinyl proton coupling constant of 5.7 Hz in close agreement with that for **1a**[6] and *cis*-β-acetylacrylic acid.[9]

Compound **2** had been prepared previously by acid treatment of either **1b** or **1c** in 25 and 46% yields, re-

(1) Agricultural Research Service, U. S. Department of Agriculture.

(2) S. G. Yates, H. L. Tookey, J. J. Ellis, and H. J. Burkhardt, *Phytochemistry*, **7**, 139 (1968).

(3) M. D. Grove, S. G. Yates, W. H. Tallent, J. J. Ellis, I. A. Wolff, N. R. Kosuri, and R. E. Nichols, *J. Agr. Food Chem.*, **18**, 734 (1970); H. L. Tookey, S. G. Yates, J. J. Ellis, M. D. Grove, and R. E. Nichols, *J. Amer. Vet. Med. Ass.*, **160**, 1522 (1972).

(4) For a recent review see S. G. Yates in "Microbial Toxins," Vol. 7, S. Kadis, A. Ciegler, and S. J. Ajl, Ed., Academic Press, New York, N. Y., 1971, pp 191–206.

(5) E. P. White, *J. Chem. Soc. C*, 346 (1967).

(6) H. J. Burkhardt, R. E. Lundin, and W. H. McFadden, *Tetrahedron*, **24**, 1225 (1968).

(7) S. H. Schroeter, R. Appel, R. Brammer, and G. O. Schenck, *Justus Liebigs Ann. Chem.*, **697**, 42 (1966).

(8) G. O. Schenck, *ibid.*, **584**, 156 (1953).

(9) S. S. Seltzer and K. D. Stevens, *J. Org. Chem.*, **33**, 2708 (1968).

TABLE I
NMR DATA OF MALEALDEHYDIC AND FUMARALDEHYDIC ACIDS

Compd	Chemical shifts, δ			Coupling constants, Hz		
	H_A	H_B	H_X	J_{AB}	J_{AX}	J_{BX}
1b[a]	6.25	6.20	7.41	1.2	1.2	5.7
2[b]	6.91	6.72	9.77	15.8	0.4	7.8

[a] In acetone-d_6. [b] In DMSO-d_6.

spectively.[7] We found that **2** can be prepared conveniently in 26% yield by treating a crude photooxygenation mixture containing **1b** and **1c** with sodium bicarbonate. No **2** was detected in the mixture by tlc before the bicarbonate was added. Likewise, treating pure **1b** with bicarbonate for 2 days gave an isomerization mixture containing **2** and **1b** in the ratio of approximately 3:2. The three C protons of **2** exhibit an ABX pattern with coupling constants near those reported for *trans*-crotonaldehyde.[10] The typically large trans-vinyl proton coupling constant of 15.8 Hz in **2** is also near that found for *trans*-β-acetylacrylic acid.[9]

Since an initial attempt to hydrolyze **1a** with 0.1 *N* HCl at room temperature resulted in less than 50% hydrolysis, the compound was hydrolyzed with refluxing 2 *N* HCl by the method of White.[5] Purification of the ethyl acetate extractables by adsorption chromatography gave, as the major product, 28% of crystalline **1b**, plus less than 2% of **2**. Identity of the hydrolysis products from **1a** was established by ir, tlc, and melting point.

Alkaline hydrolysis of **1a** was carried out at room temperature with 0.1 *N* NaOH according to the procedure of Burkhardt, *et al.*[6] In view of the ease of bicarbonate-induced ring opening and concomitant isomerization of **1b** to **2**, the expected product in this reaction was again **2**. Indeed, examination of the ether extract from the acidified reaction mixture by ir and tlc showed **2** as the major product, plus a minor amount of **1b**. Thus, contrary to implications of earlier reports,[5,6] formation of **2** from **1a** is favored under alkaline conditions. Silica gel chromatography of the ether extractables afforded a 24% yield of **2**, plus less than 1.5% **1b**. The low yield of **2** is not due to loss of significant amounts of material on the silica, but rather to formation of considerable polymeric material during hydrolysis.

Experimental Section

Melting points were determined on a Fisher-Johns block and are uncorrected. The following spectrometers were used: ir, Perkin-Elmer 337 ($CHCl_3$); uv, Beckman DK-2A (EtOH); nmr, Varian HA-100 with TMS as an internal standard.[11] Thin layer chromatograms were run on silica gel G coated plates.

Malealdehydic Acid (1b).—Oxygen was passed into an irradiated mixture of 100 g of furfural and 2.0 g of eosin (yellowish) in 1400 ml of H_2O–EtOH (1:1) for 4 days. Light was provided by a circular arrangement of 26 20-W cool-white fluorescent lamps; wavelengths shorter than 460 nm were filtered out by an aqueous solution of 1.25 *M* $CaCl_2$.[12] After most of the solvent was removed, the solution was diluted with H_2O and filtered to remove eosin. The filtrate was washed with CCl_4 and extracted thoroughly with ethyl acetate. After the ethyl acetate extract was dried (Na_2SO_4), the solvent was removed; the residual oil crystallized upon refrigeration. The crystals were washed with benzene and recrystallized from $CHCl_3$–benzene to give 25.8 g (25%) of **1b**: mp 53–56°; additional recrystallizations raised the melting point to 54.5–56.5° (lit.[7] mp 58–59°); tlc R_f 0.44 [$CHCl_3$–acetone–acetic acid (85:10:5), sprayed with 3% ceric sulfate in 3 *N* H_2SO_4, and heated at 120°]; ir 3580 (OH), 1790, 1760 (C=O), 1115, 1003 cm^{-1}; uv max 202 nm (ε 6870); phenylhydrazone[6] mp 159–161°, tlc R_f 0.48 [hexane–ether–acetic acid (47:50:2), I_2 vapor].

Fumaraldehydic Acid (2).—The reaction was carried out as described for **1b**. Two-thirds of the solvent was removed, 126 g of $NaHCO_3$ was added, and the mixture was kept at room temperature for 3 days. The solution was acidified to pH 1.5 with 10 *N* HCl, washed with CCl_4, and extracted thoroughly with ethyl acetate. The crystalline residue, obtained by drying (Na_2SO_4) and removal of the ethyl acetate solvent, was passed through 600 g of silica gel (70–325 mesh). Elution of the column with acetone–$CHCl_3$ (1:4), concentration of the fractions containing **2**, and recrystallization from acetone–$CHCl_3$ gave 26.8 g (26%) of **2**: mp 125–126°; additional recrystallizations raised the melting point to 126.5–127° (lit.[7] mp 127°); tlc R_f 0.55 [$CHCl_3$–acetone–acetic acid (85:10:5), sprayed with 3% ceric sulfate in 3 *N* H_2SO_4, and heated at 120°]; ir 3510 (OH), 1740, 1700 (C=O), 1100, 978 cm^{-1}; uv max 216 nm (ε 11,000); phenylhydrazone[6] mp 159.5–161°, mixture melting point with **1b** phenylhydrazone 146–151°, tlc R_f 0.33 (hexane–ether–acetic acid, 47:50:2).

Isomerization of Malealdehydic Acid (1b).—A solution of 1.0 g of **1b** and 2.1 g of $NaHCO_3$ in 20 ml of H_2O was kept at 20° for 2 days. The solution was acidified to pH 1 with 4 *N* HCl and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and concentrated, leaving 780 mg of residue. Examination of the ir carbonyl region of the residue showed compound **2** and starting **1b** in approximately a 3:2 ratio.

Acid Hydrolysis of 4-Acetamido-4-hydroxy-2-butenoic Acid γ-Lactone (1a).—A solution of 1.0 g of **1a** (obtained by synthesis[3]) in 40 ml of 2 *N* HCl was refluxed for 3 hr, cooled, and extracted with ethyl acetate. The ethyl acetate extract was dried (Na_2SO_4), and the solvent was removed. Chromatography of the residue on 25 g of silica gel ($CHCl_3$ eluent) plus crystallization from $CHCl_3$–benzene gave 202 mg (28%) of **1b**, mp 53.5–56.5°. Ir analysis of the carbonyl region of the mother liquor indicated less than 10 mg (2%) of **2**.

Alkaline Hydrolysis of 4-Acetamido-4-hydroxy-2-butenoic Acid γ-Lactone (1a).—A solution of 1.0 g of **1a** in 78 ml of 0.1 *N* NaOH was kept at room temperature for 16 hr. The solution was acidified to pH 1.5 with 1 *N* HCl and extracted with ether. After the ether extract was dried (Na_2SO_4), the solvent was removed. The residue (410 mg) was examined by ir and tlc and chromatographed on 25 g of silica gel [acetone–$CHCl_3$ (5:95) eluent]. Recrystallization from $CHCl_3$ gave 169 mg (24%) of **2**, mp 126.5–127.5°. Subsequent column fractions were combined and by ir analysis contained less than 9 mg (1.5%) of **1b**.

Registry No.—**1a**, 16275-44-8; **1b**, 14032-66-7; **2**, 4437-06-3; furfural, 98-01-1.

Acknowledgment.—We thank M. V. Wakeman for technical assistance.

(10) A. W. Douglas and J. H. Goldstein, *J. Mol. Spectrosc.*, **16**, 1 (1965).

(11) Mention of firm names or trade products is for identification only and does not imply endorsement by the U. S. Department of Agriculture.

(12) C. R. Masson, V. Boekelheide, and W. A. Noyes, Jr., in "Technique of Organic Chemistry," Vol. 2, 2nd ed, A. Weissberger, Ed., Interscience, New York, N. Y., 1956, p 283.

"Dimers" from the Reaction of Propargyl Halides with Organometallic Reagents

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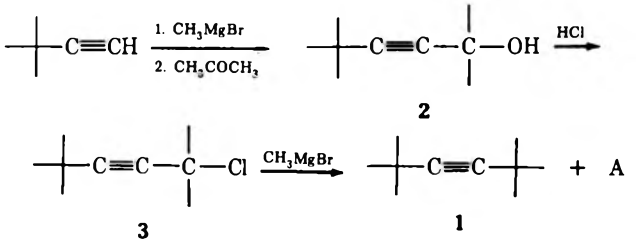
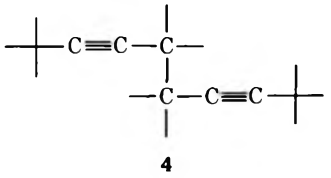
In connection with another study, we had occasion to prepare di-*tert*-butylacetylene (**1**). Its synthesis was first described by Hennion and Banigan,[1] then

(1) G. F. Hennion and T. F. Banigan, Jr., *J. Amer. Chem. Soc.*, **68**, 1202 (1946).

later by Puterbaugh and Newman,[2] who used the unexceptional reactions below. Each step proceeded in

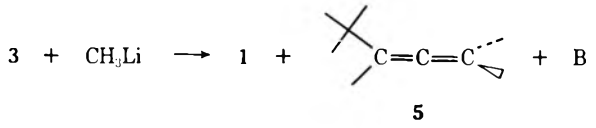


reasonable yield, but the purification of **1** was laborious because several chemically similar side products accompanied its formation. Among these was a material (A) variously described as a high-boiling unsaturate[1] and a crystalline "dimer,"[2] the structure of which was tentatively assigned as 2,2,5,5,6,6,9,9-octamethyldeca-3,7-diyne (**4**) on the basis of elemental



analysis, (osmotic?) molecular weight, and hydrogenation.

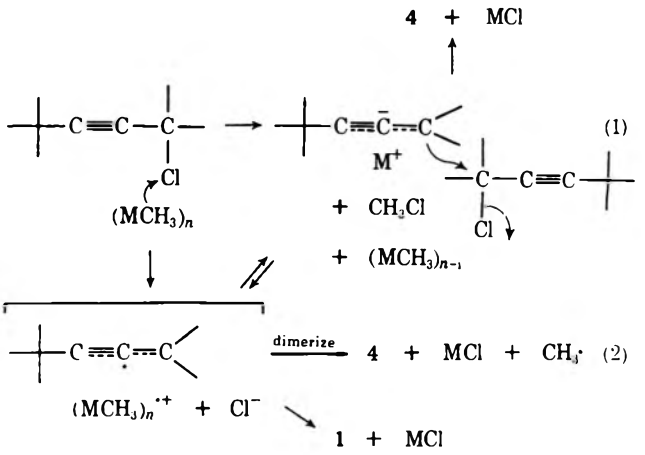
Somewhat later Jacobs and Prempree[3] carried out an extensive study of the coupling reactions of propargyl chlorides with organometallic reagents. They found that the reaction of **3** with methyllithium in ether gave a low (isolated) yield of **1** accompanied by its allenic isomer 2,2,3,5-tetramethyl-3,4-hexadiene (**5**) in the



ratio 65:35, respectively. The major isolated product, however, was a solid (B) of mp 100–102° (that of A was 112.5–113°), which was also assigned structure **4** on the basis of elemental analysis and ^{1}H nmr.

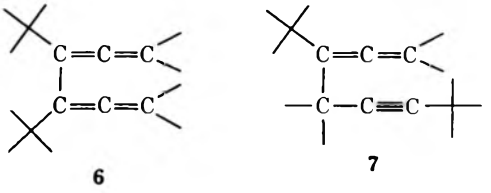
Thus there remained some uncertainty regarding the identity and properties of A (= B = **4**?), as well as a lack of knowledge about the mechanism of its formation.

The exact mechanisms of reactions involving methyllithium are known to be quite complex,[4] because this reagent is oligomeric in solution. Nonetheless, one can write two mechanistic extremes for the formation of **4** under these conditions. The first involves preliminary halogen–metal exchange[5] and subsequent



attack by a tertiary carbanion on a tertiary halide (!) while the other involves electron transfer followed by dimerization of the incipient radical.

With either of the above two mechanisms there is the possibility (even the likelihood in the case of a mechanism involving propargyl radicals[6]) that at least one allenic system might be incorporated into A (= B?). Although the ^{1}H chemical shifts might distinguish between **4** and **6**, with so much proximate unsaturation



an assignment based solely on this could be incorrect. In the hope of unifying the earlier work[1-3] and unequivocally establishing the structure of A (= B = **4**?), we reinvestigated the reaction of **3** with methyllithium in ether.

When **3** was treated with a slight excess of methyllithium at 25°, three major and at least three minor products (the latter totaling *ca.* 1%) were observed by glc (Table I). The two most volatile major products

TABLE I

PRODUCTS FROM THE REACTION OF **3** WITH METHYLLITHIUM[a]

Conditions[b]	Temp, °C	Mol %[c] 1	5	4[d]
3 added to CH_3Li	25	60.0	24.7	15.3
CH_3Li added to **3**	25	59.4	25.2	15.4

[a] Although these values are relatively percentages within the product mixture, the product masses indicate that yields are virtually quantitative. See Experimental Section. [b] Reaction times 24.7 and 24.3 hr, respectively. [c] Determined by disc-integrated peak areas which *were* corrected for differences in detector response factors. Precision is estimated to be ±0.2%, with accuracy similar. Each of the products was stable to the reaction conditions. [d] Recall that each mole of **4** requires 2 mol of **3**.

were separated from the third by distillation, and from one another by preparative glc. They were shown to be the expected products **1** and **5**. The least volatile major product was isolated by sublimation and recrystallization.[7] This compound had mp 112.4–112.7° and

(2) W. H. Puterbaugh and M. S. Newman, *J. Amer. Chem. Soc.*, **81**, 1611 (1959).

(3) T. L. Jacobs and P. Prempree, *ibid.*, **89**, 6177 (1967).

(4) For continuing timely reviews on organolithium chemistry, see W. H. Glaze, *Organometal. Chem. Rev.*, **4**, 161 (1968); **5**, 189 (1969); **6**, 1 (1970).

(5) The mechanism of Wurtz-type reactions between alkyllithiums and alkyl iodides and bromides can involve caged radicals [see, for example, H. R. Ward, R. G. Lawler, and R. A. Cooper, *J. Amer. Chem. Soc.*, **91**, 746 (1969)]. There is evidence, however, that halogen–metal exchange and subsequent coupling reactions of conjugated systems may prefer an "ionic" mechanism [J. Sauer and W. Braig, *Tetrahedron Lett.*, 4275 (1969); W. D. Korte, L. Kinner, and W. C. Kaska, *ibid.*, 603 (1970); L. H. Sommer and W. D. Korte, *J. Org. Chem.*, **35**, 22 (1970)]. The two mechanistic extremes above are classified on the basis of the step leading to **4**: is the precursor radical-like or carbanion-like?

(6) P. S. Engel and D. J. Bishop, *J. Amer. Chem. Soc.*, **94**, 2148 (1972).

(7) Compound **4** is exceptionally volatile for a solid. It sublimes at 90° (1 atm), and care must be exercised to avoid volatilization during recrystallization from hot solvents and melting-point determinations.

was >99% pure by glc. Its mass spectrum (Table II) confirmed the molecular formula $C_{18}H_{30}$, as well as ex-

TABLE II
70-eV MASS SPECTRUM OF 4

m/e	Rel intensity	Assignment
246	5	$M\cdot^+$
231	15	$M - CH_3$
189	10	$M - C_4H_9$
165	8	
149	26	
123	100[a]	$M/2^+$ (or M^{+2})
109	32	
107	26	
95	20	
93	17	
91	30	
81	84	
69	34	
67	41	
57	42	$C_4H_9^+$
55	32	
41	44	

[a] Base peak.

hibiting a base peak at *m/e* 123 for the symmetrical fragmentation expected of **4**. The ultraviolet spectrum (pentane) showed only end absorption ($\epsilon_{210\ nm}$ 150), suggesting that the compound did not possess conjugated unsaturation (such as in **6**). Its ^1H nmr spectrum consisted of singlets at δ 1.19 and 1.21 (those for B occur at δ 1.17 and 1.20[3]) and, although the exact integration was difficult owing to the proximity of the peaks, the ratio was close to 3:2, respectively. We recently established the normal position for methyl groups β to a carbon–carbon triple bond (δ 1.23 ± 0.03)[3] and the above values fall squarely in this region.

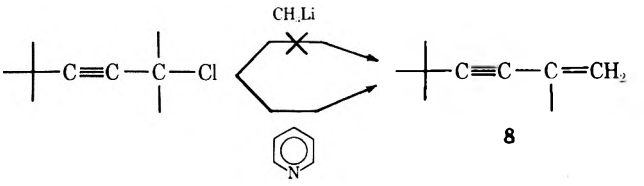
It would seem that the (as yet unreported) infrared spectrum of **4** would provide confirmation of its structure, by ruling out **6** and **7**. Unfortunately, at normal concentrations (10% in carbon tetrachloride) and path lengths (0.05 mm) no absorptions could be detected for triple bonds or allenic systems. However, examination of a saturated solution through a path of 0.2 mm revealed two extremely weak bands[9] ($\epsilon \sim 1$) at 2225 ± 3 and 2278 ± 3 cm^{-1}, while the 1900–2000-cm^{-1} region remained totally flat. Because these two values were nearly equally displaced above and below the band positions for **2** and **3** (2260 ± 5 cm^{-1}), perhaps the stretching of the two symmetry-equivalent triple bonds in **4** might be coupled through a combination interaction. Unfortunately, there were bands at 1109 ± 1 (m) and 1141 ± 1 cm^{-1} (s) whose first overtones would be exceedingly close to the above values. The Raman spectrum of **4** proved that the former explanation was indeed correct, by exhibiting bands at 2222 and 2274 cm^{-1} (intensity ratio 9:1, respectively). Again no absorptions were observed in the region 1900–2000 cm^{-1}. The structure of A (= B = **4**) is thus unambiguously confirmed, and the symmetry of the system allows significant vibrational coupling between the triple bonds.

With the structure of **4** secure, what could be said about the mechanism of its formation? As can be seen from Table I, the mode of addition has essentially no effect. If the reactants are mixed immediately, the reaction (25°) proceeds 20% after 1.0 hr and 35% after 1.5 hr (as gauged by monitoring the disappearance of **3** by glc). Yet, even if addition of reactants takes place slowly (1.0 hr), the relative amounts of products are nearly identical.

It was possible that, if the reaction involved dimerization of caged radicals, it might exhibit chemically induced dynamic nuclear polarization (CIDNP)[10] when carried out in an nmr cavity. A solution of **3** in ether was added to a solution of methyllithium in the probe at 35°, and the spectrum was repeatedly scanned. No evidence for enhanced emission or absorption could be detected in the lines of any product throughout the reaction.[11]

It is clear from the lack of addition effects that, regardless of the detailed mechanism, the outcome of each encounter of a methyllithium "molecule" with a molecule of **3** is determined at the instant of that encounter. This is certainly consistent with an all-ionic mechanism such as 1 above. It would be true for mechanism 2 only if the ratio of radical escape (and dimerization to **4**) to collapse (to **1**) were independent of concentration effects. The absence of CIDNP, while suggestive of nonradical pathways forming **1** and **5**, is meaningful for **4** only if the mechanism leading to **4** is dependent on and similar to those leading to **1** and **5**. Finally, we were unable to detect ethane or other products which might have arisen from the methyl radicals required in mechanism 2. For these admittedly inconclusive reasons, we prefer mechanism 1 at this point.

It is significant that, even under such basic conditions as these, **3** is stable toward dehydrochlorination to **8**, even though similar propargyl halides yield enynes under comparable conditions.[3] An authentic sample of **8** was produced by the pyridine-promoted elimination of HCl from **3**, and it was found to be well resolved from **1** and **5** by glc.[12]



8

Finally, the structure of **4** is interesting in another regard. Of all the compounds one might design to cyclize to cyclobutadienes,[13] **4** should be an excellent candidate, owing to the twin *gem*-dimethyl groups,

(8) R. S. Macomber, *J. Org. Chem.*, **37**, 1205 (1972).

(9) It is well known that triple bond stretching absorptions for relatively symmetrically substituted acetylenes are often weak or absent owing to the operation of the dipole moment selection rule in infrared spectroscopy. This limitation is of course lifted in Raman spectroscopy.

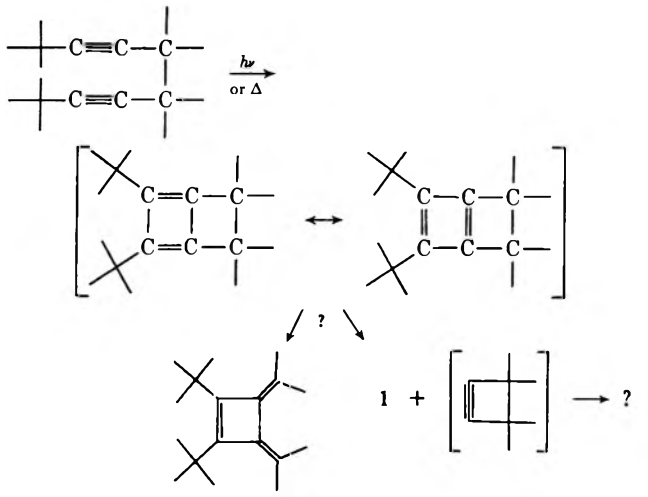
(10) For a recent review on the phenomenon of CIDNP, see H. R. Ward, *Accounts Chem. Res.*, **5**, 18 (1972).

(11) Although this observation is *suggestive* of nonradical processes leading to **1** and **5**, it is of questionable value in the case of **4**. Because **4** is presumed to arise from a symmetrical dimerization ($\Delta g = 0$), net polarization is normally not expected,[10] and only multiplet effects would be anticipated. Since the pmr spectrum of **4** consists solely of singlets, lack of CIDNP in its spectrum does not rule out a radical mechanism for its formation. It should also be noted that the ether proton signals partially obscured those of the products, but any enhanced emission would have been easily observed.

(12) Interestingly, glc analysis of **3** showed significant amounts of **8** (up to 15%) unless the injection port was kept at ambient temperature.

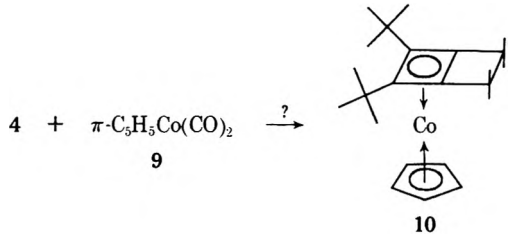
(13) See, for example, W. D. Huntsman and H. J. Wristers, *J. Amer. Chem. Soc.*, **89**, 342 (1967); D. E. Applequist, *et al.*, *ibid.*, **94**, 4272 (1972).

which help favor conformations from which cyclization is accessible.[14]

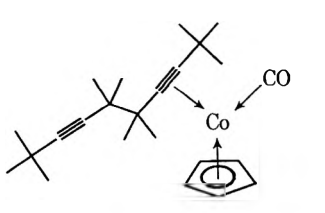


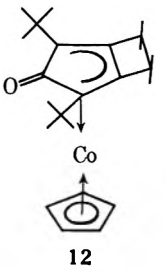
Several experiments were carried out to determine if this was the case. A sample of **4** could be heated to 170° (neat, sealed tube) for 23.5 hr without change. Next, the compound was irradiated at 253.7 nm under a variety of conditions, which included direct irradiation in degassed pentane (see uv spectrum above) and photosensitization by solvent (degassed acetone and benzene). In each case, after irradiation for *ca.* 23 hr, **4** was found to be totally stable; only products arising from primary photoprocesses of the solvents were observed.

A more promising method for stimulating intramolecular cycloadditions of triple bonds has recently been described by King,[15] involving the reaction of π-cyclopentadienylcobalt dicarbonyl (**9**) with cyclic diynes.



Indeed the reaction of **4** with **9** provided in low yield a deep red-orange, air-stable compound (C), but its mass spectrum and elemental analysis disappointingly indicated a molecular formula of $C_{24}H_{35}OCo$, with one retained carbon monoxide. A possible assignment was a structure with only one of the triple bonds coordinated to the cobalt, as in **11**. However, the spectral data for C (Experimental Section) immediately ruled this out. Although the pmr spectrum indeed showed two types of methyl groups (one strongly deshielded at δ 1.54 and one mildly deshielded at 1.27), it showed but one 18-proton singlet for the *tert*-butyl protons. Moreover, the ir spectrum exhibited no bands in the region 2850–1600 cm^{-1}, but a very intense band at 1595 cm^{-1}, ruling out metal carbonyls and triple bonds! A structure which fulfills all the data arises from cycloaddition of the triple bonds in **1** *with a molecule of carbon monoxide* to give a π-cyclopentadienonecobalt complex (**12**), in much the same way that diphenylacetylene reacts with **9**[16] to yield π-cyclopentadienyltetraphenylcyclopentadienonecobalt (ir 1590 cm^{-1}).





Thus, although the *gem*-dimethyl effect should facilitate the cycloaddition as well as stabilizing the product, the ring strain, steric hindrance of the *tert*-butyl groups, and antiaromaticity associated with the incipient bicyclic cyclobutadiene **10** are apparently more significant, and cause a detour to the cyclopentadienone. Nonetheless, this reaction provides even more evidence for the structure of **1**.

Experimental Section

General.—The microanalysis was performed by Chemalytics, Tempe, Ariz. The following instruments were employed: pmr (carbon tetrachloride solution, internal TMS), Varian A-60; mass spectra, Hitachi RMU-7; uv, Cary Model 14; ir, Perkin-Elmer 337. Melting points were determined with sealed capillaries in an oil bath, and *are* corrected. Analytical glc was carried out with a Hewlett-Packard Model 700 (TC detection) equipped with two 10 ft × 0.125 in. aluminum columns packed with 12% squalane on 80/100 Chromosorb W-AW DMSC. Using the separation parameters below, the retention times for all relevant compounds were observed to be as compiled in Table III: injection port[12] 60°; helium flow rate 30 cc/min; column temperature 65° for 2 min, then programmed to 130° at 30°/min.

TABLE III
GLC RETENTION TIMES

Compd	Retention time, min	Response factor[a]
1	1.10	1.00
2	2.60	
3	3.35	
4	7.5	0.795
5	2.40	1.11
8	1.60	
Decane	4.9	

[a] Defined by the equation moles = factor × area, with a value of 1.00 arbitrarily assigned to **1**.

Preparative glc was performed on a Varian Model 700 preparative gas chromatograph, fitted with a 5 ft × 0.25 in. steel column packed with 3% SE-30 on 100/120 Diatomite CLO. The separation parameters were injection port 128°, column temperature 79°, helium flow rate 46 cc/min. Under these conditions the retention times of 1 and 5 were 1.6 and 2.7 min, respectively.

2,5,5-Trimethyl-3-hexyn-2-ol (**2**) was prepared essentially as previously described,[1,2] except that *tert*-butylethynyllithium

(14) For a recent invocation of the *gem*-dimethyl effect, see M. Harfenist and E. Thom, *J. Org. Chem.*, **37**, 841 (1972).

(15) R. B. King and A. Efratz, *J. Amer. Chem. Soc.*, **94**, 3021 (1972).

(16) M. D. Rausch and R. A. Genneti, *J. Org. Chem.*, **35**, 3888 (1970).

(from the acetylene and methyllithium) was substituted for the Grignard reagent. This method gives yields of 70%, about 15% lower than the other method: ^{1}H nmr δ 1.20 (s, 9 H), 1.44 (s, 6 H), 2.12 (s, 1 H); ir 3400 (broad), 2255 cm^{-1}.

2-Chloro-2,5,5-trimethyl-3-hexyne (3) was prepared as before[1,2] by passing HCl gas through a pentane solution of 2 at $-15°$ for 6 hr. The yield was 85%:[12] ^{1}H nmr δ 1.21 (s, 9 H), 1.78 (s, 6 H); ir 2260 cm^{-1}.

Reaction of 3 with Methyllithium (Supplied by PCR). A. Addition of 3 to Methyllithium.—To 15.4 ml (37 mmol) of freshly opened 2.4 *M* methyllithium in ether at room temperature under nitrogen was added a solution of 4.00 g (25.2 mmol) of 3 in 5.0 ml of ether over 60 min. The mixture was stirred magnetically throughout the reaction. The solution became cloudy (suspended lithium chloride) about 30 min after addition ceased. After 24.7 hr 20 ml of water-saturated ether was added to the milky suspension, followed by 7 ml of ether-saturated water, and 2 ml of 1 *N* sulfuric acid to partially neutralize the solution. The ether phase was separated and immediately analyzed by glc. The aqueous phase was neutralized and extracted with 3 × 10 ml of ether. The combined ether solutions were washed once with saturated aqueous sodium chloride and dried at room temperature over molecular sieves. Product isolation is described below.

B. Addition of Methyllithium to 3.—To a solution of 1.77 g (11.2 mmol) of 3 in 2.0 ml of ether at room temperature under nitrogen was added 6.26 ml (15 mmol) of 2.6 *M* methyllithium in ether over 60 min. Cloudiness became apparent immediately. After 24.3 hr the mixture was worked up as above and analyzed.

C. Product Isolation.—The ether solutions from A and B, containing the total products from 36.4 mmol of 3, were combined and found to exhibit the mole ratio of 1:5:4 of 59.8:24.9:15.3. Since 1 mol of 4 derives from 2 mol of 3, the above mixture should contain (assuming quantitative yield) 2.61 g of 1, 1.09 g of 5, and 1.18 g of 4, totaling 4.88 g. The solution was slowly distilled at 1 atm through a 9-in. Vigreux column until nearly all of the ether had been collected (bp 34°). This ether contained $<10^{-2}$ mol % 1. The pot residue (4.90 g), containing 5% ether by glc, was flash distilled down to 0.2 mm into a Dry Ice–acetone cooled receiver. The distillate (2.62 g) was redistilled to yield 2.24 g (45%) of ether, 1, and 5 in the mole ratio 5:69.7:24.1. The boiling point of this mixture was 56–77° (152 mm); earlier fractions were richer in 1, later fractions in 5. When run on the mole scale, distillation alone will separate 1 from 5,[1,2] while at this level preparative glc is preferable.

Di-*tert*-butylacetylene (1)[1-3] had ^{1}H nmr δ 1.17; ir no C≡C discernible.[9]

2,2,3,5-Tetramethyl-3,4-hexadiene (5)[3] had ^{1}H nmr δ 1.01 (s, 9 H), 1.62 (s, 3 H), 1.65 (s, 6 H); ir 1960 cm^{-1}.

Isolation of 4.—The combined semisolid residues from the flash and subsequent distillations were combined (2.6 g) and sublimed at 0.15 mm bulb-to-bulb to give 1.10 g (12%) of crude 4. The sole contaminant was 5% of a minor product with slightly greater retention time.[17] Acetonitrile recrystallizations gave a high recovery of material with mp 109–110°, still contaminated with 3% of the minor product. Three recrystallizations of the crude material from ethanol gave >99% pure 4, mp 112.4–112.7°, but the recovery was only 20–30%. The spectral data for 4 are given in the text.

Reaction of 3 with Pyridine.—To an nmr tube containing 40 mg of 3 and 2 drops of TMS was added 0.4 ml of dry pyridine. The tube was sealed and heated to 88° for 44 hr. Upon cooling the solution deposited crystals of pyridine hydrochloride. The tube was centrifuged and the spectrum of its contents was recorded, showing 100% conversion to 8: ^{1}H nmr δ 1.24 (s, 9 H), 1.87 (d of d, J = 1.5, 0.9 Hz, 3 H), 5.20 (sym m, 1 H), 5.32 (sym m, 1 H). No attempt was made to isolate 8, owing to the known proclivity of enynes toward polymerization. 8 seems to be stable indefinitely at $-15°$ in pyridine.

Thermal Stability of 4.—A 20-mg sample of 4 was sealed in a thick-walled tube and immersed in an oil bath heated to 170°; the sample melted immediately. Heating was continued for 23.5 hr, and the sample crystallized quickly after being removed from the bath. Glc analysis indicated no decomposition, and the melting point was undepressed.

Photochemistry of 4.—The exploratory procedure was as follows: 15 mg of 4 and 7 μl of decane (internal standard) were weighed into a quartz tube (i.d. 5 mm) and exactly 6.0 ml of purified solvent was added. After dissolution was complete the contents were analyzed by glc, degassed, and irradiated using a Srinivasen apparatus fitted with mercury vapor lamps (253.7 nm). After the indicated period, the tubes were again analyzed; the results are given in the text.

Reaction of 4 with 9 (Supplied by Alfa Inorganics).—Following the method of King,[15] a solution of 318 mg (1.29 mmol) of 4 and 238 mg (1.32 mmol) of 9 in 5 ml of octane was heated under nitrogen to 133° for 41.4 hr. The pentane-soluble portion of the product mixture was chromatographed on alumina (activity grade II), eluting first with pentane, then with ether. Unreacted 4 (270 mg, 85%) eluted almost immediately, followed by unreacted 9 (16 mg), a minor band (9.8 mg), then the major product (57 mg crude yield, 79% based on consumed 4). This material was sublimed (87°, 0.05 mm) to yield *ca.* 30 mg of deep red-orange microcrystalline solid: mp 229–233° (without apparent decomposition);[18] ^{1}H nmr (deuteriochloroform, internal TMS) δ 5.09 (s, 5 H), 1.54 (s, 6 H), 1.32 (s, 18 H), 1.27 (s, 6 H); ir (carbon tetrachloride) 2960 (s), 2920 (s), 2865 (m), 1595 (vs), 1484 (m), 1458 (s), 1387 (m), 1369 (m), 1360 (s), 1229 (w), 1190 (w), 1084 (m), 821 (s), 721 cm^{-1} (m); mass spectrum (70 eV) m/e 398 (parent and base peak).

Anal. Calcd for $C_{24}H_{35}OCo$: C, 72.34; H, 8.85. Found: C, 72.79; H, 9.17.

Registry No.—1, 17530-24-4; 2, 1522-16-3; 3, 17553-43-4; 4, 17553-35-4; 5, 17530-17-5; 8, 37439-53-5; 9, 12078-23-8; 12, 37584-03-5; methyllithium, 917-54-4; pyridine, 110-86-1.

Acknowledgment.—The author wishes to express his gratitude to Professor Jack Katon and Mr. Michael Griffin of Miami University (Ohio) for obtaining the Raman spectrum of 4, and to the Research Corporation for partial support in the form of a Frederick Gardner Cottrell Grant. Acknowledgment is further made to the donors of the Petroleum Research Fund administered by the American Chemical Society for partial support of this work. The mass spectrum of 12 was graciously supplied by Dr. Daniel Gartiez, University of Cincinnati Medical School.

(17) The contaminating side product must be chemically and physically quite similar to 4, as judged from its glc characteristics and the fact that sublimation and recrystallization only inefficiently separate it from 4. Evidence that it is neither 6 nor 7 comes from the infrared spectrum of impure 4 containing 30% of the contaminant (from concentrated mother liquors), which showed no trace of absorptions in the 1900–2000-cm^{-1} region.

(18) The yield of 12 is unaffected by doubling the amount of dicarbonyl, or by extending the reaction period to 62 hr. Additionally, it is volatile enough to survive passage through an OV-1 glc column at 225°.

Organophosphorus Enamines. VII. Synthesis and Stereochemistry of Enamine Phosphonates

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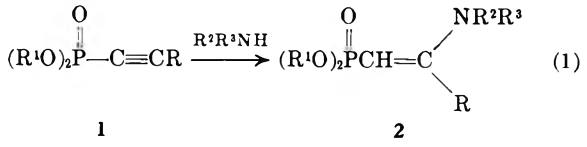
Received August 23, 1972

Recently we reported a general synthesis of diphenyl and dialkyl 1-alkynylphosphonates 1.[2a] The literature contains a very limited amount of information on the nucleophilic addition of amines to the carbon–carbon

(1) The work was initiated at Tulane University, New Orleans, La.

(2) (a) M. S. Chattha and A. M. Aguiar, *J. Org. Chem.*, **36**, 2719 (1971); (b) B. C. Saunders and P. Simpson, *J. Chem. Soc.*, 3351 (1963).

triple bond in **1**.[2b,3,4] We now wish to describe in detail that the addition of primary and secondary aliphatic amines to the triple bond in **1** is rather facile, giving enamine phosphonates **2** in fair to good yields (eq 1).



(1)

1 **2**

R = alkyl, phenyl; R^1 = ethyl, phenyl; R^2 = alkyl; R^3 = alkyl, H

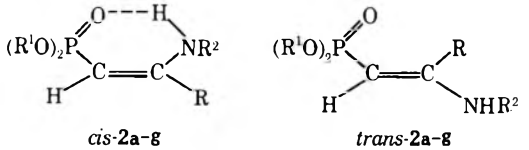
Enamine phosphonates **2** produced in this manner are listed in Table I together with their boiling points and yields.

TABLE I
ENAMINE PHOSPHONATES 2[a]

Compd	R	R^1	R^2	R^3	Bp, °C (mm)	Yield, %
2a	*n*-C_4H_9	C_2H_5	*n*-C_4H_9	H	126–127 (0.07)	81
2b	*n*-C_6H_{13}	C_2H_5	*n*-C_4H_9	H	136–138 (0.07)	82
2c	C_6H_5	C_2H_5	*n*-C_4H_9	H	135–136 (0.05)	72
2d	*n*-C_4H_9	C_2H_5	*t*-C_4H_9	H	108–109 (0.05)	73
2e	*n*-C_6H_{13}	C_2H_5	*t*-C_4H_9	H	134–136 (0.08)	90
2f	C_6H_5	C_2H_5	*t*-C_4H_9	H	129 (0.08)	76
2g	CH_3	C_6H_5	*t*-C_4H_9	H	192–193 (0.06)	65
2h	*n*-C_4H_9	C_2H_5	C_2H_5	C_2H_5	121 (0.06)	80
2i	$C_6H_5CH_2CH_2$	C_2H_5	C_2H_5	C_2H_5	163–164 (0.04)	79

[a] Satisfactory analytical data (C, H, N, P) were reported for all new compounds listed in the table; exceptions were **2c** (P 0.68% high) and **2g** (H 0.82% low).

The ir spectra of all of the compounds **2a–i** show strong absorption in the region of 6.25–6.46 μ (C=C). The nmr spectra of enamines **2a–g** (R^2 = alkyl, R^3 = H) display the amino proton signal at two different chemical shifts (Table II), which indicates that **2a–g** (R^2 = alkyl, R^3 = H) exist as cis–trans mixtures as shown below.



cis-**2a–g** *trans*-**2a–g**

Considering the deshielding effect of the phosphonate group, the lower field amino proton signal has been assigned to the cis isomer and the higher field signal to the trans isomer. Similar differences in chemical shifts for various protons are used as the basis for assignment of configuration. For example, in the nmr spectrum of compounds **2g** (R = CH_3, R^1 = C_6H_5, R^2 = *t*-C_4H_9, R^3 = H), the doublet (J = 2 Hz) at δ 2.17 has been assigned to the propenyl methyl protons when this methyl group lies cis to the phosphonate group (*trans*-**2g**), and the doublet (J = 2 Hz) at δ 2.08 is assigned to the propenyl methyl protons when the methyl group is trans to the phosphonate group (*cis*-**2g**). Similarly the *tert*-butyl group in **2g** displayed resonances at two different chemical shifts (δ 1.26, 1.28); the lower field signal has been assigned to the cis isomer and the higher field signal to the trans isomer. The chemical shifts of the α-vinyl protons can also be used to assign configurations and provide supporting evidence for the configurational assignments based on the amino proton shifts.[5–7]

This method also permits configurational assignments in the absence of amino protons. In compounds **2a–g**, a cis relationship between the amino group and the vinyl proton is indicated by a larger chemical shift of the vinyl proton (see Table II). In compounds **2c–f**, the vinyl proton signals of the trans isomers were found to be obscured by the methylene proton signals from the *O*-ethyl groups. With the application of a strong field (100 MHz), both the vinyl proton signals in **2d,e** could be identified but, in the spectra of **2c** and **2f**, only the higher field proton signal could be seen clearly. However, in **2f**, the *tert*-butyl group signals due to both the isomers could be seen distinctly (δ 1.10, 1.43) in the 60-MHz nmr spectrum; all the chemical shifts listed in Table II represent 60-MHz spectra.

Compounds **2h,i**, resulting from the addition of diethylamine to 1-alkynylphosphonates **1**, seem to exist only in one stereochemical form, as indicated by the presence of only one doublet (J = 8.5 Hz) due to the vinyl proton. These two compounds, **2h,i**, were assigned the trans configuration, since in the most stable configuration the electron-releasing and the electron-withdrawing groups should lie trans to each other.[6,8] In enamines **2a–g**, the cis isomer also exists because of the stability gained by it through hydrogen bonding between the amino proton and the oxygen atom (P=O). The presence of hydrogen bonding was demonstrated by taking ^1H nmr ($CDCl_3$) spectra of **2g** at different concentrations. The higher field chemical shift due to the amino proton (trans isomer) was found to be concentration dependent, while the lower field signal (cis isomer) had a constant chemical shift. This is because, in the cis isomer, the amino proton is already hydrogen bonded and is not significantly affected by the change in concentration, while, in the trans isomer, the increasing dilution with deuteriochloroform shifts the amino proton signal toward the lower field. Further support for the presence of the two isomers, one of which has the amino proton involved in the intramolecular hydrogen bonding, comes from the observation of two weak bands at 2.95 and 2.31 μ in the infrared spectra of **2a–g**.

The trans addition of amines to carbon–carbon triple bonds activated by the phosphoryl group has been described.[5] Through nmr studies it has also been demonstrated that, on raising the temperature, the cis

(3) A. N. Pudovik, N. G. Khusainova, and A. B. Agreeva, *Zh. Obshch. Khim.*, **34**, 3938 (1964).
(4) M. S. Chattha and A. M. Aguiar, *Tetrahedron Lett.*, 1419 (1971).
(5) W. Hagens, H. J. T. Bos, W. Voskuil, and J. R. Arens, *Recl. Trav. Chim. Pays-Bas*, **88**, 71 (1969).
(6) W. E. Truce and D. G. Brady, *J. Org. Chem.*, **31**, 3543 (1966).
(7) C. J. M. Stirling, *J. Chem. Soc.*, Suppl. I, 5863 (1964).
(8) G. Isaksson, J. Sandstrom, and I. Wennerbeck, *Tetrahedron Lett.*, 2233 (1967).

TABLE II
DISTRIBUTION OF ISOMERS[a] AND NMR[b] DATA FOR ENAMINE PHOSPHONATES 2a–i

Compd	Isomer % cis	Isomer % trans	Cis PCH δ	Cis PCH J, Hz	Trans PCH δ	Trans PCH J, Hz	NH, δ cis	NH, δ trans	CH_2OP, δ, qn (J = 7.5, 15 Hz)	Other proton chemical shifts, δ
2a	50	50	3.60	13	3.76	10.5	7.32	5.59	4.05	3.08 (m, NCH_2), 2.55 (m, allyl), 1.34 (m, containing t, J = 7 Hz, 20 H)
2b	55	45	3.50	13	3.72	10.5	7.28	5.12	4.03	3.04 (m, NCH_2), 2.45 (m, allyl), 1.28 (m containing t, J = 7 Hz, 24 H)
2c	80	20	3.82	13			7.51	5.22	4.08	7.42 (C_6H_5), 2.92 (m, NCH_2), 1.30 (m, 13 H)
2d	15	85	3.62	13	3.75	11	7.36	4.46	4.02	2.42 (m, allyl), 1.32 (m containing t, J = 7 Hz, 22 H)
2e	10	90	3.67	13	3.74	11	7.42	4.36	4.05	2.43 (m, allyl), 1.36 (m containing t, J = 7.5 Hz, 26 H)
2f	15	85	3.79	13			7.23	4.54	4.11	7.42 (C_6H_5), 1.32 (t, J = 7.5 Hz, CH_3CO), 1.43 and 1.10 (two s, *tert*-butyl)
2g	30	70	3.63	13	4.15	11	7.12	4.39		7.35 (C_6H_5), 2.15 and 2.08 (two d, J = 2 Hz, allyl), 1.28 and 1.26 (two s, *tert*-butyl)
2h		100			3.75	8.5			4.05	3.25 (q, J = 7.5 Hz, NCH_2), 2.65 (m, allyl), 1.31 (m containing two t, J = 7, 7.5 Hz, 19 H)
2i		100			3.87	8.5			4.10	7.32 (C_6H_5), 3.25 (q, J = 7.5 Hz, NCH_2), 2.90 (s, allyl and benzyl), 1.25 (t, J = 7 Hz, CH_3CO), 1.15 (t, J = 7 Hz, CH_3CN)

[a] Configuration cis and trans refer to the amino and the phosphonate groups being cis or trans to each other. [b] In the nmr description, s, d, t, q, qn, and m represent a singlet, doublet, triplet, quartet, quintet, and multiplet, respectively.

isomer rapidly isomerized to the trans product.[6] Conceivably, the trans addition of amines to 1-alkynylphosphonates **1** results in the cis isomers, which, on heating, isomerize to the trans products. Under the reflux conditions employed in this investigation, a different mode of addition may also be taking place.[5,6]

The isomerization of the cis to the trans isomers is in accordance with the concept that the electron-withdrawing substituents on one end and electron-releasing substituents on the other end of the double bond favor cis–trans isomerization.[5,6,8] The excess of amine in the reaction mixture may also be playing some role in the cis–trans isomerization.

A comparison of the amounts of cis and trans isomers in adducts **2a–c** (N-*n*-C_4H_9) and **2d–g** (N-*t*-C_4H_9) shows that the greater steric requirements of the *N*-alkyl group result in the increasing amount of the trans product. In compound **2c** (R = C_6H_5), the cis isomer predominates because the phenyl ring is probably in conjugation with the ring formed through hydrogen bonding of the amino proton to the oxygen atom of the phosphonate group. However, in adduct **2f** (R = C_6H_5), resulting from the addition of *tert*-butylamine to **1** (R = C_6H_5), this effect is found to be offset by the bulkiness of the *tert*-butyl group and the trans isomer predominates.

Experimental Section

The amines were dried over potassium hydroxide pellets and the starting 1-alkynylphosphonates **1** were redistilled before use. The nmr spectra were determined on a Varian A-60 and 100 MHz spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard. Chemical analyses were performed by Geller Microanalytical Laboratories, Saddle River, N. J.

Preparation of Enamine Phosphonates 2a–i. General Procedure.—The 1-alkynylphosphonates **1** were refluxed with a 10–12 molar excess of the amines. The reflux was continued for 3–6 days until the ir spectra of a test portion of the reaction mixture showed almost complete disappearance of the absorption band in the region of 4.5–4.6 μ (C≡C). The excess amines were evaporated *in vacuo* at aspirator pressure. The resulting adducts were short path distilled at reduced pressure from anhydrous potassium carbonate.

Registry No.—**1a**, 3450-61-1; **1b**, 3450-66-6; **1c**, 3450-67-7; **1g**, 3095-09-8; **1i**, 30238-19-8; *cis*-**2a**, 37692-17-4; *trans*-**2a**, 37692-18-5; *cis*-**2b**, 37692-19-6; *trans*-**2b**, 37692-20-9; *cis*-**2c**, 37692-21-0; *trans*-**2c**, 37692-22-1; *cis*-**2d**, 37692-23-2; *trans*-**2d**, 37692-24-3; *cis*-**2e**, 37692-25-4; *trans*-**2e**, 37692-26-5; *cis*-**2f**, 37692-27-6; *trans*-**2f**, 37692-28-7; *cis*-**2g**, 37692-29-8; *trans*-**2g**, 37692-30-1; *trans*-**2h**, 37755-04-7; *trans*-**2i**, 37692-31-2; butylamine, 109-73-9; diethylamine, 109-89-7; *tert*-butylamine, 109-73-9.

Acknowledgment.—We wish to acknowledge the National Institutes of Health for support of this work under Grant GM-16828 and the National Science Foundation under Grant GP-10739. We also wish to thank Hoffmann-La Roche, Inc., Nutley, N. J., for their unrestricted grant which helped us to complete this work.

Reductive Cleavage of Phenylhydrazones of α-Keto Acids to Amino Acids

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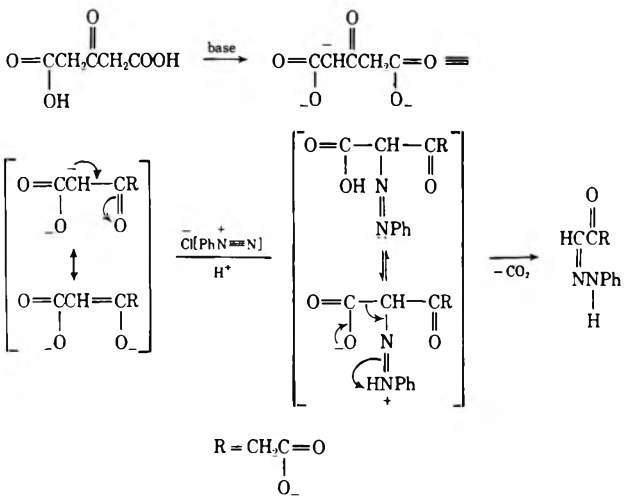
Reductive cleavage of phenylhydrazones of α-keto acids is an important method for the synthesis of α-amino acids, because of the easy availability of these phenylhydrazones by the Japp–Klingemann reaction.[1] This reaction, which takes place between a phenyl-

(1) R. F. Japp and F. Klingemann, *Ber.*, **20**, 2942, 3284, 3398 (1887).

diazonium salt and a reactive methylene group, may be exemplified with reference to β-oxoglutaric acid.



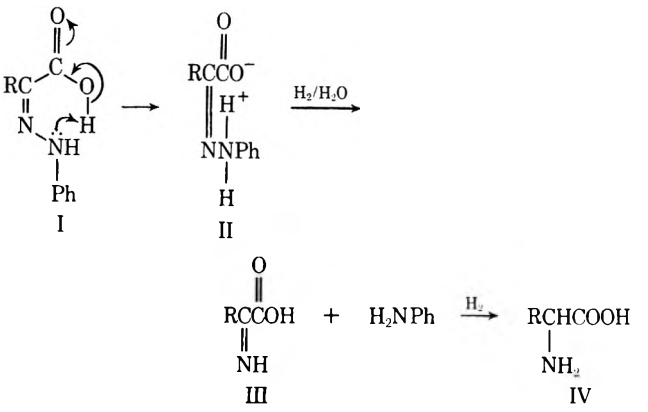
The phenylhydrazones are thus obtained in good yields and in a one-step operation.

Phenylhydrazones thus obtained were subsequently reduced by Feofilaktov and his associates[2-9] to the corresponding amino acids by means of zinc dust in acidic medium at 0°. Our attempts at following this procedure[4] were not successful. The isolation of the amino acid from the reaction mixture was unsatisfactory, as it involved several operations. Another undesirable feature of the procedure is that the conditions employed also favor Fischer cyclization to the corresponding indoles.[10]

In view of these facts we have attempted different methods of reductive cleavage of phenylhydrazones of α-keto acids to the corresponding amino acids. Sodium hydrosulfite and sodium sulfite have been successfully used in the reduction of diazonium compounds,[11] but these reagents proved ineffective in the reduction of phenylhydrazones of α-keto acids.

Zinc dust in 75% alcohol in the presence of mercuric chloride was quite satisfactory and gave glycine, valine, and phenylalanine in 43, 74, and 55% yields, respectively. Mercuric chloride could be replaced by calcium chloride without any loss in the yields of the amino acids. Zinc dust in alkaline medium (sodium hydroxide or ammonium hydroxide) did not reduce pyruvic acid phenylhydrazone satisfactorily. By using zinc dust in acetic acid, alanine, valine, and phenylalanine could be obtained in 50, 53, and 48% yields, respectively. Formic acid alone did not effect reductive cleavage of phenylhydrazones to amino acids, but cyclized them to indoles.[12] Sodium and ammonium formates were useful neither for cyclization nor for the reductive cleavage of the phenylhydrazones. Catalytic reduction of α-oximino acids to amino acids has been successful in an acidic medium.[13,14] In the case of phenylhydrazones of α-keto acids, acidic conditions had to be avoided lest Fischer indole cyclization take place.

Nitrogen attached to the aromatic nucleus has a great tendency to undergo protonation, thus making it a potential electron-withdrawing group, necessary for the cleavage of the N–N linkage as represented. It was felt, however, that in the six-membered transition state the proton migrates to nitrogen so as to form the inner salt II which could provide the driving force for



cleavage of the N–N bond and hydrogenation under neutral conditions should thus also lead to amino acids.

This expectation was fully realized when it was found that alcoholic solutions of phenylhydrazones of α-keto acids, when subjected to reduction with palladium over carbon, platinum, or palladium at room temperature and pressure, took up hydrogen readily with precipitation of the amino acid formed.

Reduction in alcoholic medium had one disadvantage. The phenylhydrazone is soluble in alcohol while its reduction product, the amino acid, in many cases is not. The result is that, as reduction proceeds, the precipitated amino acid sticks to the catalyst and makes it ineffective. Fortunately, it has been found that aqueous suspensions of phenylhydrazones can be advantageously used for catalytic reduction. As reduction proceeds, the phenylhydrazones go into solution and the amino acid produced also remains in solution in most cases. When reduction is complete, the catalyst is filtered off and the filtrate is washed with ether. The concentration of the aqueous layer afforded the desired pure amino acid in high yield.

Table I shows the amino acids obtained by catalytic reduction of phenylhydrazones of α-keto acids.

Experimental Section

Phenylhydrazones used in this work were prepared by the Japp-Klingemann reaction. Only pyruvic acid phenylhydrazone and levulinic acid phenylhydrazones were prepared from their respective keto acids. Satisfactory analyses were obtained for all the reported compounds. Melting points were taken on a Gallenkamp melting point apparatus in open capillaries and are uncorrected. Hydrogenation was conducted in a

(2) V. V. Feofilaktov and V. N. Zaitseva, *J. Gen. Chem. USSR*, **10**, 258, 1391 (1940).
(3) V. V. Feofilaktov, *C. R. Acad. Sci. URSS*, **24**, 755 (1939); *J. Gen. Chem. USSR*, **10**, 247 (1940).
(4) V. V. Feofilaktov and E. Vinogradova, *C. R. Acad. Sci. URSS*, **24**, 759 (1939); *J. Gen. Chem. USSR*, **10**, 225, 258 (1940); **21**, 399, 1684 (1951); **23**, 463, 699 (1953).
(5) V. V. Feofilaktov and N. K. Semenova, *J. Gen. Chem. USSR*, **23**, 887 (1953).
(6) V. V. Feofilaktov, *Bull. Acad. Sci. URSS, Cl. Sci. Chem.*, 521 (1941); *Chem. Abstr.*, **37**, 2347 (1943).
(7) V. V. Feofilaktov and F. Blanko, *J. Gen. Chem. USSR*, **11**, 859 (1941).
(8) V. V. Feofilaktov and A. Onischenko, *C. R. Acad. Sci. URSS*, **20**, 133 (1938).
(9) V. V. Feofilaktov and T. N. Ivanova, *Zh. Obshch. Khim.*, **21**, 1684 (1951); *J. Gen. Chem. USSR*, **21**, 1851 (1951).
(10) R. R. F. Manske, E. Robinson, and W. H. Perkin, Jr., *J. Chem. Soc.*, 1 (1927).
(11) J. B. Conant, R. E. Lutz, and B. B. Corson, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1946, p 49.
(12) A. R. Kidwai and N. H. Khan, *C. R. Acad. Sci.*, **256**, 3709 (1963).
(13) K. E. Hamlin and W. H. Hartung, *J. Biol. Chem.*, **145**, 349 (1942).
(14) D. Shemin and R. M. Herbst, *J. Amer. Chem. Soc.*, **60**, 1951 (1938).

TABLE I

Registry no.	Phenylhydrazone of	Catalyst	Solvent[b]	Conditions of reduction[a]	Amino acid obtained	Registry no.	Yield, %	Time, hr	Remarks
6000-60-8	Glyoxylic acid	Pd/C	A	X	Glycine	56-40-6	96	6	
10475-63-5	Ethyl α,β-diketobutyrate	Zn, $HgCl_2$	B	Y	Glycine		43	4	
5330-70-1	Pyruvic acid	Pd/C	A	X	Alanine	302-72-7	92	6	
		PdO	A	X	Alanine		98	6	
		PtO	A	X	Alanine		42	6	
		Zn, $CaCl_2$	B	Y	Alanine		60	4	
		Zn, AcOH	B	Y	Alanine		50	4	
36963-34-5	α-Ketoisovaleric acid	Pd/C	A	X	Valine	516-06-3	85	6	
		PtO	A	X	Valine		17		
		Zn, $HgCl_2$	B	Y	Valine		74		
		Zn, $CaCl_2$	B	Y	Valine		75		
		Zn, AcOH	B	Y	Valine		53		
36963-35-6	α-Ketocaproic acid	Pd/C	A	X	Norleucine	616-06-8	94	5	
		PdO	D	X	Norleucine		92	6	
36963-36-7	α-Ketoisocaproic acid	Pd/C	A	X	Leucine	328-39-2	87	6	
36963-37-8	α-Keto-*sec*-caproic acid	Pd/C	A	X	Isoleucine	443-79-8	83	6	
36963-38-9	Phenylpyruvic acid	Pd/C	A	X	Phenylalanine	150-30-1	88	6	
		PtO	A	X	Phenylalanine		80	6	
		PtO	C	X					Not completely hydrogenated
		Zn, $HgCl_2$	B	Y	Phenylalanine		55	4	
		Zn, $CaCl_2$	B	Y	Phenylalanine		58	4	
		Zn, AcOH	B	Y	Phenylalanine		48	4	
		Zn, NaOH	B	Y					No reduction
		Am, Formate	B	Y					No reduction
		Na, Formate	B	Y					No reduction
		HCOOH		Y	3-Phenylindole-2-carboxylic acid[c]				
36963-39-0	*p*-Methoxyphenylpyruvic acid	Pd/C	A	X	*O*-Methyltyrosine	7635-29-2	95	6	
		PtO	A	X	*O*-Methyltyrosine		91	6	
123-76-2	Levulinic acid	Pd/C	A	X	γ-Aminovaleric acid	627-61-2	94	6	

[a] X = room temperature and pressure; Y = reflux temperature and pressure. [b] A = water; B = aqueous alcohol (78%); C = absolute alcohol; D = alcohol (95%). [c] Reference 12.

semimicro Tower's hydrogenation apparatus at room temperature and pressure. Yields and melting points reported in this work are of analytically pure products.

DL-**Valine.**—Powdered α-ketoisovaleric acid phenylhydrazone[15] (0.5 g) was suspended in 50 ml of water in a hydrogenation flask containing 0.5 g of 5% Pd/C. Absorption was complete in 6 hr. The catalyst was filtered off. The filtrate on evaporation on a water bath under reduced pressure gave a residue which was thrice washed with 10-ml portions of ether and then thrice with 10-ml portions of cold alcohol. The alcohol-insoluble residue on drying weighed 0.25 g (89%), mp 276° dec on rapid heating. The crude amino acid was dissolved in 5 ml of hot water and subsequently diluted with 15 ml of alcohol. This was allowed to stand overnight in a refrigerator. The crystalline amino acid obtained on filtration weighed 0.245 g, mp 286° dec with rapid heating, mmp 286° with an authentic sample (lit.[16a] mp 293°, lit.[16b] mp 280–282°).

N-Benzoyl-DL-valine was prepared from 0.25 g of DL-valine, 4 ml of 1 *N* sodium hydroxide solution, and 0.5 ml of benzoyl chloride by the usual Schotten–Baumann reaction. The crude derivative after recrystallization from benzene–petroleum ether (bp 40–60°) melts at 131.5° (lit.[17] mp 132°).

N-(*p*-Toluenesulfonyl)-DL-valine was obtained by usual method, mp 166.5° (lit.[18] mp 166–167°), mmp 166.5° with an authentic sample.

DL-**Phenylalanine.**—Phenylpyruvic acid phenylhydrazone[19] (2.5 g) was reduced using 5% Pd/C to give 1.4 g of amino acid, mp 265° dec,[4] benzoyl derivative mp 181.5°,[20] *p*-toluenesulfonyl derivative mp 134–135°.[21,22]

γ-Aminovaleric Acid. Levulinic Acid Phenylhydrazone.—Levulinic acid (10.2 ml, 0.1 mol) was dissolved in 80 ml of water. Phenylhydrazine (9.8 ml) containing acetic acid (1 ml) was added with stirring. In a few minutes straw-colored phenylhydrazone was obtained. This was washed and dried, mp 102°, yield 20.8 g (100%). On recrystallization from benzene–petroleum ether, the melting point was raised to 106.5° (lit.[23] mp 108°).

DL-**γ-Aminovaleric Acid.**—Levulinic acid phenylhydrazone (1.6 g) on hydrogenation over 5% Pd/C (0.6 g) for 5 hr gave DL-γ-aminovaleric acid, mp 191° dec, yield 0.85 g (93.6%) (lit.[16a] mp 193°).[24]

N-Benzoyl-DL-aminovaleric acid was prepared from DL-γ-aminovaleric acid (0.5 g) and benzoyl chloride (0.5 ml). Recrystallization twice from benzene–petroleum ether yielded *N*-benzoyl-DL-γ-aminovaleric acid, mp 135.5° (lit.[16a] mp 132°).

DL-**α-Alanine. A.**—A mixture of pyruvic acid phenylhydrazone (1 g) dissolved in alcohol (30 ml, 78%), zinc dust (8 g), and calcium chloride (0.2 g) was heated under reflux for 4 hr and then filtered hot. The zinc sludge was washed with two 20-ml portions of boiling water. The combined filtrate and washings were saturated with water-washed hydrogen sulfide gas, boiled, and filtered. This process of passing hydrogen sulfide was repeated to ensure complete removal of zinc. The filtrate obtained was concentrated to dryness under reduced pressure. The residue was dissolved in water (15 ml) and extracted with ether. The aqueous layer was boiled with active carbon (1 g) and filtered. The filtrate was concentrated to 5 ml under reduced pressure and then diluted with alcohol (15 ml, 95%). The contents were cooled overnight in a refrigerator. The crystalline amino acid was filtered, dried, and weighed, 0.3 g, mp 285° dec, yield 60%. The ether layer was extracted with sodium bicarbonate solution (5%). The alkaline solution thus obtained was heated on a steam bath to remove dissolved ether, treated with active carbon, and filtered. The clear filtrate on acidification with hydrochloric acid (10%) gave 0.1 g of unreduced product, mp 168–170°.

B.—Pyruvic acid phenylhydrazone (10 g) was dissolved in alcohol (300 ml, 75%) in a 1-l. flask. To this zinc dust (75 g) and mercuric chloride (1 g) were added and the mixture was heated under reflux on a steam bath for 8 hr and filtered hot. Zinc dust was washed with three 20-ml portions of hot water. The filtrate and aqueous washings were combined and saturated with hydrogen sulfide gas (water washed), boiled, and filtered. The filtrate was evaporated to dryness under reduced pressure on a steam bath. The dry substance thus obtained was washed

(15) V. V. Feofilaktov and V. N. Zaitseva, *J. Gen. Chem. USSR*, **10**, 1391 (1940).

(16) (a) L. Senfter and J. Tafel, *Ber.*, **27**, 2313 (1894); (b) C. S. Marvel, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 848.

(17) M. D. Slimmer, *Ber.*, **35**, 402 (1902).

(18) A. E. Beecham, *J. Amer. Chem. Soc.*, **79**, 3257 (1957).

(19) W. Wislecenus, *Ber.*, **20**, 593 (1887).

(20) E. Erlenmeyer, Jr., *Justus Liebigs Ann. Chem.*, **275**, 15 (1893).

(21) W. E. McChesney and W. K. Swan, Jr., *J. Amer. Chem. Soc.*, **59**, 1116 (1937).

(22) T. Oseki, *Bull. Chem. Soc. Jap.*, **41**, 8 (1920).

(23) E. Fischer, *Justus Liebigs Ann. Chem.*, **236**, 146 (1886).

(24) J. Tafel, *Ber.*, **19**, 2415 (1886).

several times with 20-ml portions of dry ether until the ether washings were colorless. The ether-insoluble residue was dissolved in 10 ml of hot water to which 35 ml of alcohol (95%) was added and the contents were cooled in a refrigerator overnight. Next morning this was filtered and the crystalline amino acid was dried, 2.8 g, mp 285° dec. Mother liquor was concentrated to 6 ml, diluted with alcohol (20 ml, 95%), and cooled. A further amount of alanine (0.9 g) was obtained, yield 74%. The amino acid obtained in this manner was recrystallized from aqueous alcohol when pure alanine (3.5 g), mp 288° dec, was obtained, yield 70%. A mixture melting point with DL-α-alanine (BDH) showed no depression.

The Reactions of 2-Diazo-3-butanone and 2-Diazocyclopentanone with Dimethyl Acetylenedicarboxylate

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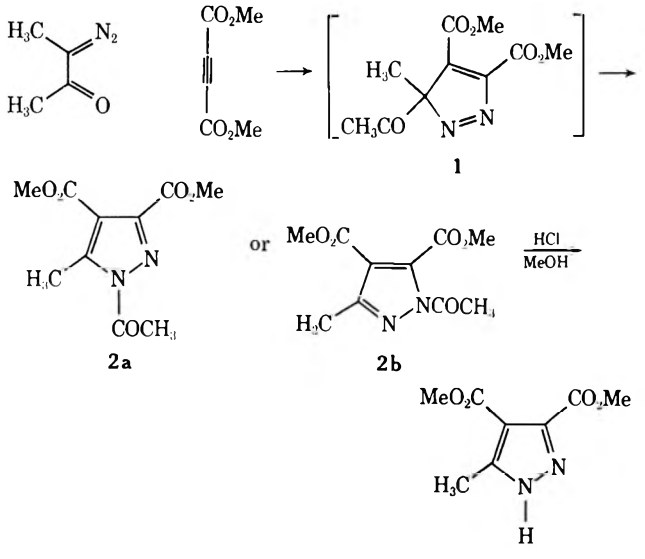
The product from the reaction of 2-diazo-3-butanone with dimethyl acetylenedicarboxylate (DMAD) was first assigned a dimethyl 3-acetyl-3-methyl-3*H*-pyrazole-4,5-dicarboxylate structure (**1**) by Diels and König.[1] Franck–Neumann and Buchecker report that this product is, in fact, an *N*-acetylpyrazole (**2a** or **2b**) resulting from thermal rearrangement of **1** with isomer **2a** being preferred on mechanistic grounds.[2,3]



We had also investigated this reaction and reached the same conclusions as Franck–Neumann and Buchecker. However, in view of the fact that *N*-acylpyrazoles are known to undergo thermal isomerization,[4,5] we felt that additional evidence was needed to confirm that **1** rearranged to **2a** and not to **2b**.

(1) O. Diels and H. König, *Chem. Ber.*, **71**, 1179 (1938).
(2) M. Franck-Neumann and C. Buchecker, *Tetrahedron Lett.*, 937 (1972).
(3) Similar rearrangements of diazocyclopentadiene–acetylene adducts have been reported recently: H. Düss and R. Sergio, *ibid.*, 3479 (1972).
(4) R. H. Wiley, Ed., in "Chemistry of Heterocyclic Compounds," Vol. 22, A. Weissberger, Ed., Interscience, New York, N. Y., 1967, p 137, and references cited therein.
(5) J. Castells, *Chem. Commun.*, 709 (1972).

Treatment of the 2-diazo-3-butanone–DMAD product with hot methanolic HCl gave dimethyl 3(5)-methylpyrazole-4,5(3,4)-dicarboxylate (**3**).[6] Acetylation of **3** under different conditions permitted the isolation of pure **2a** and **2b**. Treatment of **3** with acetic anhydride gave isomer A (identical with the 2-diazo-3-butanone–DMAD product) as the major product, whereas with acetyl chloride and pyridine in ether at room temperature the other isomer (B) was formed almost exclusively.

The results of thermal isomerization studies on A and B (Tables I and II) show A to be the more thermodynamically stable isomer. The data suggest, however, that B would not isomerize appreciably to A under the conditions used in the 2-diazo-3-butanone–DMAD reaction (refluxing ether, 2 hr). Thus, the presence of only A in the product indicates that the intermediate 3*H*-pyrazole (**1**) rearranges directly and entirely to A.

Unlike the spectroscopic properties listed above, the ultraviolet spectra of A and B were significantly different (Table III). The assignment of structures to A and B on the basis of this difference is discussed below.

Franck–Neumann and Buchecker referred to an investigation of the reactions of cyclic α-diazo ketones with DMAD but presented no results.[2] We have

TABLE I

	N-acetyl isomer mixture (by vpc) %A	%B
Ac2O, 24°, 2 hr	72	28
Ac2O, reflux, 2 hr	80	20
AcCl, pyridine	8	92
Et2O, 22°, 2.5 hr		

	A (2-Diazo-3-butanone–DMAD product)	B
Mp, °C	66–67	51–53
ν_{max} ($CHCl_3$), cm^{-1}	1742 (broad, ester, amide)	1739 (broad, ester, amide)
Nmr ($CDCl_3$), δ, ppm	2.75 (3 H, s)	2.50 (3 H, s)
	2.81 (3 H, s)	2.70 (3 H, s)
	3.88 (3 H, s)	3.87 (3 H, s)
	3.97 (3 H, s)	4.02 (3 H, s)

TABLE II

THERMAL ISOMERIZATION OF A AND B

Isomer	Temp, °C	Time	Product[a] % A	% B
A	Ambient	15 months	100	0
B	Ambient	15 months	>99[b]	<1
A	53	16 hr	100	0
B	53	16 hr	5	95
A	90	16 hr	100	0
B	90	16 hr	73	27
A	250	30 min	73	27
B	250	30 min	71	29
A	Reflux, ether	24 hr	100	0
B	Reflux, ether	24 hr	5	95

[a] By vpc analysis. [b] Melting point changed from 51–53° to 66–67°.

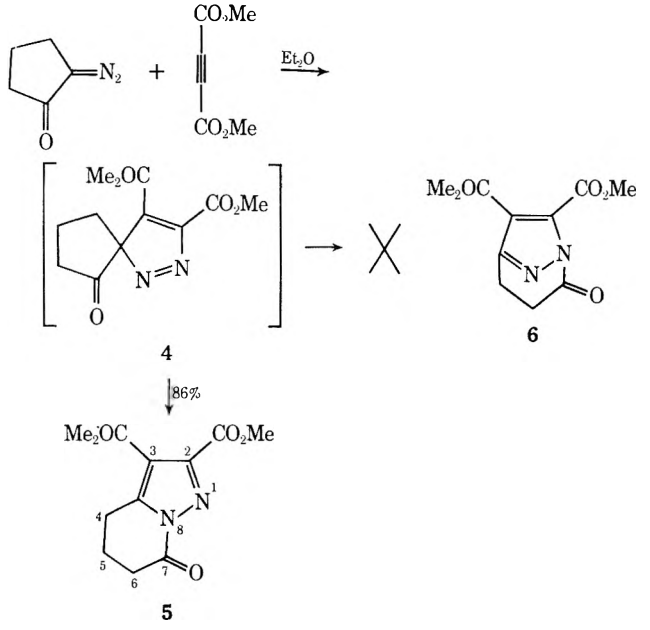
(6) H. Reimlinger, *Chem. Ber.*, **93**, 1857 (1960).

TABLE III

Compd	λ_{max}, nm (ϵ)[a]
A (2a)	237 (8700)
5	240 (8200)
B (2b)	251 (13,400)

[a] In 95% EtOH.

studied the reaction of 2-diazocyclopentanone[7] with DMAD.[8] Physical data confirmed that the product was dimethyl-4,5-dihydro-7(6*H*)-oxopyrazolo[1,5-*a*]pyridine-2,3-dicarboxylate (**5**) (rearrangement of the intermediate 3*H*-pyrazole **4** to **6** would violate Bredt's rule).



The similarity between the uv spectra of **5** and A (Table III) provides considerable support for the assignment of the dimethyl 1-acetyl-5-methylpyrazole-3,-4-dicarboxylate (**2a**) structure to the 2-diazo-3-butanone–DMAD product (isomer A) and the dimethyl 1-acetyl-3-methylpyrazole-4,5-dicarboxylate (**2b**) structure to isomer B.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Nmr spectra were recorded on Varian A-60A and HA60 instruments at 60 MHz in 5–10% deuteriochloroform solution with tetramethylsilane as an internal standard. Infrared spectra were obtained with a Perkin-Elmer Model 21 in chloroform solution, and ultraviolet spectra were determined in 95% ethanol solution on a Carey Model 15. Vpc analyses were performed on a Hewlett-Packard Model 402 instrument equipped with a flame ionization detector. A 4 ft × 4 mm, 3% OV-1 on Chromosorb W (HP) 80/100 mesh column at 125° and a He flow rate of 60 ml/min were used. Mass spectral data were obtained on a CEC Model 110 spectrometer.

Dimethyl 3(5)-Methylpyrazole-4,5(3,4)dicarboxylate (3).—A solution of 2.5 g (10.4 mmol) of the 2-diazo-3-butanone–DMAD adduct[1] in 140 ml of methanol and 0.5 ml of concentrated HCl was heated under reflux for 20 min and poured into 500 ml of water. The mixture was extracted with 3 × 50 ml of CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated. The residual oil was crystallized from benzene–hexane to give 1.7 g (82%) of **3** as tan crystals: mp 104–106° alone and mixed with an authentic specimen prepared from the reaction of diazoethane with DMAD;[6] ir 3425, 3180 (broad, NH), 1724 cm^{-1} (broad, C=O); nmr δ 2.52 (s, 3 H), 3.87 (s, 3 H), 3.91 (s, 3 H); mass spectrum *m/e* 198 (M^+).

Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.70; H, 5.34; N, 14.33.

Dimethyl 1-Acetyl-5-methylpyrazole-3,4-dicarboxylate (2a, Isomer A).—A solution of 0.7 g (3.54 mmol) of **3** in 20 ml of acetic anhydride was heated under reflux for 2 hr and then concentrated at 50° under reduced pressure. The residual oil was shown by vpc to contain isomers A (retention time 16 min) and B (retention time 12 min) in an 80:20 ratio (Table I). Crystallization from ether/Skelly B gave 0.5 g (59%) of **2a** (isomer A) (homogeneous by vpc) as colorless needles, mp 64–66° alone and mixed with 2-diazo-3-butanone–DMAD adduct.[1] Ir and nmr are presented in Table I and uv in Table III.

Acetylation of **3** in acetic anhydride at 24° for 24 hr gave a 72:28 mixture of isomers A and B (vpc, Table I).

Dimethyl 1-Acetyl-3-methylpyrazole-4,5-dicarboxylate (2b, Isomer B).—A mixture of 1 g (5.05 mmol) of **3**, 0.75 g of pyridine, 0.75 g of acetyl chloride, and 50 ml of ether was stirred for 2.5 hr at 22°. Water (40 ml) was added and after stirring for 0.5 hr the ether layer was separated, washed with water (2 × 50 ml) and brine (50 ml), and dried (Na_2SO_4). Removal of solvent under reduced pressure at <25° left a pale yellow oil which crystallized on standing. Vpc indicated that the product was a mixture of isomers A and B in the ratio 8:92 (Table I). Recrystallization from ether–hexane gave 0.5 g (41%) of **2b** (isomer B), mp 51–53°. This material was homogeneous by vpc. Ir and nmr are shown in Table I and uv in Table III; mass spectrum *m/e* 240 (M^+).

Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 49.90; H, 5.21; N, 11.79.

Dimethyl 4,5-Dihydro-7(6*H*)oxopyrazolo[1,5-*a*]pyridine-2,3-dicarboxylate (5).—A solution of 2.8 g (25.5 mmol) of 2-diazocyclopentanone[7] and 3.7 g (26.0 mmol) of DMAD in 70 ml of ether was warmed to boiling and then allowed to stand at ambient temperatures for 72 hr. The crystalline product (5.5 g, 86%) was separated and washed with a little ether: mp 108–110°; ir 1739 cm^{-1} (broad, C=O); nmr δ 2.28 (m, 2 H), 2.95 (t, 2 H, J = 6.25 Hz), 3.29 (t, 2 H, J = 6.25 Hz), 3.87 (s, 3 H), 3.94 (s, 3 H); uv 240 nm (ϵ 8200); mass spectrum *m/e* 252 (M^+).

Anal. Calcd for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.17; H, 5.02; N, 10.96.

Registry No.—1, 37387-70-5; **2a**, 37387-71-6; **2b**, 37387-72-7; **3**, 37387-73-8; **5**, 37387-74-9; 2-diazo-3-butanone, 14088-58-5; 2-diazocyclopentanone, 14088-61-0; dimethyl acetylenedicarboxylate, 762-42-5.

(7) M. Regitz and J. Rüter, *Chem. Ber.*, **101**, 1263 (1968).

(8) NOTE ADDED IN PROOF.—Additional examples of the reactions of acetylenes with five-membered ring α-diazo ketones have recently been described by T. Yamazaki and H. Shechter, *Tetrahedron Lett.*, 4533 (1972).

Sulfur–Oxygen Bond Cleavage in the Condensation of Cinnamyl Tosylate with Carbonium Ions

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The enormous utility of tosyl esters as substrates in nucleophilic substitution reactions arises from the extreme readiness with which the tosyl residue departs as an anion, after cleavage of the C–O bond. Cleavage of the S–O bond in tosylates has been reported, but only in special cases, as for example during electrolytic reduction,[1] or where the tosylate carbon atom is not susceptible to nucleophilic attack for steric or other reasons,[2] or where loss of the tosylate anion would lead

(1) P. Yousefzadeh and C. K. Mann, *J. Org. Chem.*, **33**, 2716 (1968).

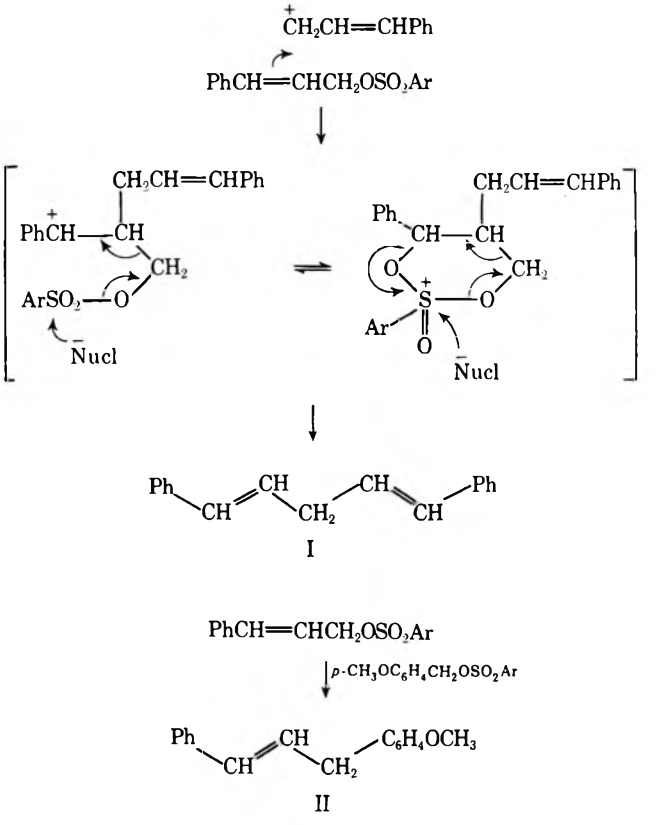
(2) (a) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949); (b) H. M. Walborsky, *ibid.*, **36**, 1251 (1953); (c) F. G. Bordwell, B. M. Pitt, and M. Knell, *J. Amer. Chem. Soc.*, **73**, 5004 (1951).

to an unstable carbonium ion, as in aryl tosylates.[3] Even then, attack on the sulfur atom requires the use of powerful nucleophiles. We wish to report a condensation reaction of cinnamyl tosylate which proceeds under very mild conditions, and which appears to involve an unusual S–O bond cleavage with loss of formaldehyde in the tosylate intermediate.

The tosyl ester of *trans*-cinnamyl alcohol may be isolated as a white, crystalline solid, but it decomposes within minutes at room temperature to a red oil.[4,5] A freshly prepared solution of it, prepared *in situ* by treating cinnamyl alcohol in ether with sodium hydride followed by tosyl chloride, was heated under reflux for 6 hr. Chromatographic separation of the products afforded dicinnamyl ether, cinnamyl alcohol, cinnamyl chloride, and some unreacted tosyl chloride, together with a nonpolar polymeric material. In addition, however, an unsaturated hydrocarbon, *trans,trans*-1,5-diphenylpenta-1,4-diene (I), was obtained in 20% yield. Its structure was shown by ir, uv, and nmr spectroscopy, by its mass spectrum, by hydrogenation to 1,5-diphenylpentane, and by comparison of it with an authentic sample of the diene prepared[6] by the Wittig reaction of 1,3-di(triphenylphosphonium)propane dibromide with benzaldehyde.

Formation of 1,5-diphenylpenta-1,4-diene (I) in this reaction may be explained by an initial condensation of a cinnamyl cation with the double bond of a molecule of cinnamyl tosylate. Decomposition of the resulting intermediate by S–O bond cleavage and elimination of a molecule of formaldehyde would yield diene I. This decomposition could be concerted, as shown, or could proceed by initial cleavage to give the cationic species $ArSO_2O{=}CH_2^+$, which could then lose formaldehyde. To test this mechanism, a carbonium ion incapable of self-condensation was generated in the presence of cinnamyl tosylate. Thus a cooled ethereal solution of the highly unstable tosylate[5] of *p*-methoxybenzyl alcohol was added to an ethereal solution of cinnamyl tosylate and the mixture was allowed to warm up to room temperature. Among other products, the expected condensation product *trans*-1-*p*-methoxyphenyl-3-phenylprop-2-ene (II) was isolated.

To show that these condensation products are not formed by reaction between the carbonium ion and cinnamyl alcohol, *p*-methoxybenzyl tosylate in ether solution was treated with cinnamyl alcohol. No 1-*p*-methoxyphenyl-3-phenylprop-2-ene (II) was obtained. Furthermore, when cinnamyl cations were generated by acid catalysis from cinnamyl alcohol in the presence of excess cinnamyl alcohol, we found that dicinnamyl ether was formed as previously reported[7] but no 1,5-diphenylpenta-1,4-diene (I) could be detected. This latter experiment also suggests that the condensation is not between cinnamyl cation and dicinnamyl ether. A related reaction mechanism has recently been suggested[8] for the decomposition of the tosylate of a β-hydroxy ketone system, involving cleavage of an S–O bond with subsequent loss of formaldehyde.



Experimental Section[9]

***trans,trans*-1,5-Diphenylpenta-1,4-diene** (I).—A solution of *trans*-cinnamyl *p*-toluenesulfonate in superdry ether (50 ml) at −70° was prepared *in situ* from cinnamyl alcohol (5.0 g) as previously described.[5] It was allowed to warm to room temperature and was then refluxed for 6 hr. The solution was diluted with ether, washed (H_2O), dried ($MgSO_4$), and evaporated, and the resulting black oil was chromatographed on a column of silica gel. Elution with ether:light petroleum (1:9) gave the diene I (0.68 g): bp 170° (0.5 mm) [lit.[6a] bp 205–211° (12 mm)]; uv max (EtOH) 208 nm (log ε 5.85), 259 (5.53), 279 (3.83), 293 (3.67), and 311 (3.25) [lit.[6b] 260 (5.39), 312 (3.25)]; ir (neat) 1642 (C=C), 1600, 1580, 1495 (Ph), and 965 cm^{-1} (CH=CH trans) (lit.[6b] ir 965 cm^{-1}); nmr (CCl_4) 2.81 (s, 10), 3.74 (m, 4), and 6.91 (br t, 2); mass spectrum (70 eV) *m/e* (rel intensity) 220 (37) M^+, 129 (100), 115 (80), 91 (78), 77 (48), and 51 (48). Also isolated from the column were a polymeric hydrocarbon material (0.05 g) (*Anal.* Found: C, 86.3; H, 14.2.), cinnamyl chloride (0.28 g), dicinnamyl ether (0.72 g), cinnamyl alcohol (0.60 g), and *p*-toluenesulfonyl chloride (0.70 g).

Hydrogenation of diene I in ethyl acetate over palladium on charcoal gave 1,5-diphenylpentane:[6a] nmr (CCl_4) 2.91 (s, 10), 7.50 (m, 4), 8.2–8.6 (m, 6); mass spectrum (70 eV) *m/e* (rel intensity) 224 (5) M^+, 154 (22), 91 (100), 65 (26); ir identical with that previously reported.[10]

***trans*-1-*p*-Methoxyphenyl-3-phenylprop-2-ene** (II).—Cooled (−70°), ethereal solutions of *trans*-cinnamyl *p*-toluenesulfonate (from 10 g of alcohol) and of *p*-methoxybenzyl *p*-toluenesulfonate[5] (from 10 g of alcohol) were mixed and allowed to warm to

(3) (a) J. F. Bunnett and J. Y. Bassett, Jr., *J. Org. Chem.*, **27**, 2345, 1887 (1962); (b) C. A. Bunton and Y. F. Frei, *J. Chem. Soc.*, 1872 (1951).

(4) O. A. Prib, L. V. Glushkova, and R. V. Sendega, *Ukr. Khim. Zh.*, **34**, 497 (1968).

(5) P. H. Boyle, J. H. Coy, and H. N. Dobbs, *J. Chem. Soc., Perkin Trans. 1*, 1617 (1972).

(6) (a) G. Wittig, H. Eggers, and P. Duffner, *Justus Liebigs Ann. Chem.*, **619**, 10 (1958); (b) S. Brenner and J. Klein, *Israel J. Chem.*, **7**, 735 (1969).

(7) M. G. J. Beets and H. van Essen, *Recl. Trav. Chim. Pays-Bas*, **74**, 98 (1955).

(8) F. Nerdel, D. Frank, W. Metasch, K. Gerner, and H. Marschall, *Tetrahedron*, **26**, 1589 (1970).

(9) Uv spectra were measured on a Unicam S. P. 800 recording spectrophotometer, ir spectra on a Perkin-Elmer 157 spectrophotometer, and nmr spectra on a Perkin-Elmer R.10 instrument. Mass spectra were measured on a Hitachi Perkin-Elmer RMU-4 mass spectrometer. Light petroleum refers to the fraction of bp 40–60°.

(10) E. Kuss and P. Pollmann, Collection of the Institute for Petroleum Research, Hanover, ir card no. 16496.

room temperature. After standing for 6 hr the mixture was diluted with ether, washed (H_2O), dried ($MgSO_4$), and evaporated to give a black oil, which when chromatographed on silica (300 g), eluting with ether:light petroleum (1:9), gave the alkene II[11] (0.46 g): mass spectrum (70 eV) *m/e* (rel intensity) 224 (100) M^+, 209 (47), 193 (64), 115 (100), 91 (54), and 77 (42); uv, ir, and nmr spectral values correspond with those reported in the literature.[12] Also isolated from the column were the same polymeric hydrocarbon as mentioned previously (0.80 g), *p*-toluenesulfonyl chloride (1.3 g), di-*p*-methoxybenzyl ether (0.74 g), dicinnamyl ether (0.60 g), *p*-methoxybenzyl cinnamyl ether (1.00 g), cinnamyl alcohol (0.66 g), and *p*-methoxybenzyl alcohol (0.50 g).

Registry No.—I, 26057-48-7; II, 35856-80-5; *trans*-cinnamyl *p*-toluenesulfonate, 37611-16-8; *p*-methoxybenzyl *p*-toluenesulfonate, 14670-03-2.

Acknowledgment.—We are grateful to the Irish Government Department of Education for support of this work.

(11) C. S. J. Rondestvedt, Jr., *J. Amer. Chem. Soc.*, **73**, 4509 (1951).
(12) T. Hase, *Acta Chem. Scand.*, **23**, 2403 (1969).

Anhydrous Hydrofluoric Acid as a Cyclizing Agent in the Preparation of Several Substituted Oxazoles from *N*-Aroyl-α-amino Ketones[1a]

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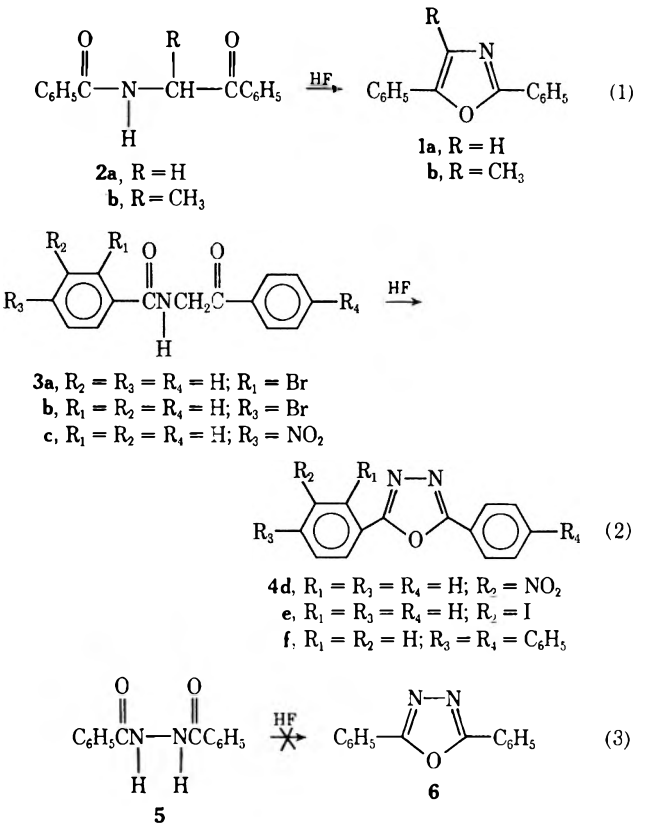
In the course of our studies of the photooxidation of 2,5-diphenyloxazole (PPO) (**1a**) it was necessary to prepare 4-methyl-2,5-diphenyloxazole (**1b**).[2] Attempts to cyclize α-benzamidopropiophenone (**2b**) to **1b** (Scheme I, eq 1) with concentrated sulfuric acid in accordance with the procedure given by Cleland and Nieman[3] gave a maximum yield of 12.5% of the desired product. Consequently, it was decided to try anhydrous hydrofluoric acid as a condensing agent in this reaction, and a 95% yield of the oxazole **1b** was isolated.

The customary condensing agents used by Hayes and coworkers[4] in the preparation of oxazoles from the corresponding *N*-aroyl-α-amino ketones were phosphorus oxychloride or concentrated sulfuric acid and the recorded yields generally ranged from 50 to 80%. In another paper[5] we reported yields of 39–62% of 2,5-diaryloxazoles when phosphorus oxychloride was used as a cyclizing agent. The nearly quantitative yield of 4-methyl-2,5-diphenyloxazole (**1b**) obtained when anhydrous hydrofluoric acid was used led to a

SCHEME I



study of the general efficiency of the acid in condensations of this type.

Anhydrous hydrofluoric acid was used for the cyclization of α-benzamidoacetophenone (**2a**), α-(2-bromobenzamido)acetophenone (**3a**), α-(4-bromobenzamido)-acetophenone (**3b**), α-(4-nitrobenzamido)acetophenone (**3c**), α-(3-nitrobenzamido)acetophenone (**3d**), α-(3-iodobenzamido)acetophenone (**3e**), and 2-aza-1,4-di-(4-biphenylyl)-1,4-butanedione (**3f**) to the corresponding oxazoles, **1a** and **4a–f** (Scheme I, Table I).

TABLE I
CYCLIZATION OF *N*-AROYL-α-AMINO KETONES TO OXAZOLES

Substrate	Product	Yield,[a] %
α-Benzamidopropiophenone (**2b**)	4-Methyl-2,5-diphenyloxazole (**1b**)	95
α-Benzamidoacetophenone (**2a**)	2,5-diphenyloxazole (**1a**)	91[b]
α-(2-Bromobenzamido)-acetophenone (**3a**)	2-(2-Bromophenyl)-5-phenyloxazole (**4a**)	61[c]
α-(4-Bromobenzamido)-acetophenone (**3b**)	2-(4-Bromophenyl)-5-phenyloxazole (**4b**)	62
α-(4-Nitrobenzamido)-acetophenone (**3c**)	2-(4-Nitrophenyl)-5-phenyloxazole (**4c**)	Trace
α-(3-Nitrobenzamido)-acetophenone (**3d**)	2-(3-Nitrophenyl)-5-phenyloxazole (**4d**)	64
α-(3-Iodobenzamido)-acetophenone (**3e**)	2-(3-Iodophenyl)-5-phenyloxazole (**4e**)	79
2-Aza-1,4-di(4-biphenylyl)-1,4-butanedione (**3f**)	2,5-Di(4-biphenylyl) oxazole (**4f**)	96[d]
1,2-Dibenzoylhydrazine (**5**)	2,5-Diphenyloxadiazole (**6**)	0[e]

[a] In all cases the yield reported is of crystallized product (or crude product) having a melting point corresponding to that of pure material reported in the literature. [b] Using sulfuric acid yields of 53–81% are obtained. [c] Treated with two portions of HF. [d] Using phosphorus oxychloride the yield was 51%. [e] Using phosphorus oxychloride the yield was 55%.

(1) (a) From the Ph.D. dissertation of Margaret E. Ackerman (1971). This investigation was supported in part by a research grant from the Division of Biology and Medicine of the U. S. Atomic Energy Commission, Contract No. AT (29-2) 915. (b) Work performed under the auspices of the U. S. Atomic Energy Commission.
(2) We are indebted to Arapahoe Chemicals, Inc., for their generous gift of 100 g of the α-benzamidopropiophenone for use in this synthesis.
(3) G. H. Cleland and C. Niemann, *J. Amer. Chem. Soc.*, **71**, 841 (1949).
(4) F. N. Hayes, B. S. Rogers, and D. G. Ott, *ibid.*, **77**, 1850 (1955).
(5) M. D. Barnett, G. H. Daub, F. N. Hayes, and D. G. Ott, *ibid.*, **82**, 2282 (1960).

Yields of 2,5-diphenyloxazole (**1a**) and 2,5-di(4-biphenylyl)oxazole (**4f**) greater than 90% were obtained from compounds **2a** and **3f**, respectively. The other amido ketones gave yields of the oxazoles ranging from 61 to 79% with the exception of **3c**, which gave only a trace of product.

An attempt to condense 1,2-dibenzoylhydrazine (**5**) to 2,5-diphenyloxadiazole (**6**) with anhydrous hydrofluoric acid failed (Scheme I, eq 3). In initial experiments only benzoic acid was isolated. The experiment was repeated with the exclusion of moisture following the addition of the hydrofluoric acid; this precaution did prevent cleavage to benzoic acid but only the starting material **5** was recovered. The use of phosphorus oxychloride gave a 55% yield of **6** from **5**.

Experimental Section[6]

General Procedure.—The *N*-aroyl-α-amino ketone was dissolved in anhydrous hydrofluoric acid (10 ml of acid/1 g of ketone) in a polyethylene beaker, and the resulting solution was allowed to evaporate to dryness. The dry, crystalline material obtained was slurried in saturated aqueous sodium bicarbonate to destroy any hydrogen fluoride salts which may have formed. The product was then extracted into benzene; this benzene extract was washed with water, dried (Na_2SO_4), and chromatographed on neutral Woelm alumina. The solvent was removed *in vacuo* from the eluate and the crude product obtained was crystallized from cyclohexane or benzene–cyclohexane except for **4f**, which was recrystallized from dimethylformamide.

Registry No.—**1a**, 92-71-7; **1b**, 2549-31-7; **2a**, 4190-14-1; **2b**, 16735-29-8; **3a**, 37611-22-6; **3b**, 37611-23-7; **3d**, 37611-24-8; **3e**, 37611-25-9; **3f**, 37061-76-0; **4a**, 37611-27-1; **4b**, 14492-02-5; **4d**, 22397-43-9; **4e**, 37610-63-2; **4f**, 2083-09-2; hydrofluoric acid, 7664-39-3.

(6) All melting points were taken in Pyrex capillary tubes in a Hoover-Thomas melting point bath and in all cases were identical with those reported in the literature.

Hydrogen–Deuterium Exchange of *N*-Methylpyridinium Ion in Methanol Containing Amines. Identity of the Catalyzing Base

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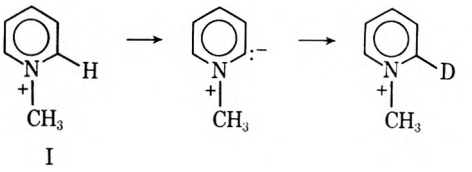
Received October 11, 1972

An attractive and useful solvent–base mixture for the study of hydrogen exchange reactions of weak carbon acids is found in alcohol–amines. Although a number of deprotonation studies have been carried out using such nonaqueous mixtures, the identity of the catalyzing base or bases has seldom been established.[1-4] Not only may the more abundant amine base catalyze the deprotonation reaction, but also the less abundant and more reactive alkoxide ion may serve as a catalyst. This ion is formed by the solvolysis reaction given in eq 1 where Am represents an amine. Without knowing

$$\mathrm{Am} + \mathrm{CH_3OD} \underset{}{\overset{K_b}{\rightleftharpoons}} \mathrm{AmD^+} + \mathrm{CH_3O^-} \qquad (1)$$

the identity of the catalyst(s), the significance of comparisons involving the reactivities of various carbon acids in such mixtures is obscured.

We here provide clear and unambiguous evidence concerning the identity of the base catalyst in the H–D exchange reaction of *N*-methylpyridinium ion (I) at the 2,6-positions in methanol-*O*-*d* containing amines. Considerable evidence is available to establish that the mechanism of hydrogen exchange of this substrate involves base-catalyzed deprotonation to give an ylide which then captures a deuteron from the solvent to give product, eq 2.[5,6] Exchange at only the 2 position is shown although the equivalent 6 position reacts as well.



(2)

I

Results and Discussion

Two amine bases in CH_3OD were used to catalyze H–D exchange of I at 75.0°. They are morpholine (pK_a[7] in H_2O at 25° is 8.3) and 1,4-diazabicyclo[2.2.2]-octane (DABCO) (pK_a[8] in H_2O at 25° is 8.8). In both cases the rate of H–D exchange increased with increasing amine concentration and the more basic amine, DABCO, was the more effective. However, a tenfold change in the concentration of morpholine resulted in only a 3.1-fold change in the value of the pseudo-first-order rate constant, k_ψ. Similarly, a sevenfold change in DABCO concentration gave rise to a 3.0-fold change in k_ψ. If the amine were the sole catalyst, then the magnitude of the change in k_ψ would be the same as the magnitude of the change in the amine concentration, *i.e.*, the reaction rate would be first order in amine. This clearly is not the case. Methoxide ion resulting from the solvolysis reaction involving the amine (eq 1) must be acting as a catalyst.

Consider now the rate expression for H–D exchange given by eq 3 which includes terms for catalysis by both

$$k_\psi[\mathrm{CH}] = k_{\mathrm{MeO}}[\mathrm{CH}][\mathrm{CH_3O^-}] + k_{\mathrm{Am}}[\mathrm{CH}][\mathrm{Am}] \qquad (3)$$

methoxide ion and amine. In this equation k_{MeO} and k_{Am} are second-order rate constants for methoxide ion and amine catalysts and [CH] is the concentration of H at positions 2 and 6 as indicated by nmr. If the reaction mixture contains substrate and amine as in the experi-

(1) I. F. Tupitsyn, N. N. Zatsepina, and A. V. Kirova, *Org. Reactiv. (USSR)*, **5**, 626 (1968); N. N. Zatsepina, Yu. L. Kaminsky, and I. F. Tupitsyn, *ibid.*, **4**, 433 (1967); K. W. Ratts, R. K. Howe, and W. G. Phillips, *J. Amer. Chem. Soc.*, **91**, 6115 (1969).

(2) For an authentic example of an amine-catalyzed deprotonation of a carbon acid in methanol, see F. G. Bordwell and M. W. Carlson, *ibid.*, **92**, 3370 (1970).

(3) It has been established that ethoxide ion is the catalyst for H–D exchange at position 2 of a thiazolium ion in ethanol containing an acetic acid–acetate ion buffer.[4]

(4) J. Crosby and G. E. Lienhard, *J. Amer. Chem. Soc.*, **92**, 5707 (1970).

(5) J. A. Zoltewicz and L. S. Helmick, *ibid.*, **92**, 7547 (1970).

(6) J. A. Zoltewicz, G. M. Kauffman, and C. L. Smith, *ibid.*, **90**, 5939 (1968).

(7) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution," Butterworths, Washington, D. C., 1965.

(8) J. Hine, J. C. Kaufmann, and M. S. Cholod, *J. Amer. Chem. Soc.*, **94**, 4590 (1972).

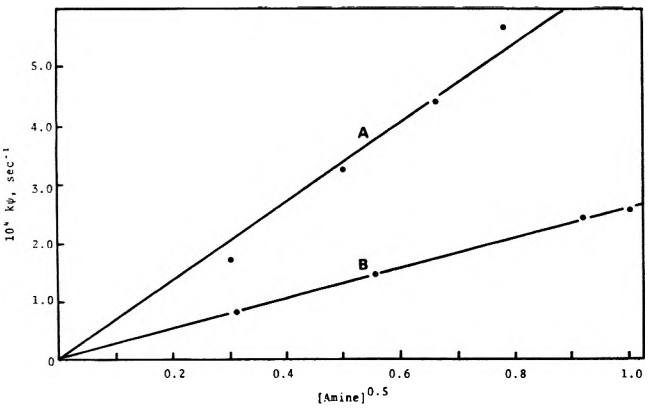


Figure 1.—Plot of the pseudo-first-order rate constants for H–D exchange at the 2,6 positions of *N*-methylpyridinium iodide in CH_3OD at 75.0° *vs.* the square root of the amine concentration. Line A refers to DABCO and B to morpholine bases.

ments just described, the methoxide ion concentration resulting from solvolysis (eq 1) is given by $K_b^{0.5}[Am]^{0.5}$; *i.e.*, $[CH_3O^-] = [AmD^+]$. Substituting into rate eq 3 and eliminating the concentration of substrate gives eq 4. According to eq 4, if methoxide ion alone catalyzes

$$k_\psi = k_{MeO}K_b^{0.5}[Am]^{0.5} + k_{Am}[Am] \quad (4)$$

the reaction, then a plot of k_ψ *vs.* $[Am]^{0.5}$ will be linear, having slope $k_{MeO}K_b^{0.5}$ and intercept $k_{Am}[Am] = 0$. If both methoxide ion and the amine significantly catalyze the reaction, then such a plot will be curved and will have a zero intercept. Figure 1 shows such a plot for I undergoing H–D exchange in the presence of morpholine and DABCO. The plots are *linear* and have a zero intercept. The scatter in line A in is keeping with the ~10% uncertainty often found in kinetic nmr experiments.[5] These results clearly show that only methoxide ion and not the amine catalyzes the reaction. The observed rate increases with increasing amine concentration are due to increases in methoxide ion concentration resulting from the solvolysis of the amine according to eq 1.[9]

A critical test of this conclusion was made in two additional experiments. These involve reactions similar to the above except that DABCO along with its conjugate acid were employed. In the first, part of the amine was neutralized with methanesulfonic acid and, in the second, partial neutralization employed hydrochloric acid. Now, in the presence of the added acid the methoxide ion concentration is reduced by a factor of about 10^4.[11] This large reduction in methoxide ion concentration while maintaining the concentration of free amine at its usual levels greatly enhances the possibility of detecting amine catalysis. After 6000–7000 min no more than 20% H–D exchange occurred. This time period is equivalent to 300–350 half-lives in the absence of added acid. Without a doubt, catalysis by DABCO acting directly on substrate is insignificant.

The conclusions from the above experiments are clear and unmistakable. They establish that H–D exchange of I at its 2,6 positions in methanol–amine mixtures kinetically is specific base (lyate ion) and not general base catalyzed. This is consistent with our earlier conclusion involving H–D exchange of I in aqueous solutions.[5] Here too only lyate ion catalysis is significant.

It is likely that the above conclusions concerning catalyst identity will carry over to hydrogen exchange reactions of a large number of other carbon acids. The conclusions will apply directly to the large number of heterocyclic compounds now known to undergo exchange in aqueous solutions by specific and not by general base catalyzed reactions.[13]

Experimental Section

Materials.—DABCO (Aldrich Chemical Co.) was recrystallized before use. Morpholine was distilled from KOH pellets. CH_3OD was purchased from Thompson-Packard, Inc.

Kinetic Runs.—*N*-Methylpyridinium iodide and amine were weighed into a 1-ml volumetric flask and then diluted to mark with CH_3OD. An aliquot was sealed in an nmr tube, and a time zero spectrum was obtained on a Varian A-60A spectrometer. The sample was heated in a constant temperature bath; following this, a spectrum was obtained on the cooled sample. This cycle of heating and cooling was repeated so that about ten points were obtained over 2–4 half-lives. The sample then was heated for at least 10 half-lives to obtain an "infinity" value. The area of the 3,5 positions were employed as the area standard, since they are known to be considerable less reactive than the 2,6 positions.[5,6] Linear plots were constructed as described earlier.[14] Concentrations are corrected for a 6.3% expansion of methanol on heating.[15] The substrate concentration generally was about 0.5 *M;* amine concentrations were in the range 0.1–1.0 *M* and are given in Figure 1.

To check the stability of the substrate control runs were carried out. Two samples were prepared as indicated above except that CH_3OH was used in place of CH_3OD and *tert*-butyl alcohol was added as internal standard. The mixtures, each containing one amine, were heated at 75.0° and occasionally examined. After 3995 min of heating, the area of the 2,6 protons relative to that of the internal standard had not changed, indicating no decomposition. This heating period corresponds to more than 50 half-lives for hydrogen exchange. Substrate and amine concentrations were 0.5 *M*.

The reactivity of *N*-methylpyridinium iodide was examined in buffers consisting of DABCO and its conjugate acid. In sample "A," methanesulfonic acid was employed; the concentration of free DABCO was 0.70 *M* and its conjugate acid was 0.48 *M*. After heating this sample at 75.0° for 6790 min, the area of the 2,6 protons decreased by 20%. Sample "B" was prepared using concentrated hydrochloric acid. The free DABCO concentration was 0.59 *M* and its conjugate acid, 0.76 *M*. After heating at 75.0° for 6330 min the area of the 2,6 protons decreased by 8%. Substrate concentrations were 0.6 *M*.

Registry No.—*N*-Methylpyridinium iodide, 930-73-4.

Acknowledgment.—This project was kindly supported by the National Science Foundation (GP 25500).

(9) The pK_a values for our two amines in methanol are not likely to be very different from those for aqueous solutions.[10] The K_a ratio is 3 for aqueous and 6 for methanol solutions. The latter value was calculated using the slopes obtained from the plot in Figure 1.

(10) C. D. Ritchie and P. D. Heffley, *J. Amer. Chem. Soc.*, **87**, 5402 (1965); R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, Chapter IV.

(11) This value is based on the pK_a value for an aqueous solution of DABCO[8] and the ion product[12] for CH_3OH, both at 25°.

(12) J. Koskikallio, *Suom. Kemistilehti B*, **30**, 111 (1957).

(13) This assumes the existence of valid Brønsted relationships which include lyate ion with $\beta \sim 1$.

(14) J. A. Zoltewicz and G. M. Kauffman, *J. Org. Chem.*, **34**, 1405 (1969).

(15) J. Timmermans, "Physico-Chemical Constants of Pure Organic Compounds," Vol. 1, Elsevier, Amsterdam, 1950, p 303.

Orientation Studies in the Coumaran Series. Revised Structure of the Nitration Product of 5-Acetamido-2-methylcoumaran *via* the Elucidation of the Claisen Rearrangement of *m*-Acetoamidophenyl Allyl Ether

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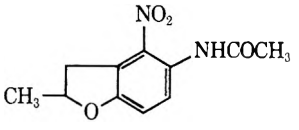
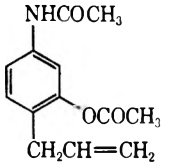
Arnold and McCool[1] reported that 2-methyl-5-acetamidocoumaran, on nitration, gave 2-methyl-4-nitro-5-acetamidocoumaran (**1**). This orientation appeared somewhat surprising since the above authors reported that the nitration of 2-methyl-4-acetamidoanisole yielded the 5-nitro isomer.[1]



1



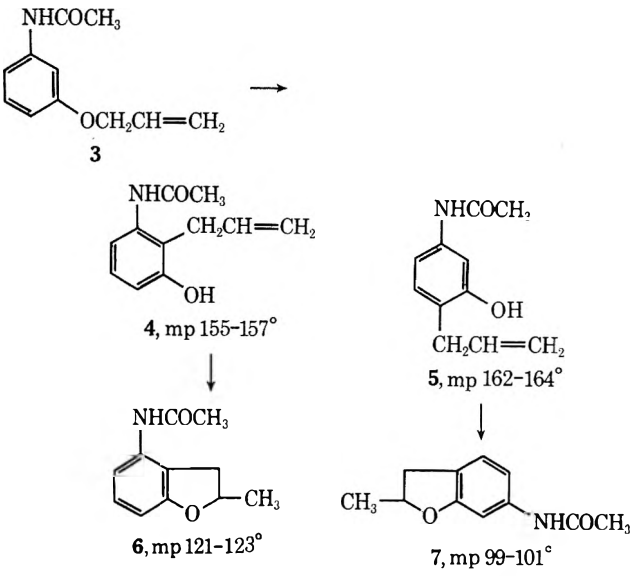
2

We now give evidence that the orientation in the two series is quite comparable and that the nitro coumaran obtained by Arnold and McCool was, in fact, the 6-nitro isomer.

The structure **1** assigned by Arnold, *et al.*,[1] to the nitration product of 2-methyl-5-acetamidocoumaran was based on the following considerations: (1) formation of a steam-volatile nitrophenol obtained from the nitration product by a Sandmeyer reaction; (2) conversion of the nitration product, by hydrolysis → deamination → reduction → acetylation, into an acetamido compound (mp 96–97°) different from 2-methyl-6-acetamidocoumaran (mp 126–126.5°) prepared by the cyclization of 3-acetoxy-4-allyl-acetanilide (**2**).[2]

The correctness of the last piece of evidence is, of course, based on the unquestionability of the structure of **2**. In our hands, following the method as described by Arnold, McCool, and Schultz[2] for the synthesis of **2**, the thermal rearrangement (Claisen reaction)[3] of *m*-acetamidophenyl allyl ether (**3**) yielded the two isomers (**4** and **5**) we expected from this type of reaction.[4]

The structures **4** and **5**, we respectively assigned to the two isomers, were supported by uv, ir, and nmr analyses and by conversion of **5** into the known 2-propyl-5-acetamidophenol.[2] It is probable that the product (mp 132–133°) obtained by Arnold, *et al.*,[2] and assumed by these authors to be 3-acetoxy-4-allylacetanilide (**2**) was in fact a mixture of the two isomers **4** and **5**. Consequently, on cyclizing the product (mp 132–133°) the above authors would have obtained both



3

4, mp 155–157°

5, mp 162–164°

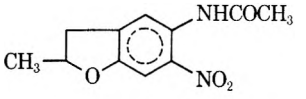
6, mp 121–123°

7, mp 99–101°

4- and 6-acetamidocoumarans. From this mixture they isolated only the higher melting isomer **6**, to which they assigned structure **7**.

We have cyclized the compounds **4** and **5**, respectively, to the corresponding acetamidocoumarans (**6** and **7**); the one derived from **5** was proved to be identical with the acetamidomethylcoumaran obtained by deamination and reduction of the nitroacetamidomethylcoumaran prepared by Arnold and McCool.[1]

In conclusion, the correct structure of the nitration product of 2-methyl-5-acetamidocoumaran must be **8**, which is also consistent with uv, ir, and nmr spectra.[5]



8

Experimental Section[6]

Thermal Rearrangement of *m*-Acetamidophenyl Allyl Ether (3).—This reaction was carried out according to the directions of Arnold, McCool, and Schultz.[2] The solid, mp 129–132°, by thin layer chromatography revealed the presence of two spots and was treated as follows in order to separate the two isomers.

2-Allyl-3-hydroxyacetanilide (4).—The rearranged product of **3** (35 g) was dissolved in 150 ml of hot AcOEt. The solution was allowed to stand at room temperature overnight. The crystalline precipitate was separated from the supernatant (L_1) and dissolved in 200 ml of boiling AcOEt. The white crystals separated from the cooled solution (L_2) were collected, washed with cold AcOEt, and dried, 10.4 g, mp 155–157°. An analytical sample was recrystallized from AcOEt: mp 155–157°;[7] uv max 278 mμ (ε 2450); ir, a strong peak at 13.1 μ (characteristic of three adjacent aromatic C–H bonds); nmr (Me_2SO) 6.5–7.25 ppm (complex, 3-H phenyl); tlc, one spot (R_f 0.35). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.27; H, 6.86; N, 7.24.

(1) R. T. Arnold and J. C. McCool, *J. Amer. Chem. Soc.*, **64**, 1315 (1942).

(2) R. T. Arnold, J. C. McCool, and E. Schultz, *ibid.*, **64**, 1023 (1942).

(3) For a detailed study of the Claisen reaction see, for instance, K. Schmid, W. Haegale, and H. Schmid, *Helv. Chim. Acta*, **37**, 1080 (1954).

(4) Analogously, K. D. Kaufman and W. E. Russey [*J. Org. Chem.*, **30**, 1320 (1965)] reported the isolation of 2-allyl- and 4-allylresorcinol in the thermal rearrangement of resorcinol monoallyl ether.

(5) Nmr ($CDCl_3$) δ 2.72 (m, H_3), 3.22 (m, H_3'), 4.85 (m, H_2), 5.59 (t, H_4), 7.3 ppm (s, H_7), $J_{H_{3,4}}$ = 1.5, $J_{H_{4,7}}$ = 0.0 Hz.

(6) Melting points were taken in capillary tubes in a heated copper block and are corrected. Ultraviolet spectra were determined on a Cary Model 15 spectrophotometer in 95% EtOH. Infrared spectra were recorded on a Perkin-Elmer 157 spectrophotometer in KBr pellets. Nmr spectra were recorded on a Varian A-60A instrument. Thin layer chromatography was carried out on silica gel plates using chloroform, concentrated ammonia, and methanol (95:0.25:5) as developing solvent system.

(7) Arnold, *et al.*,[2] assigned to this compound mp 160.5–162°. Probably, from the mixture of the two isomers they isolated the 4 isomer, which they assumed to be the 2 isomer.

3-Hydroxy-4-allylacetanilide (5).—The solutions L_1 and L_2 (see above) were combined and the resulting solution was evaporated under reduced pressure to dryness. The residue (22.5 g, mp 124–139°) was suspended in 500 ml of H_2O. The suspension was heated to the boiling point; EtOH was gradually added until a clear solution was obtained.

The solution was heated for a further 15 min and allowed to stand at room temperature overnight. The crystalline solid was filtered and dried, 15.2 g, mp 161–163°. An analytical sample was recrystallized from an EtOH–H_2O mixture: mp 162–164°; uv max 247 mμ (ε 13,600), 285 (4570); ir, a strong peak at 12.1 μ (characteristic of two adjacent aromatic C–H bonds) and at 11.4 μ (characteristic of an isolated aromatic C–H bond); nmr (Me_2SO) δ 6.9 (s, $H_{5,6}$), 7.3 ppm (s, H_2); tlc, one spot (R_f 0.25). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.38; H, 6.93; N, 7.23.

2-Allyl-3-acetoxyacetanilide.—A solution of 1.3 ml of AcCl in 15 ml of anhydrous PhH was added dropwise and with stirring to a cooled (10°) mixture of 2 g of 4 and 1.5 ml of pyridine in 85 ml of anhydrous PhH. After the addition was completed, the reaction mixture was stirred for an additional 2 hr and then filtered. The filtrate was shaken with H_2O, $NaHCO_3$ solution and again with H_2O until neutral. The PhH solution was dried (Na_2SO_4) and evaporated. The residue was crystallized from AcOEt to constant melting point (151–152°), tlc one spot (R_f 0.45). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.94; H, 6.42; N, 5.90.

3-Acetoxy-4-allylacetanilide.—This compound was prepared by a procedure similar to the one used for the 2-allyl isomer. After crystallization from PhH–petroleum ether (bp 30–60°), it melted at 103–104°, uv max 246 mμ (ε 18,500), tlc one spot (R_f 0.35). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.98; H, 6.42; N, 6.17.

2-Propyl-3-hydroxyacetanilide.—An ethanolic solution of 1.74 g of 4 in 25 ml of EtOH was hydrogenated under 3 atm in the presence of 0.15 g of PtO_2. After 3 hr the reaction mixture was filtered and the filtrate was evaporated to dryness. The residue (1.5 g, mp 163–165°) was crystallized twice from an EtOH–H_2O mixture: mp 167–169°; uv max 278 mμ (ε 2280); tlc one spot (R_f 0.20). *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.39; H, 7.82; N, 7.25. Found: C, 68.51; H, 7.84; N, 7.32.

3-Hydroxy-4-propylacetanilide.—This compound was prepared following the above procedure from 5. After recrystallization from an EtOH–H_2O mixture it melted at 173–175° (lit.[2] mp 173–174.5°): uv max 248 mμ (ε 12,800), 285 (4550); tlc one spot (R_f 0.25). *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.39; H, 7.82; N, 7.25. Found: C, 68.26; H, 7.78; N, 7.32.

2-Methyl-4-acetamidocoumaran (6).—Two grams of 2-allyl-3-hydroxyacetanilide was cyclized by means of fuming hydrobromic acid according to Arnold and McCool.[1] The obtained solid (1.7 g) was crystallized from PhH–petroleum ether to constant melting point (121–123°[8]): uv max 237 mμ (ε 8600), 283 (2550); tlc one spot (R_f 0.55). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.25; H, 6.83; N, 7.25.

2-Methyl-6-acetamidocoumaran (7).—This compound was obtained from 5 using the above procedure. After crystallization from PhH–petroleum ether, it had mp 99–101° and was identical (mixture melting point determination, ir and uv analyses) to the acetamidomethylcoumaran derived from the nitro compound prepared as described by Arnold and McCool:[1] uv max 249 mμ (ε 10,200), 291 (5780); tlc one spot (R_f 0.35). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.99; H, 7.02; N, 7.45.

Registry No.—**3**, 37439-78-4; **4**, 37439-79-5; **4** acetate, 37439-80-8; **5**, 28583-69-9; **5** acetate, 37439-82-0; **6**, 37439-83-1; **7**, 37439-84-2; 2-propyl-3-hydroxyacetanilide, 37439-85-3; 3-hydroxy-4-propylacetanilide, 28583-72-4.

Acknowledgment.—We are indebted to Miss A. De Leonibus for the microanalyses and to Mrs. M. L. Reviglio Lembo for the tlc data and uv and ir spectra.

(8) This compound was identified previously[1] as 2-methyl-6-acetamidocoumaran, mp 126–126.5° (from water).

An Alternate Synthesis of 5-Thio-D-glucose Pentaacetate[1]

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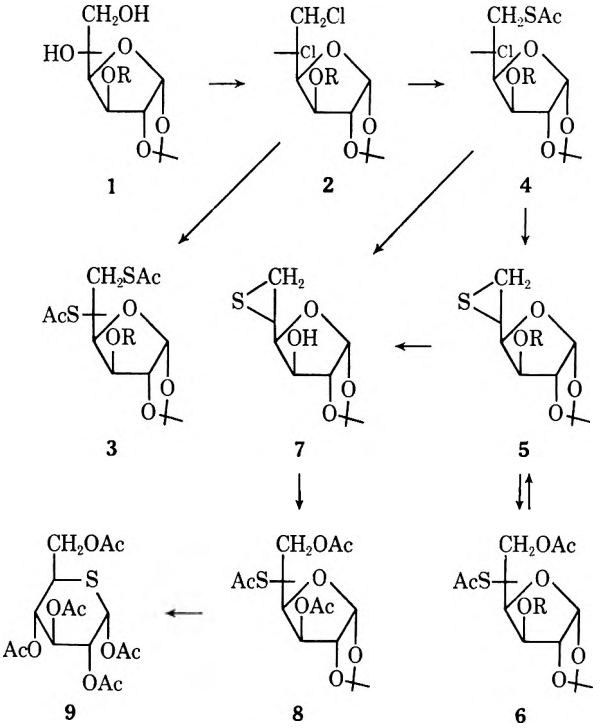
Because of growing interest in the biochemistry of 5-thio-D-glucose,[2] a shorter route to its synthesis would be highly desirable. It occurred to us that, since chloro sugars have proved valuable intermediates in the preparation of deoxy[3,4] and amino sugars,[5–7] they might be used to provide a shorter synthesis of 5-thio-D-glucose.

We find that 3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (1) can be easily chlorinated to produce 3-*O*-benzoyl-5,6-dichloro-5,6-dideoxy-β-L-idofuranose (2) in 72% yield, by using triphenylphosphine in carbon tetrachloride.[8] The L-ido configuration of compound 2 is established through its conversion to 5,6-dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose (7).[9]



Selective displacement of the primary chloro group on 2 produces 6-*S*-acetyl-5-chloro-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-idofuranose (4) in 60% yield if 1 mol of potassium thioacetate is used at low tempera-

(1) This work was supported by Public Health Service Research Grant No. AM 15641. Journal Paper No. 4861 of the Purdue Agricultural Experiment Station, Lafayette, Indiana 47907.

(2) R. L. Whistler and W. C. Lake, *Biochem. J.*, in press.
(3) M. F. Evans, L. Long, Jr., and F. W. Parrish, *J. Org. Chem.*, **33**, 1074 (1968).
(4) B. T. Lawton, D. J. Ward, W. A. Szarek, and J. K. N. Jones, *Can. J. Chem.*, **47**, 2899 (1969).
(5) S. Hanessian and N. R. Plessas, *Chem. Commun.*, 1152 (1967).
(6) B. T. Lawton, W. A. Szarek, and J. K. N. Jones, *ibid.*, 787 (1969).
(7) E. Hardeggar, G. Sanetti, and K. Steiner, *Helv. Chim. Acta*, **46**, 282 (1963).
(8) J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966).
(9) L. D. Hall, L. Hough, and R. A. Pritchard, *J. Chem. Soc.*, 1537 (1961).

ture (*ca.* 45°). However, if an excess of potassium thioacetate is used or a higher reaction temperature is employed, 5,6-di-*S*-acetyl-3-*O*-benzoyl-5,6-dideoxy-1,-2-*O*-isopropylidene-α-D-glucofuranose (**3**) is also formed as the principal product.

5,6-Dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-D-glucopyranose (**7**) can be obtained in 91% yield from **4** by hydrolysis and cyclization or **4** can be converted to 3-*O*-benzoyl-5,6-dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose (**5**) which gives 6-*O*-acetyl-5-*S*-acetyl-3-*O*-benzoyl-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**). Either **5** or **6** can give **7** in 94–97% yield and a cyclization similar to the conversion of **6** to **7** was reported by Owen and coworkers.[10,11]

Nucleophilic ring opening of the episulfide **7** to give 3,6-di-*O*-acetyl-5-*S*-acetyl-5-deoxy-α-D-glucofuranose (**8**) is accomplished essentially according to the published procedure.[12] Acetolysis of **8** produces crystalline 1,2,3,4,6-penta-*O*-acetyl-α-D-glucothiopyranose (**9**) in 69% yield.

Thus, the outlined procedure offers fewer steps to the synthesis of 5-thio-D-glucose starting from normal D-glucose but the overall yield is in the neighborhood of 23% compared to 30% by the longer route.[13] The present route also has two column-chromatographic purification steps not present in the longer synthesis.

Experimental Section

Reactions were monitored by thin layer chromatography (tlc) on silica gel G[14] coated glass plates (5 × 13 cm). Components were located by spraying with 5% sulfuric acid in ethanol and heating until permanent char spots were visible. Column chromatography used alumina and silica gel.[15] Optical rotations were measured yn a Perkin-Elmer Model 141 polarimeter.

3-*O*-Benzoyl-5,6-dichloro-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-idofuranose (2).—A mixture of 3-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**1**)[16] (3.5 g), triphenylphosphine (14 g), and anhydrous $CaSO_4$ (2 g) in carbon tetrachloride (150 ml) was refluxed for 5 hr. The reaction mixture was filtered and concentrated to give a solid mass, which was extracted three times with hexane. The combined extracts were evaporated to give a thick syrup which was chromatographed on a silica gel column with a mixture of ether–hexane (1:4, v/v) to yield 3-*O*-benzoyl-5,6-dichloro-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-idofuranose (**2**) as a colorless syrup (2.80 g, 71.7%): $[\alpha]^{25}D$ −5.82° (*c* 1.1, chloroform); ν_{max} (film) 1730 cm^{-1} (OCOPh).

Anal. Calcd for $C_{16}H_{18}Cl_2O_5$: C, 53.21; H, 5.02; Cl, 19.63. Found: C, 53.62; H, 5.16; Cl, 19.29.

5,6-Di-*S*-acetyl-3-*O*-benzoyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (3).—To a solution of **2** (800 mg) in dry acetone (20 ml) was added potassium thioacetate (1.01 g), and the mixture was refluxed under stirring in a current of nitrogen for 4 hr. The reaction mixture was filtered and concentrated to a syrup, which was washed with cold water, dried, and purified by silica gel column chromatography using ethyl acetate–carbon tetrachloride (1:19, v/v) as eluent. Compound **3** was obtained in 82.7% yield (848 mg). Recrystallization from hexane gave fine needles: mp 114–115°; $[\alpha]^{25}D$ −65.5° (*c* 1.2, chloroform); ν_{max}^{Nujol} 1730 (-OCOPh) and 1680 cm^{-1} (-SCOCH$_3$); nmr ($CDCl_3$) δ 1.33, 1.57 (2 s, 6 H, CMe_2), 2.15, 2.33 (2 s, 6 H, *S*-acetyl), 2.9–5.0 (m, 5 H, H-2,4,5,6), 5.48 (d, 1 H, $J_{3,4}$ = 3 Hz, H-3), 6.0 (d, 1 H, $J_{1,2}$ = 4 Hz, H-1), 7.2–8.3 (m, 5 H, aromatic protons).

Anal. Calcd for $C_{20}H_{24}O_7S_2$: C, 54.53; H, 5.49; S, 14.55. Found: C, 54.51; H, 5.64; S, 14.70.

6-*S*-Acetyl-3-*O*-benzoyl-5-chloro-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-idofuranose (4). **A.**—A mixture of **2** (200 mg) and potassium thioacetate (95 mg) in dry acetone (20 ml) was stirred under nitrogen at a temperature of 40–45°. After 16 hr, the reaction mixture was filtered and the filtrate was concentrated to a pale yellow syrup, which was chromatographed on a silica gel column using ether–hexane (2:3, v/v) as eluent. Starting material was recovered as an oil (90 mg) and the product **4** was collected as a colorless syrup (232 mg, 70%): $[\alpha]^{25}D$ −37.3° (*c* 1.56, chloroform); nmr ($CDCl_3$) δ 1.35, 1.57 (2 s, 6 H, CMe_2), 2.21 (s, 3 H, *S*-acetyl), 3.33 (m, 2 H, H-6), 4.0–4.8 (m, 1 H, H-5), 4.48 (d, 1 H, $J_{3,4}$ = 3 Hz, H-4), 4.71 (d, 1 H, $J_{1,2}$ = 4 Hz, H-2), 5.54 (d, 1 H, $J_{3,4}$ = 3 Hz, H-3), 6.03 (d, 1 H, $J_{1,2}$ = 4 Hz, H-1), 7.2–8.3 (m, 5 H, aromatic protons).

Anal. Calcd for $C_{18}H_{21}ClO_6S$: C, 53.93; H, 5.28; S, 7.99; Cl, 8.84. Found: C, 54.03; H, 5.52; S, 7.90; Cl, 8.60.

B.—A mixture of **2** (200 mg) and potassium thioacetate (63 mg, 1 mol) in dry acetone was treated under nitrogen at a temperature of 50° for 24 hr. After treatment as above, 12 mg of the starting material, 59 mg of **3** (25.8%), and 131 mg (63%) of **4** were obtained.

3-*O*-Benzoyl-5,6-dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose (5).—A mixture of **4** (150 mg) and triethylamine (5 ml) in methanol (15 ml) was stirred overnight at 40°. The solution was evaporated to dryness, and the syrup was washed with ice water (2 × 5 ml). After drying in a vacuum desiccator, the episulfide **5** was collected as a colorless syrup in quantitative yield (121 mg): $[\alpha]^{25}D$ −91.0° (*c* 1.44, chloroform); nmr ($CDCl_3$) δ 1.33, 1.52 (2 s, 6 H, CMe_2), 2.5 (m, 2 H, H-6), 3.10 (m, 1 H, H-5), 3.86 (q, 1 H, $J_{3,4}$ = 3 Hz, $J_{4,5}$ = 8 Hz, H-4), 4.68 (d, 1 H, $J_{1,2}$ = 4 Hz, H-2), 5.53 (d, 1 H, $J_{3,4}$ = 3 Hz, H-3), 6.03 (d, 1 H, $J_{1,2}$ = 4 Hz, H-1), 7.2–8.3 (m, 5 H, aromatic protons).

Anal. Calcd for $C_{16}H_{18}O_5S$: C, 59.61; H, 5.63; S, 9.94. Found: C, 59.42; H, 5.90; S, 9.66.

When 1 mol of methanolic potassium hydroxide was used instead of triethylamine, only 80.6% of **5** was isolated and compound **7** was obtained as a minor product in 9.2% yield.

5,6-Dideoxy-5,6-epithio-1,2-*O*-isopropylidene-α-D-glucofuranose (7). **A. From 5.**—To a cold methanolic solution of episulfide **5** (50 mg), a methanolic potassium hydroxide solution (1 equiv) was added dropwise. After 20 min, the solution was treated with Amberlite IR-120 (H^+). The reaction mixture was filtered and evaporated to give crystalline **7**, which was purified by passing through an alumina column using ether–hexane (1:10, v/v) as the eluent to yield 31.8 mg (94%). It melted at 140–141°: $[\alpha]^{25}D$ −75.8° (c 1.2, chloroform) [lit.[16] mp 138–140°; $[\alpha]^{25}D$ −76.2° (c 1.9, chloroform)].

B. From 4.—**4** (80 mg) was dissolved in anhydrous methanol and cooled to 0°. Methanolic potassium hydroxide solution (2 equiv) was added dropwise. After treatment as above, **7** was isolated in 91.5% yield (40 mg).

3,6-Di-*O*-acetyl-5-*S*-acetyl-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (8).—Compound **8** was prepared according to the published procedure[9] with slight modification.

Thus, a crude product of **7**, prepared from 50 mg of **5** as described in the above section (omitting the purification step by chromatography), was dissolved in a mixture of acetic acid and acetic anhydride (1:10, v/v, 3 ml). Potassium acetate (30 mg) was added and the mixture was heated at 140° for 12 hr. The resulting yellow solution was coevaporated with toluene to give a solid mixture which was extracted three times with ether and evaporated to dryness. The slightly yellow crystals thus obtained were pure enough for the next reaction. Pure **8** could be obtained, after column chromatography, as a white, crystalline compound (52 mg, 92% based on **5**), mp 149–150°, $[\alpha]^{25}D$ +7.5° (*c* 1.5, chloroform) [lit.[9] mp 149°, $[\alpha]^{25}D$ +7.2° (*c* 1.8, chloroform)].

1,2,3,4,6-Penta-*O*-acetyl-α-D-glucothiopyranose (9).—Crude **8** (25 mg) was acetolyzed with 3 ml of a mixture of acetic anhydride–acetic acid–sulfuric acid (70:30:1, v/v). After 3 days, anhydrous ether (20 ml) was added, followed by sodium acetate (300 mg). The mixture was filtered and the residue was washed with ether (2 × 20 ml). The combined solutions were coevaporated with toluene to give a thick syrup, which was chromatographed on a silica gel column using ether–hexane (1:4, v/v) as eluent. Pure pentaacetate **9** was collected as white crystals (20 mg, 68.6%). Recrystallization from ether–hexane gave long needles, mp 103°, $[\alpha]^{25}D$ +213° (*c* 1.4, chloroform) [lit.[9] mp 103°, $[\alpha]^{25}D$ +213° (*c* 1.35, chloroform)].

(10) A. M. Creighton and L. N. Owen, *J. Chem. Soc.*, 1024 (1960).

(11) L. W. C. Miles and L. N. Owen, *ibid.*, 817 (1952); J. S. Harding and L. N. Owen, *ibid.*, 1528 (1954); P. S. Fitt and L. N. Owen, *ibid.*, 2240 (1957).

(12) R. M. Rowell and R. L. Whistler, *J. Org. Chem.*, **31**, 1514 (1966).

(13) U. G. Nayak and R. L. Whistler, *ibid.*, **34**, 97 (1969).

(14) L. Merk Ag, Darmstadt, Germany. Distributors: Brinkman Instruments Inc., Westbury, N. Y. 11590.

(15) J. T. Baker Chemical Co., Phillipsburg, N. J.

(16) E. Fischer, *Ber.*, **48**, 268 (1915).

6-*O*-Acetyl-5-*S*-acetyl-3-*O*-benzoyl-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (6).—A mixture of 5 (34 mg) and potassium acetate (300 mg) in 5 ml of acetic acid–acetic anhydride (1:5, v/v) was heated at 140°. After 16 hr, the reaction mixture was coevaporated with toluene to dryness, extracted with ether, and concentrated. The crystalline product was purified by column chromatography on silica gel, using ether–hexane (2:3, v/v) as eluent to give 6 (440 mg, 96.7%), mp 129–30°, $[\alpha]^{25}D$ −80.8° (*c* 0.5, chloroform).

Anal. Calcd for $C_{20}H_{24}O_8S$: C, 56.57; H, 5.69; S, 7.55. Found: C, 56.75; H, 5.83; S, 7.50.

Reaction of 6 with Sodium Methoxide.—Compound 6 (100 mg) was dissolved in anhydrous methanol (10 ml) and cooled to 0°. A solution of sodium methoxide in methanol was added and the pH was adjusted to 10. Progress of the reaction was monitored by tlc using ether–hexane (2:3, v/v) as the irrigant. After 1 hr, the reaction mixture was neutralized with Amberlit IR-120 (H^+) resin, evaporated, and chromatographed on alumina with ether–hexane (1:10, v/v) to give 7 (40 mg, 77.81 %).

Registry No.—1, 37614-73-6; 2, 37614-74-7; 3, 37614-75-8; 4, 37614-76-9; 5, 37614-77-0; 6, 37614-78-1; 7, 37614-79-2; 8, 10227-17-5; 9, 10227-18-6.

Protection of Carbonyl Groups as Bromomethylethylene Ketals

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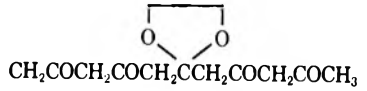
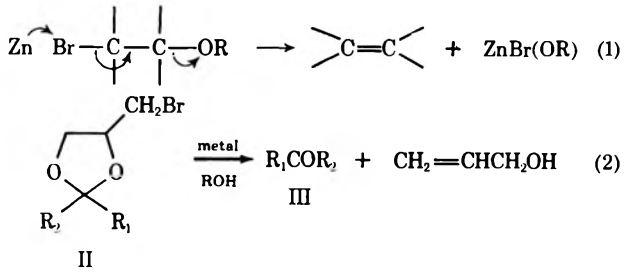
Ketalization has proven to be an invaluable method for the protection of a carbonyl group during various transformations. However, a ketal protecting group necessitates the use of acid catalysis for its removal. During the course of studies directed toward a total synthesis of the spiro alkaloid histrionicotoxin,[1] a carbonyl protecting group which could be removed under neutral conditions was required. Other instances of the inadequacy of conventional methods for carbonyl protection have been noted previously; *e.g.*, removal of the ketal blocking group from the polyketide I could not be achieved.[2]



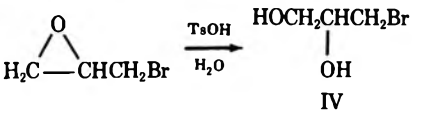
I

A promising approach seemed to be the use of a bromomethylethylene ketal which could be cleaved by the familiar β-bromo ether reductive elimination (eq 1; *cf.* ref 3). More specifically, the simplest cyclic ethylene ketal (II) was selected for use, the unmasking step then being expressed by eq 2.



II

Following the procedure of Winstein and Goodman, the requisite starting material, 1,2-dihydroxy-3-bromopropane[4] (IV), was prepared in one step from epibromohydrin. Three substrates, V–VII, were chosen to



IV

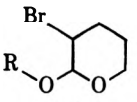
illustrate the generality of the sequence ketalization–deketalization. The first step, ketalization, was accomplished in excellent yield by treatment of an aldehyde or ketone with bromoglycol IV in refluxing benzene using *p*-toluenesulfonic acid as a catalyst (Table I). Deketalization was attempted using a variety of metals and conditions.[3,5] After some experimentation, it was found that treatment of the bromo ketal with activated zinc in refluxing methanol afforded an excellent yield of the deketalized compound (Table I).

TABLE I

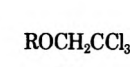
Carbonyl compd	Yield of Ketal,[a,b] %	Yield of deketalized material,[a,c] %
4-*tert*-Butylcyclohexanone (V)	98[d]	89
$CH_3(CH_2)_4COCH_2COOCH_3$ (VI)	95[e]	96
$CH_3(CH_2)_{10}CHO$ (VII)	93[f]	89

[a] Evaporatively distilled. [b] The ketals showed the expected spectral and analytical properties. [c] Infrared and nmr spectra were identical with those of authentic material. [d] Mass spectrum M^+ calcd 290.0082, found 290.0879. [e] ($M^+ - CH_3OM$) calcd 277, found 277 (no parent ion). [f] M^+ calcd 320.1350, found 320, 1342.

The bromomethylethylene ketal unit has been found to be stable to a variety of reagents which are commonly used in synthesis. Thus, treatment of the ketal obtained from 4-*tert*-butylcyclohexanone with *m*-chloroperbenzoic acid, liquid ammonia, $NaBH_4$ in ethanol at room temperature, MeLi in ether at 0° for 1 hr, or Jones (CrO_3) reagent led to a *quantitative recovery* of starting ketal. In addition, it should be noted that there are many hydroxyl, amino, and carbonyl protecting groups which can survive the deketalization conditions and only a few, for example the alcohol protecting groups VIII and IX, which cannot.



VIII



IX

Experimental Section

The following experiments illustrate the procedures utilized.

Ketalization.—Dodecanal (634 mg, 3.40 mmol) in 2 ml of benzene was added portionwise to a refluxing benzene solution (50 ml) of bromoglycol IV (5.3 g, 34.0 mmol) and *p*-toluenesulfonic acid (50 mg) over 10 hr. The solution was heated at reflux for an additional 5 hr, and the product was isolated after washing with water and removal of benzene to afford 1.10 g (100%) of crude bromo ketal. Evaporative distillation (120°,

(1) J. W. Daley, I. Karle, C. W. Meyers, T. Tokuyama, J. A. Waters, and B. Witkop, *Proc. Nat. Acad. Sci. U. S.*, 1870 (1971).

(2) A. J. Birch, P. Fitton, D. C. C. Smith, D. E. Steerie, and A. R. Stelfox, *J. Chem. Soc.*, 2209 (1963).

(3) H. O. House and R. S. Ro, *J. Amer. Chem. Soc.*, **80**, 182 (1958).

(4) S. Winstein and L. Goodman, *ibid.*, **76**, 4368 (1954).

(5) Representative metals tried were Zn, Al–Hg, Mg–Hg, Zn–Cu, Zn–Hg, and Li–Hg.

0.08 mm) afforded 1.040 g (93%) of dodecanal bromo ketal as a colorless oil: infrared peaks (film) at 8.75 and 8.90 μ; nmr $\delta_{TMS}^{CDCl_3}$ 4.99 (HCOO, multiplet), 4.58–3.17 [OCH(CH_2Br)CH_2O, complex], and 0.89 ppm (CH_3, triplet, J = 4.0 Hz); mass spectrum calcd for $C_{15}H_{29}O_2Br$ 320.1350; found 320.1342.

Deketalization.—A solution of 162 mg (0.505 mmol) of dodecanal bromo ketal and 500 mg of zinc dust in 10 ml of methanol was heated at reflux under argon for 12 hr. The zinc was removed by filtration, and the product was isolated by ether extraction and evaporatively distilled (bp 80°, 0.07 mm), yielding 83 mg (89%) of dodecanal, identical with an authentic sample. The zinc was activated by brief treatment with acetic acid followed by washing with methanol.

The efficiency of introduction and removal of the bromomethylethylene ketal group, its stability toward many synthetic reagents, and the selectivity with which it can be removed[6] all indicate a real utility in synthesis.[7]

Registry No.—IV, 4704-77-2; V, 98-53-3; V bromo ketal, 37447-43-1; VI; 22348-95-4; VI bromo ketal, 37447-45-3; VII, 112-54-9; VII bromo ketal, 37447-47-5.

(6) For controlled potential electrolytic removal of such groups, see M. F. Semmelhack and G. E. Heinsohn, *J. Amer. Chem. Soc.*, **94**, 5140 (1972).

(7) This research was financially assisted in part by the National Institutes of Health and the National Science Foundation.

Acid Hydrolysis Products of DDD and DDT Precursors[1]

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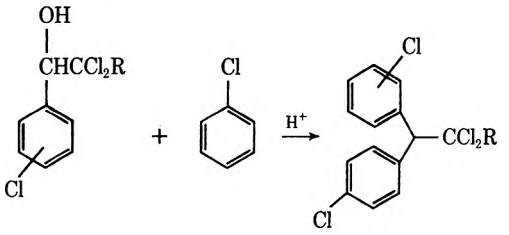
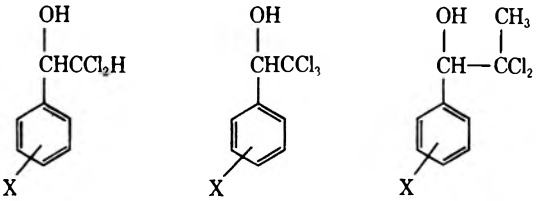
The widespread use of 2,2-di(*p*-chlorophenyl)-1,1,1-trichloroethane (DDT) as a pesticide as well as the more limited use of 2-(*o*-chlorophenyl)-2-(*p*-chlorophenyl)-1,1-dichloroethane (*o,p'*-DDD) as the only clinically approved agent for the treatment of adrenocortical carcinoma has prompted numerous chemical investigations in these classes of compounds.[3-13] Studies in our laboratories have been devoted to (1) preparing derivatives of *o,p'*-DDD which lack the serious toxicity of this drug and (2) studying the chemistry of the precursors used in the synthesis of these derivatives.

The conventional and most direct method for the preparation of DDD derivatives involves the acid-catalyzed condensation of 1-(chlorophenyl)-2,2-dichloroethanols with chlorobenzene.[3,8] This method is commonly employed, since usable amounts of DDD's are obtained from readily available starting materials. However, the yields are generally rather poor (*ca.* 30–50%).[3,8] An investigation of the products and by-products in this reaction was, therefore, undertaken to aid in delineating the scope and limitations of this reaction. Moreover, ramifications of this work can be extended to the synthesis and hydrolysis of DDT and its precursors. This paper reports the products formed when phenyldichloroethanols **1**, phenyltrichloroethanols **2**, and phenyldichloropropanols **3** are subjected to concentrated sulfuric acid,[14] conditions normally employed for the synthesis of DDT[3] and DDD.[8]





1a, X = *o*-Cl; **b**, X = *m*-Cl; **c**, X = *p*-Cl

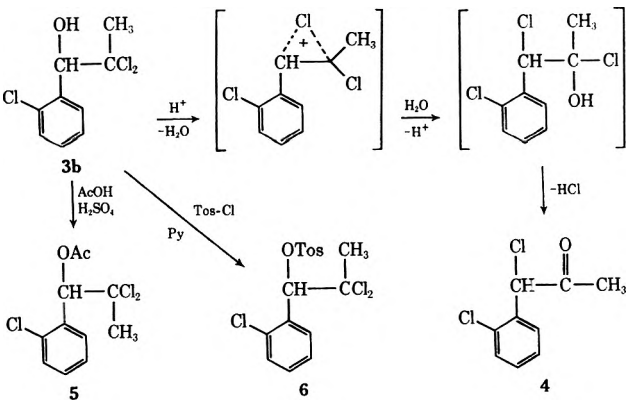
2a, X = H; **b**, X = *o*-Cl

3a, X = H; **b**, X = *o*-Cl; **c**, X = *p*-Cl

Glc–mass spectral analysis and infrared and nuclear magnetic resonance spectroscopy were employed for characterization of the products.

Results and Discussion

Unexpected results were obtained in the acid hydrolysis of the phenyldichloropropanols **3**. Treatment of 2,2-dichloro-1-(*o*-chlorophenyl)propanol (**3b**) with concentrated sulfuric acid at 40–45° for 3 hr afforded, exclusively, 1-(*o*-chlorophenyl)-1-chloropropanone (**4**). One possible means for such a conversion can be explained as proceeding through a chloronium ion as shown below.



(1) This investigation was supported by the U. S. Public Health Service under Research Grants No. CA-49340 and CA-08349 from the National Cancer Institute.

(2) (a) Department of Chemistry, University of Maine, Orono, Maine 04473; (b) National Institutes of Health Postdoctoral Fellow, 1970–1972.

(3) H. L. Haller, *et al.*, *J. Amer. Chem. Soc.*, **67**, 1591 (1945).

(4) S. J. Cristol and H. L. Haller, *ibid.*, **70**, 1323 (1948).

(5) T. Inoi, P. Gericke, and W. J. Horton, *J. Org. Chem.*, **27**, 4597 (1962).

(6) K. Y. Zee-Cheng and C. C. Cheng, *J. Med. Pharm. Chem.*, **5**, 1008 (1962).

(7) R. Riemschneider, I. Ahrlé, W. Cohnen, and E. Heilmann, *Chem. Ber.*, **92**, 900 (1959).

(8) R. E. Counsell and R. E. Willette, *J. Pharm. Sci.*, **55**, 1012 (1966).

(9) W. Tadros, A. B. Sakla, and M. K. Khalil, *J. Chem. Soc. C*, 373 (1966).

(10) R. E. Counsell, V. V. Ranade, L. K. Lala, and B. H. Hong, *J. Med. Chem.*, **11**, 380 (1968).

(11) R. E. Counsell, V. V. Ranade, P. Pocha, R. E. Willette, and W. Diguilo, *J. Pharm. Sci.*, **57**, 1657 (1968).

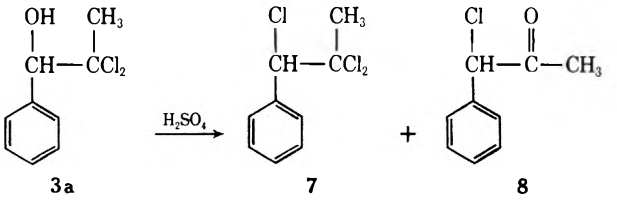
(12) A. B. Sakla, W. Tadros, and A. A. A. Helmy, *J. Chem. Soc. C*, 1044 (1969).

(13) A. B. Sakla, W. Tadros, and M. K. Khaliel, *ibid.*, 409 (1970).

(14) A recent report by P. B. Blumbergs and M. P. LaMontagne, *J. Org. Chem.*, **37**, 1248 (1972), has shown that phenyldichloromethylcarbinols on hydrolysis with potassium carbonate afford α-hydroxyaldehydes.

By following this rearrangement using an acidified nmr sample, it was shown that the small amount of water formed by the protonation of the alcohol in acid is sufficient for the conversion to the ketone **4** even before aqueous work-up conditions are employed. The rearrangement occurs so rapidly, in fact, that attempted condensations with chlorobenzene in sulfuric acid failed completely and only **4** was formed. Normal esterification methods were, on the other hand, completely successful using acetic acid–sulfuric acid and *p*-toluenesulfonyl chloride–pyridine. The structures of the esters **5** and **6** were confirmed by their mass spectra, which showed distinct loss of Cl_2CCH_3.

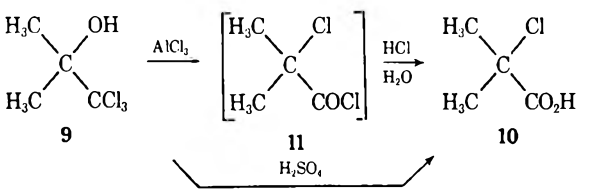
When 2,2-dichloro-1-phenylpropanol (**3a**) was treated under identical conditions, two compounds were formed. Separation of these compounds by preparative glc afforded materials with virtually identical nmr spectra. The nmr spectrum of the less volatile component showed a five-proton multiplet at τ 2.48 assigned to aromatic protons, a single-proton singlet at 4.70 assigned to a benzylic proton, and a three-proton singlet at 7.74 assigned to a methyl group. Its infrared spectrum lacked both OH and C=O stretching bands. Mass spectrometry showed molecular ions at *m/e* 222, 224, and 226 in the correct ratio for three chlorine atoms. The structure of this compound was assigned as 1-phenyl-1,2,2-trichloropropane (**7**). The nmr spectrum of the more volatile component showed a five-proton singlet at τ 2.55 assigned to aromatic protons, a single-proton singlet at 4.64 assigned to a benzylic proton, and a three-proton singlet at 7.80 assigned to protons. Its infrared spectrum showed a very intense C=O stretching band at 1715 cm^{-1}. The mass spectrum of this component showed molecular ions at *m/e* 168 and 170 in the correct ratio for one chlorine atom. This information was consistent for 1-chloro-1-phenyl-2-propanone (**8**).



3a **7** **8**

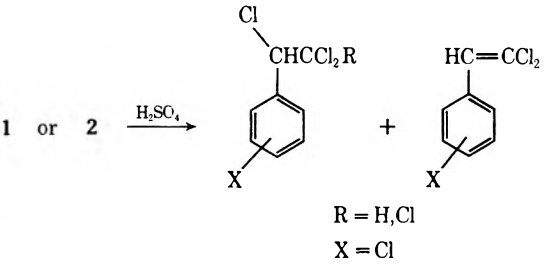
During the course of this work, a literature search revealed that Kundiger and Pledger[15] had observed a related product resulting from attempted Friedel–Crafts condensations with 1,1,1-trichloro-2-methyl-2-propanol (**9**) (Chloretone). In the presence of aluminum chloride, **9** was shown to afford only α-chloroisobutyric acid (**10**) after a work-up procedure employing aqueous hydrochloric acid. These workers assumed that **10** was formed *via* α-chloroisobutyroyl chloride (**11**). Under the conditions of this reaction it would be impossible, however, to postulate what the true intermediate species would be and by what means it was formed, since several sources of chloride ion were present. Moreover, our further examination of this reaction showed that concentrated sulfuric acid afforded the same α-chloro acid **10** in quantitative yield. Under these conditions, the only source of chloride ion was 1,1,1-trichloro-2-methyl-2-propanol (**9**).

(15) D. G. Kundiger and H. Pledger, Jr., *J. Amer. Chem. Soc.*, **78**, 6098 (1956).



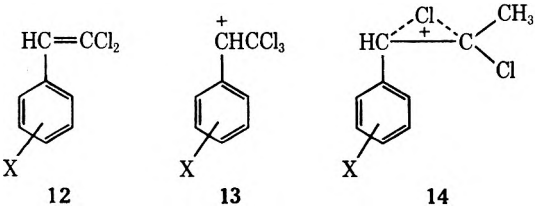
9 **11** **10**

In contrast to the above results, acid hydrolysis of **1** and **2** afforded no oxidative rearrangement carbonyl products. In general, the two types of products which predominated were those formed by the replacement of the hydroxyl group by a halogen and/or the acid-catalyzed elimination of the elements of HOX.[16]



Summary

From the products obtained, it appears as though three different intermediates are involved in the acid-catalyzed syntheses of DDD and DDT. Schriesheim[17] has pointed out that phenyldichloroethanols **1** probably proceed through the olefin **12** *via* elimination of water. This olefin is the true electrophile in the reaction with chlorobenzene. On the other hand, phenyltrichloroethanols **2** form stable carbonium ions **13** when treated with acid.[18] The carbonium ions **13** are the reacting species in the condensation with chlorobenzene. Phenyldichloropropanols **3** rearrange in acid *via* chloronium ion **14** before condensation products form. In virtually every case, chloride ion resulting from liberated HCl or from disproportionation reactions reacts with the alcohol to afford benzylic chlorinated derivatives. A summary of the hydrolysis products is listed in Tables I, II, and III.



12 **13** **14**

Experimental Section

General.—Melting points were obtained with a Fisher-Johns melting point apparatus and are uncorrected. Boiling points are uncorrected. The nuclear magnetic resonance (nmr) spectra were recorded on a Varian A-60A spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Infrared spectra were determined on a Perkin-Elmer Model 337 spectrophotometer. Glc–mass spectral analyses were performed on a Loenco Model 160 gas chromatograph using a 6 ft × 0.125 in. stainless steel column packed with 3% OV-17 on 100/120 mesh Chromo-

(16) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959).

(17) A. Schriesheim, "Friedel–Crafts and Related Reactions," Vol. II, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, p 480.

(18) D. Bethell and V. Gold, "Carbonium Ions. An Introduction," Academic Press, New York, N. Y., 1967, p 117.

TABLE I

HYDROLYSIS OF PHENYLDICHLOROETHANOLS 1a–c

Alcohol	Major products	Other products
1a	*o*-$ClC_6H_4CH{=}CCl_2$ *m/e* 206 (3 Cl)	Starting material
1b	*m*-$ClC_6H_4CHClCHCl_2$ *m/e* 242 (4 Cl) + *m*-$ClC_6H_4CH{=}CCl_2$ *m/e* 206 (3 Cl)	
1c	*p*-$ClC_6H_4CHClCHCl_2$ *m/e* 242 (4 Cl) + *p*-$ClC_6H_4CH{=}CCl_2$ *m/e* 206 (3 Cl)	Starting material

TABLE II

HYDROLYSIS OF PHENYLTRICHLOROETHANOLS 2a–b

Alcohol	Major products	Other products
2a	$C_6H_5CHClCCl_3$ *m/e* 242 (4 Cl)	Unidentified solids
2b	*o*-$ClC_6H_4CHClCCl_3$ *m/e* 276 (5 Cl) + *o*-$ClC_6H_4CH{=}CCl_2$ *m/e* 206 (3 Cl) + *o*-$ClC_6H_4CCl{=}CCl_2$ *m/e* 240 (4 Cl)	*o*-ClC_6H_4CHO *m/e* 139 (1 Cl)

TABLE III

HYDROLYSIS OF PHENYLDICHLOROPROPANOLS 3a–c

Alcohol	Major products	Other products
3a	$C_6H_5CHClC(=O)CH_3$ *m/e* 168 (1 Cl) + $C_6H_5CHClCCl_2CH_3$ *m/e* 222 (3 Cl)	
3b	*o*-$ClC_6H_4CHClC(=O)CH_3$ *m/e* 202 (2 Cl)	
3c	*p*-$ClC_6H_4CHClC(=O)CH_3$ *m/e* 202 (2 Cl) + *p*-$ClC_6H_4CHClCCl_2CH_3$ *m/e* 256 (4 Cl)	*p*-$ClC_6H_4CO_2H$ *m/e* 156 (1 Cl)

sorb G and interfaced with a Du Pont Model 21-490 mass spectrometer. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich., and Midwest Microlab, Indianapolis, Ind.

Materials. Preparation of Phenyldichloroethanols (1a–c).—These compounds were prepared as previously described by Counsell and Willette.[8]

Preparation of Phenyltrichloroethanols (2a–b).—These compounds were prepared by the method of Bergmann, *et al.*[19]

Preparation of Phenyldichloropropanols (3a–c).—The general method is illustrated by the preparation of 2,2-dichloro-1-(*o*-chlorophenyl)propanol (**3b**).

Dry chlorine gas was bubbled slowly through a solution of *o*-chloropropiophenone[20] (19.7 g, 0.117 mol) in glacial acetic acid (150 ml) for 2 hr at 110°. The solution was flushed with nitrogen for 15 min and anhydrous sodium acetate (25.0 g) was added. Chlorine gas was again bubbled through the solution at 110° for an additional 5 hr. The cooled reaction mixture was poured into ice water (2 l.) saturated with NaCl and containing $NaHSO_3$ (5.0 g) and extracted with ether. The ethereal extract was dried (Na_2SO_4), concentrated, and distilled, giving 22.0 g (79%) of α,α-dichloro-*o*-chloropropiophenone: bp 58–59° (0.75 mm); ir (film) 1720 cm^{-1} (C=O); nmr ($CDCl_3$) τ 2.50 (m, 4, ArH) and 7.67 (m, 3, CH_3).

Anal. Calcd for $C_9H_7Cl_3O$: C, 45.51; H, 2.97. Found: C, 45.40; H, 2.88.

Over a period of 30 min, $NaBH_4$ (4.75 g, 0.126 mol) was added portionwise to a solution of α,α-dichloro-*o*-chloropropiophenone (13.1 g, 0.055 mol) in methanol (150 ml) at ice-bath temperature. Stirring was continued for 1.5 hr in the cold and for an additional 2.5 hr at room temperature. The reaction mixture was poured into ice water (1.5 l.) containing NH_4Cl (50 g), saturated with NaCl, and extracted with ether. The ethereal extract was dried (Na_2SO_4), concentrated, and distilled, yielding 11.8 g (89%) of **3b**: bp 79–81° (0.2 mm); mp 68–69° (CCl_4–hexane); ir ($CHCl_3$) 3550 cm^{-1} (OH); nmr ($CDCl_3$) τ 2.45 (m, 4, ArH), 4.34 (d, 1, CH), 6.87 (d, 1, OH), and 7.87 (s, 3, CH_3).

Anal. Calcd for $C_9H_9Cl_3O$: C, 45.12; H, 3.78. Found: C, 45.26; H, 3.92.

2,2-Dichloro-1-phenylpropanol (3a) had bp 72–76° (0.3 mm) [lit.[21] bp 85–86° (1.0 mm)]; ir (film) 3475 cm^{-1} (OH); nmr ($CDCl_3$) τ 2.55 (m, 5, ArH), 5.00 (d, 1, CH), 6.88 (d, 1, OH), and 7.95 (s, 3, CH_3).

2,2-Dichloro-1-(*p*-chlorophenyl)propanol (3c) had bp 128–129° (1.0 mm); mp 59–60° [petroleum ether (bp 30–60°)]; ir (film) 3550 cm^{-1} (OH); nmr ($CDCl_3$) τ 2.55 (m, 4, ArH), 5.02 (d, 1, CH), 6.80 (d, 1, OH), and 7.99 (d, 3, CH_3).

Anal. Calcd for $C_9H_9Cl_3O$: C, 45.12; H, 3.78. Found: C, 45.35; H, 3.79.

Product Study.—A 1.0-g sample of an alcohol was treated at 40–45° with 5 ml of concentrated sulfuric acid. After 3 hr, the mixture was poured into ice water and extracted with three 100-ml portions of ether. The ethereal extract was dried over Na_2SO_4 and concentrated *in vacuo* to leave a yellowish residue. Glc–mass spectral analyses were performed on a Loenco Model 160 (flame ionization detector) gas chromatograph interfaced with a Du Pont Model 21-490 mass spectrometer. The results are tabulated in Tables I, II, and III.

Preparation of 1-(*o*-Chlorophenyl)-1-chloropropanone (4).—At 40–45° concentrated sulfuric acid (30 ml) was added dropwise with stirring to **3b** (12.8 g, 0.054 mol). After 4 hr, the mixture was poured into ice water (400 ml) and extracted with ether. The ethereal extract was washed with water and dried (Na_2SO_4). Evaporation of the solvent left a residue which was distilled, yielding 8.0 g (74%) of **4**: bp 82–85° (0.4 mm); ir (film) 1730 cm^{-1} (C=O); nmr ($CDCl_3$) τ 2.60 (m, 4, ArH), 4.08 (s, 1, CH), and 7.74 (s, 3, CH_3); mass spectrum *m/e* 202 (M^+), 167 ($M^+ - 35$), 159 ($M^+ - 43$), 125 ($M^+ - 77$), 103 ($M^+ - 99$), and 89 ($M^+ - 113$).

Preparation of α-Chloroisobutyric Acid (10).—A mixture of 1,1,1-trichloro-2-methyl-2-propanol[22] (5.0 g, 0.028 mol) and concentrated sulfuric acid (15 ml) was heated at 40–45° for 3 hr. The mixture was poured into ice water and extracted with ether.

(19) E. D. Bergmann, D. Ginsburg, and D. Lavie, *J. Amer. Chem. Soc.*, **72**, 5012 (1950).

(20) V. L. Szotyory and E. Hamburg, *J. Prakt. Chem.*, **23**, 208 (1963).

(21) M. Ballester and J. Riera, *An. Real Soc. Espan. Fis. Quim.*, **56**, 897 (1960); *Chem. Abstr.*, **55**, 19876 (1961).

(22) C. Weizmann, E. Bergmann, and M. Sulzbacker, *J. Amer. Chem. Soc.*, **70**, 1189 (1948).

The ethereal extract was washed with water before drying over Na_2SO_4. The solvent was concentrated under vacuum and the residue was distilled, yielding 3.4 g (100%) of **10**: bp 38–39° (0.2 mm) [lit.[15] bp 51–52° (1.0 mm)]; ir (CCl_4) 3500–3200 (OH) and 1710 cm^{-1} (C=O); nmr ($CDCl_3$) τ −2.36 (s, 1, CO_2H) and 9.16 (s, 6, 2 CH_3).

Preparation of 2,2-Dichloro-1-acetoxy-1-(*o*-chlorophenyl)propane (5).—A stirred solution of **3b** (2.0 g, 0.0084 mol) in glacial acetic acid (100 ml) and concentrated sulfuric acid (5 ml) was heated at 45° for 3 hr. The solution was poured into ice water (800 ml) and extracted with ether. The combined extracts were washed with 10% $NaHCO_3$ and water before drying over Na_2SO_4. Removal of the solvent left a residue which recrystallized from methanol to afford 1.5 g (64%) of **5** as colorless crystals: mp 86–87°; ir (KBr) 1745 cm^{-1} (C=O); nmr ($CDCl_3$) τ 2.43 (m, 4, ArH), 3.24 (s, 1, CH), 7.83 (s, 3, CH_3), and 7.85 (s, 3, CH_3); mass spectrum *m/e* 280 (M^+), 245 (M^+ − 35), 183 (M^+ − 97 − Cl_2CCH_3), and 141 (M^+ − 139).

Anal. Calcd for $C_{11}H_{11}Cl_3O_2$: C, 46.92; H, 3.94. Found: C, 47.12; H, 4.19.

Preparation of 2,2-Dichloro-1-tosyloxy-1-(*o*-chlorophenyl)propane (6).—A solution of **3b** (1.2 g, 0.005 mol) and *p*-toluenesulfonyl chloride (1.6 g, 0.008 mol) in pyridine (50 ml) was stirred for 5 days at room temperature. The solution was poured into ice-cold 10% HCl (500 ml) and the product was extracted into ether. The ethereal solution was washed with water and 5% KOH before drying over Na_2SO_4. Removal of the solvent afforded **6** as an oil which crystallized from hexane–petroleum ether (bp 30–60°) as colorless crystals (1.0 g, 68%): mp 88–89°; nmr ($CDCl_3$) τ 2.55 (m, 8, ArH), 3.75 (s, 1, CH), 7.64 (s, 3, CH_3), and 7.83 (s, 3, CH_3); mass spectrum *m/e* 392 (M^+), 295 (M^+ − 97- Cl_2CCH_3), 186 (M^+ − 106), 155 (M^+ − 237), 115 (M^+ − 277), and 91 (M^+ − 301).

Registry No.—**3b**, 35996-56-6; **3c**, 37610-56-3; **4**, 37610-57-4; **5**, 37610-58-5; **6**, 37610-59-6; DDD, 72-54-8; DDT, 50-29-3; *o*-chloropropiophenone, 6323-18-8; α,α-dichloro-*o*-chloropropiophenone, 35996-45-3.

Addition of Simple Siloxanes to β-Methallyl Chloride[1]

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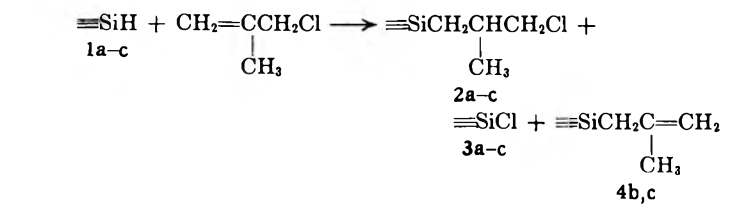
The importance of silicone surfactants prompted this investigation of the catalyzed addition of small siloxane units to β-methallyl chloride. The resulting adducts may serve as intermediates for surfactant synthesis.

Three types of products were observed from the reaction of siloxanes **1a–c** with β-methallyl chloride:



a, $Me_3SiOSiMe_2H$
b, $(Me_3SiO)_2SiMeH$
c, $(Me_3SiO)_3SiH$

adducts (**2a–c**), rearrangement products (**3a–c**), and methallylsiloxanes (**4b,c**).

β-Methallyl chloride, a siloxane, and catalyst were heated at reflux for an appropriate time. Products were identified and yields were determined by comparison with authentic samples using gas chromatography. These results are summarized in Table I.

TABLE I
SILOXANE ADDITION TO β-METHALLYL CHLORIDE

Siloxane	Catalyst	Reaction time, hr	Products (yield, %)
1a	H_2PtCl_6	2	**2a** (97)
1b	H_2PtCl_6	1	**2b** (34), **3b** (18), **4b** (9)
1b	Pt/C	72	**2b** (30), **3b** (18), **4b** (10)
1c	H_2PtCl_6	1.5	**2c** (14), **3c** (42), **4c** (23)
1a	Pd/C	Immediate	**3a** (96)
1b	Pd/C	100	**3b** (74)
1b[a]	$PdCl_2$	Immediate	**3b** (100)
1b	Ru/C	4	**3b** (60)
1c	Pd/C	48	**3c** (24)
1b	None	48	No conversion

[a] Reaction in the absence of β-methallyl chloride.

Structural proof of the adducts, **2a–c**, was based on their ir, nmr, mass spectra, and elemental analysis. The mass spectra of **2a–c** failed to show molecular ions, but did show predominant fragments at *m/e* 73 (Me_3Si^+) and M − $CH_2CH(CH_3)CH_2Cl$. The nmr spectra of **2a–c** are in full accord with the proposed structures and are summarized in Table II.

The structures of the chlorosilanes, **3a–c**, were based upon elemental analysis, mass spectra, nmr, and infrared spectra. The mass spectra of **3a–c** also failed to show molecular ions, but did have fragments at M − CH_3 and M − Cl. A predominant fragment corresponding to Me_3Si was observed for all the chlorosilanes. The nmr spectra of **3a–c** were similar to those of the corresponding siloxanes **1a–c**, and the infrared spectra of **3a–c** showed the absence of Si–H stretching at 2200 cm^{-1}.[4] Rapid hydrolysis of **3a–c** to the corresponding silanols with evolution of hydrogen chloride further supports the presence of the SiCl bond.

Methallylsiloxanes (**4b,c**) could not be purified by distillation, but were satisfactorily separated by preparative gas chromatography. Elemental analysis, ir, nmr, and mass spectra of these compounds were fully in accord with the proposed structure. Their ir spectra indicated an allylic structure[5] with absorption at 1635 and 1250 cm^{-1}. The nmr spectra are similar to those reported by Egorochkin, *et al.*, for analogous compounds.[6] The mass spectra of **4c** indicated a molecular ion at *m/e* 350 and predominant fragments at NCH_3 and M − C_4H_7 and for Me_3Si.

Two additional synthetic routes to siloxanes **2a–c** were explored. First, the reaction of **5**[7] with pyridine, followed by the addition of trimethylsilanol, gave a 20% yield of **2b**. The second route involved the cohydrolysis of **5** with trimethylchlorosilane in water to give a 32% yield of **2b**. The most convenient

(1) Reported in part at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972.

(2) National Science Foundation Undergraduate Research Participant, 1971.

(3) (a) Chemistry Department, Drexel University; (b) Research Department, National Foam System, Inc.

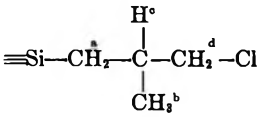
(4) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, Chapter 5.

(5) R. J. H. Voorhoeve, "Organohalosilanes: Precursors to Silicones," Elsevier, Amsterdam, 1967, p 372.

(6) A. N. Egorochkin, M. L. Khidekel, G. A. Razuvaev, G. G. Petukhov, and V. F. Mironov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1521 (1964).

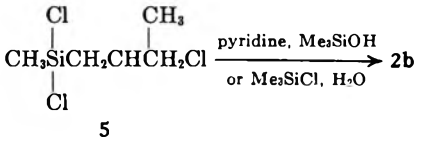
(7) J. W. Ryan, G. K. Menzie, and J. L. Speier, *J. Amer. Chem. Soc.*, **82**, 3601 (1960).

TABLE II
CHEMICAL SHIFTS FOR THE PROTONS IN ADDUCTS 2a–c



Siloxane[a]	CH_3Si	$OSi(CH_3)O$	H_a	H_b	H_c	H_d
2a	10.1 (s, 15)		9.6 (q, 2)	9.1 (d, 3)	8.2 (m, 1)	6.8 (q, 2)
2b	10.1 (s, 18)	10.00 (s, 2.5)	9.5 (q, 2)	9.0 (d, 3)	8.1 (m, 1)	6.7 (q, 2)
2c	10.1 (s, 27)		9.6 (q, 2)	9.1 (d, 3)	8.3 (m, 1)	6.7 (q, 2)

[a] Chemical shifts are τ values. Samples were run neat, referenced against benzene as an internal standard.



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method for the preparation of **2b** proved to be the platinum-catalyzed addition of **1b** to β-methallyl chloride to give a greater than 30% yield of **2b** (Table I).

The course of the reactions studied appears to be influenced by both the choice of siloxane and catalyst. Platinum, as chloroplatinic acid or platinum on charcoal, forms adducts **2a–c**, chlorosiloxanes **3b,c**, and methallylsiloxanes **4b,c**. Palladium and ruthenium, on the other hand, generate only chlorosiloxanes (**3a–c**). The formation of alkyl silanes and chlorosilanes from silanes, allyl chlorides, and chloroplatinic acid has been observed by others,[7,8] but to our knowledge this is the first report of the preparation of methallylsiloxanes under these conditions.

These results suggest that two mechanisms are at work, one pathway leading to addition and the other to chlorosiloxanes. The form of catalyst (homogeneous *vs.* heterogeneous) had little effect on reaction products; chloroplatinic acid gave essentially identical results with platinum on charcoal.

It is clear that any mechanism proposed must consider a metal center in its intermediate states. Chalk and Harrod have proposed a mechanism for homogeneous silane additions with chloroplatinic acid.[9] They suggested that platinum(IV) is reduced by the olefin to platinum(II). Platinum(II) complexes with the silane to reform a platinum(IV) structure which decomposes to the alkylsilane. This is then displacement by another olefin. Palladium, however, does not catalyze addition and is rapidly reduced to the metal.

To account for the formation of chlorosilanes from silanes, allyl chloride, and chloroplatinic acid, Ryan and Speier proposed the formation of an intermediate complex of the silane, metal, and olefin.[10] This complex or intermediate could generate either the alkyl silane or chlorosilane. Both these mechanistic schemes, however, fail to explain why platinum catalysts generate chlorosiloxanes in varying proportions along with other products, whereas palladium forms chlorosiloxanes exclusively.

Studies of platinum and palladium organic complexes reveal important structural differences.[11] When treated with mesityl oxide, for example, platinum(II) chloride tends to form localized π-olefin complexes, whereas the corresponding palladium compounds are π-allylic. Allyl and methallyl chloride palladium complexes are also known to be π-allylic.[12–14] In addition, the isomerization of olefins (which accompanies catalytic hydrosilations) occurs readily with palladium, but to a lesser extent with platinum. Both metals are generally acknowledged to accomplish this through π-allyl complex formation.[15] Localized platinum–olefin complexation is consistent with requirements for the accepted hydrosilation mechanism,[9] and leads to addition products. A delocalized π-allylic interaction characteristic of palladium and in some cases platinum apparently fails to generate the adduct. If chlorosiloxanes are produced from a metal–allylic intermediate (or transition state) which accomplishes the necessary isomerization to isobutylene, the experimental results are accounted for. Interaction of palladium with the C–Cl bond may form a transient π-allylic complex and a Pd–Cl bond which reacts with the siloxane to give **3a–c**.

In support of this interpretation, palladium chloride vigorously converted **1b** to **3b** quantitatively. Furthermore, to test the validity of a palladium complex of β-methallyl chloride as an intermediate, bis[isobutenylpalladium(II) chloride][16] was treated with **1b** to give an instantaneous, quantitative conversion to **3b**.

Effects of the siloxanes in these reactions are less obvious. Chalk and Harrod related the strength of the Si–H bond in silanes (determined from Si–H in the infrared) to that of its silicon–metal derivative. They concluded that the stronger the ≡Si–H bond, the more stable the complex derived from it would be. In siloxanes **1a–c**, the increasing electron-withdrawing effect of Me_3SiO substituents increase the strength of the silicone–hydrogen bond in the order **1c** > **1b** > **1a**. Presumably, stability of the intermediate complexes should be in the same order. Accompanying this change, however, is steric shielding of the reactive site. Together these two factors affect the reactivity of the siloxane. In the case of a platinum catalyst, these effects may destabilize the π-olefin complex resulting in a π-allylic complex, and hence the formation of the chlorosiloxanes.

One final point concerns the formation of methallylsiloxanes **4b,c**. These compounds were apparently not formed from the adducts, since heating **2c** with chloroplatinic acid or triethylamine for extended periods of time failed to give **4c**. Compounds **4b,c** may, therefore,

(8) J. L. Speier, J. A. Webster, and G. H. Barnes, *J. Amer. Chem. Soc.*, **79**, 974 (1967).
(9) A. J. Chalk and J. F. Harrod, *ibid.*, **87**, 16 (1965).
(10) J. W. Ryan and J. L. Speier, *ibid.*, **86**, 859 (1964).
(11) G. W. Parshall and G. Wilkinson, *Inorg. Chem.*, **1**, 896 (1962).
(12) W. E. Oberhansli and L. F. Dahl, *J. Organometal. Chem.*, **3**, 43 (1965).
(13) A. E. Smith, *Acta Crystallogr.*, **18**, 331 (1965).
(14) R. Mason and D. R. Russell, *Chem. Commun.*, **1**, 26 (1966).
(15) F. R. Hartley, *Chem. Rev.*, **69**, 799 (1969).
(16) R. Huttel, J. Kratyer, and M. Bechter, *Chem. Ber.*, **94**, 766 (1961).

be formed from the olefin, siloxane, platinum intermediate.

Experimental Section

Siloxanes 1a–c were obtained from Marshallton Chemical Co. and were analyzed for purity by glc. β-Methallyl chloride was purified according to literature procedures. Infrared spectra were taken on a Perkin-Elmer Model 457 spectrometer. Proton nmr spectra were measured on a Varian A-60A instrument and mass spectra were obtained on a Perkin-Elmer Hitachi RMU-6 mass spectrometer. Elemental analyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany. Gas chromatographic analyses were performed on a Perkin-Elmer 900 gas chromatograph and Perkin-Elmer F-21 preparative gas chromatograph using a 3% OV-17 on 80/100 mesh Chromosorb W (regular) and a 10% OV-1 on 60/80 mesh Chromosorb W (regular) columns, respectively.

General Reaction Procedure.—Catalyst and β-methallyl chloride were heated at reflux for 10 min prior to addition of the siloxane unless otherwise noted. After the reaction mixture was refluxed for an appropriate time period (Table I) the reaction was cooled, and a known weight of standard was added and analyzed by gas chromatography by comparison of peak areas with standard solution of the reaction products. Peak heights gave essentially the same results. Authentic samples of the reaction products were obtained by distillation of the reaction mixture or by preparative gas chromatography. Analyses were performed at least twice and the results were averaged.

Starting Materials. Pentamethyldisiloxane (1a)[17] had bp 85° (750 mm); ir (thin film) 2105 (SiH), 1250 ($SiCH_3$), 1035–1065 (SiOSi), 895–960 (SiH); nmr (neat, benzene standard) τ 10.12 (t, 17, CH_3Si), 5.43 (m, 1, SiH).

1,1,1,3,5,5,5-Heptamethyltrisiloxane (1b) had bp 142° (750 mm); ir (thin film) 2155 (SiH), 1260 ($SiCH_3$), 1050–1080 (SiOSi), 915 (SiH); nmr (neat, benzene standard) τ 9.87 (s, 19, CH_3Si), 5.20 (m, 1, SiH).

Tris(trimethylsiloxy)silane (1c) had bp 185° (750 mm); ir (thin film) 2210 (SiH), 1250–1260 ($SiCH_3$), 1040–1100 (SiOSi), 910 (SiH); nmr (neat, benzene standard) τ 10.00 (s, 27, CH_3Si), 5.83 (s, 1, SiH).

Reactions Catalyzed by Chloroplatinic Acid.—Olefin and approximately a 10^{-4} molar ratio of catalyst/reactants of a 10% chloroplatinic acid solution in isopropyl alcohol were heated to reflux under nitrogen. Siloxane was added and heated until the solution darkened (usually accompanied by an exotherm). The reaction mixture was distilled or analyzed by gas chromatography.

Pentamethyldisiloxane (1a), 7.4 g (0.05 mol), β-methallyl chloride, 4.5 g (0.05 mol), and chloroplatinic acid, 0.028 g (0.0000054 mol), were allowed to react to yield **1-(chloro-2-methylpropyl)pentamethyldisiloxane (2a)**: bp 97° (25 mm); ir (thin film) 1460, 1440, 1410, 1380 (aliphatic CH), 1250–1270 ($SiCH_3$), 1030–1090 cm^{-1} (SiOSi); mass spectrum *m/e* (rel intensity) 56 (65) C_4H_8, 73 (59) Me_3Si, 147 (89) M − $CH_2CHMeCH_2Cl$, 167 (100).

Anal. Calcd for $C_9H_{23}Si_2OCl$: C, 45.23; H, 9.67. Found: C, 45.08; H, 9.52.

1,1,1,3,5,5,5-Heptamethyltrisiloxane (1b), 22.2 g (0.1 mol), methallyl chloride, 9 g (0.1 mol), and chloroplatinic acid, 0.056 g (0.00011 mol), were allowed to react to from three major products.

3-(3-Chloro-2-methylpropyl)heptamethyltrisiloxane (2b) had bp 115° (14 mm); ir (thin film) 1460, 1443, 1410, 1380, (aliphatic CH), 1250–1270 ($SiCH_2$), 1030–1100 (SiOSi); mass spectrum *m/e* (rel intensity) 56 (63) isobutylene, 73 (100) Me_3Si, 221 (64) M − C_4H_8Cl.

Anal. Calcd for $C_{11}H_{29}Si_3O_2Cl$: C, 42.20; H, 9.33; Cl, 11.32. Found: C, 42.11; H, 9.42; Cl, 11.21.

3-Chloroheptamethyltrisiloxane (3b) had 57° (12 mm); ir 1250–1270 ($SiCH_3$), 1050–1070 (SiOSi), 560 (SiCl); nmr (neat, benzene standard) τ 10.03 (s, 18, $SiCH_3$), 9.82 (s, 3, CH_3Si–); mass spectrum *m/e* (rel intensity) 73 (75) Me_3Si, 221 (6) M − Cl, 241 (100) M − Me.

Anal. Calcd for $C_7H_{21}Si_3O_2Cl$: C, 32.72; H, 8.24. Found C, 32.86; H, 8.13.

3-(2-Methyl-1-propenyl)-1,1,1,3,5,5,5-heptamethyltrisiloxane (4b) had bp (approximate) 92° (14 mm). Analytical samples were obtained by gas chromatography: ir (thin film) 3070 (C=C), 1935 (allylic C=C),[5] 1260 ($SiCH_2$),[5] 1050–1070 (SiOSi), 840 ($SiMe_3$), and 750 cm^{-1} (SiMe); nmr ($CDCl_3$, $CHCl_3$ internal standard) τ 9.97 (d, 21, SiMe), 8.57 (s, 2, $SiCH_2$), 8.3 (d, 3, CCH_3, J = 0.5 Hz), and 5.48 (m, 2, $=CH_2$).

Anal. Calcd for $C_{11}H_{28}Si_3O_2$: C, 47.76; H, 10.20. Found: C, 47.76; H, 10.30.

Tris(trimethylsiloxyl)silane (1c), 14.8 g (0.05 mol), methallyl chloride, 4.5 g (0.05 mol), and chloroplatinic acid, 0.028 g (0.0000054 mol), were allowed to react to give three products.

3-Chloro-2-methylpropyltris(trimethylsiloxyl)silane (2c) had bp 90° (8 mm); ir (thin film) 1440, 1410, 1380 (aliphatic CH), 1255–1230 ($SiCH_3$), 1030–1060 (SiOSi); mass spectrum *m/e* (rel intensity) 56 (27) C_4H_8, 73 (65) Me_3Si, 207 (100), 268.5 (meta), 295 (5.5) M − C_4H_8Cl, 371 (3.5) M − Me.

Tris(trimethylsiloxy)chlorosilane (3c) had bp 78° (12 mm); ir (thin film) 1250–1270 ($SiCH_3$), 1050–1110 (SiOSi), 590 cm^{-1} (SiCl); nmr (neat, benzene standard) τ 9.67 (s, Me_3Si); mass spectrum *m/e* (rel intensity) 73 (64) Me_3Si, 207 (100), 295 (5) M − Cl, 315 (25) M − Me.

Anal. Calcd for $C_9H_{27}Si_4O_3Cl$: C, 32.65; H, 8.33. Found C, 32.88; H, 8.10.

(2-Methyl-1-propenyl)tris(trimethylsiloxy)silane (4c) had bp 77° (7.3 mm); ir (thin film) 3080 (olefinic CH), 1630 (allylic C=C), 1445, 1405–1420, 1378, 1330, 1320 (CH bending), 1255–1270 ($SiCH_3$), 1040–1079 cm^{-1} (SiOSi); nmr ($CDCl_3$, $CHCl_3$ internal standard) τ 9.93 (s, 27, $SiCH_3$), 8.35 (s, 2, $SiCH_2$), 8.40 (t, 3, CH_3, J = 1.0 Hz), 5.43 (m, 2, $C=CH_2$); mass spectrum *m/e* (rel intensity) 73 (100) Me_3Si, 295 (9) M − C_4H_7, 335 (5) M − Me, 350 (1.5) M^+.

Anal. Calcd for $C_{13}H_{34}Si_4O_3$: C, 44.52; H, 9.77. Found: C, 44.44; H, 9.56.

Platinum on Charcoal.—β-Methallyl chloride, 4.5 g (0.05 mol), and 0.098 g (0.000005 mol) of 1% platinum on charcoal were heated at reflux for 5 min and 11.1 g (0.05 mol) of 1b was heated at reflux until there was no further evidence (by glc) of product formation. Compounds 2b, 3b, and 4b were obtained (*vide supra*).

Reactions Catalyzed by Palladium on Charcoal.—β-Methallyl chloride (0.05 mol) and 10% palladium on charcoal, 1.06 g (0.001 mol), were heated at reflux for 10 min, at which time siloxanes 1a–c (0.05 mol) were added. The reaction mixture was refluxed until there was no further evidence of product formation by glc. Siloxane 1a gave **1-chloropentamethyldisiloxane (3a)**: bp 87° (760 mm); ir (thin film) 1265 ($SiCH_3$), 1040–1090 cm^{-1} (SiOSi); nmr (neat, benzene standard) τ 10.03 (s, 9, $OSiCH_3$), 9.75 (s, 6, $OSiMe_2Cl$); mass spectrum *m/e* (rel intensity) 73 (100) Me_3Si, 147 (29) M − Cl, 167 (47) M − Me.

Anal. Calcd for $C_5H_{15}Si_2OCl$: C, 32.85; H, 8.27. Found: C, 33.12; H, 8.38.

Siloxanes 1b,c under these conditions gave 3b,c (Table I).

Ruthenium on Charcoal.—Compounds 1b and β-methallyl chloride (0.05 mol of each) were refluxed with 2.02 g (0.001 mol) of 5% Ru/C for 4 hr. There was a 67% yield of 3b, verified by glc and nmr.

No Catalyst.—Compound 1b and methallyl chloride (0.05 mol of each) were heated at reflux without catalyst; no products were noted after 48 hr. Continued heating for 100 hr yielded adduct 2b (24%).

Dehydrohalogenation of Adduct.—A sample of pure 2b (38.6 g, 0.1 mol) was heated with chloroplatinic acid, 0.056 g (0.000011 mol), for 120 hr. No products were found by glc analysis. Treatment of 2c with excess triethylamine or 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) caused some polymerization, with no evidence of 4c having been generated.

Reaction with Palladium(II) Chloride.—Palladium(II) chloride (0.18 g, 10^{-3} mol) was added in portions to a solution of 1b (0.22 g, 10^{-3} mol) in *n*-pentane. Hydrogen chloride was evolved, and there was a quantitative conversion to the chlorosiloxane 3b.

Reaction of Bis[isobutenylpalladium(II) chloride] with 1b.—Compound 1b, 0.113 g (0.00051 mol), was dissolved in 10 ml of dry benzene in a 50-ml single-necked flask equipped with magnetic stir bar and reflux condenser. Bis[isobutenylpalladium(II) chloride][6] 0.10 g (0.00025 mol), in 1 ml of benzene was added with stirring to the above reaction mixture. Immediate reduction of the complex to palladium metal and evolution of heat was noted. Gas chromatography of the reaction mixture indicated that a quantitative yield of 3b was obtained.

Cohydrolysis of Trimethylchlorosilane and $MeCl_2SiCH_2CHMeCH_2Cl$ (5).—Compound 5 (0.24 mol, 50 g) and an excess

(17) R. Okawara and M. Sakiyama, *Bull. Chem. Soc. Jap.*, **29**, 547 (1956).

of Me_3SiCl (0.55 mol, 59.5 g) were premixed and added dropwise to 300 ml of vigorously stirring ice water in a 500-ml erlenmeyer flask. When complete, the solution was transferred to a separatory funnel, and the organic layer was separated, dried over Na_2SO_4, and distilled to give **2b** in 32% yield.

Reaction of Trimethylsilanol and $MeCl_2SiCH_2CHMeCH_2Cl$ (5).—Compound **5** (0.5 mol, 57 g) in 100 ml of dry THF was charged into a 250-ml flask equipped with stirrer, thermometer, and dropping funnel, and cooled to −5°. Pyridine (1 mol, 79 g) was added dropwise, keeping temperature below 0°; trimethylsilanol (1 mol, 90 g) was added dropwise to this solution, again keeping the temperature below 0°. When addition was complete, the mixture was brought to room temperature and water was stirred into the reaction mixture; the organic layer was washed three times with water and dried over Na_2SO_4. Distillation gave 32 g (20%) of **2b**. Triethylamine was substituted for pyridine and glyme for THF with no change in product yield.

Registry No.—**1a**, 1438-82-0; **1b**, 1873-88-7; **1c**, 1873-89-8; **2a**, 37611-45-3; **2b**, 37611-46-4; **2c**, 37611-47-5; **3a**, 2943-62-6; **3b**, 22407-46-1; **3c**, 17905-99-6; **4b**, 37611-51-1; **4c**, 37611-52-2; β-methallyl chloride, 563-47-3.

Acknowledgment.—We would like to thank Dr. A. Berry, University of Pennsylvania, for helpful discussions.

Synthesis, Reactivity, and Spectral Properties of 2,7-Difluoro-9-chloromethylenexanthene. Isoelectronicity with Heptafulvene Derivatives

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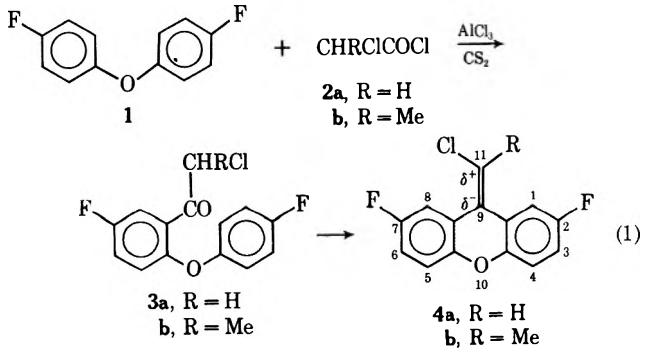
The application of the Friedel–Crafts reaction for the preparation of phenoxaphosphines[1] and phenothiaphosphines[2] from aromatic ethers and sulfides, respectively, has now been extended to the xanthene system.

Synthesis, Structure, and Spectra.—2,7-Difluoro-9-chloromethylenexanthene (**4a**) was the only product isolated (in a good yield) from the reaction of **1** with **2a** (eq 1). 2-Chloroacetyl-4,4′-difluorodiphenyl ether



(1)

(**3a**) was assumed as an intermediate since **2a** has been known to chloroacetylate aromatics.[3]

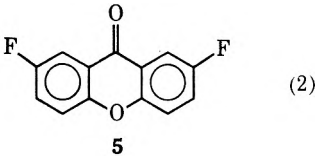
(1) J. B. Levy, G. W. Whitehead, and I. Granoth, *Israel J. Chem.*, **10**, 27 (1972), and references cited therein.

(2) I. Granoth, A. Kalir, Z. Pelah, and E. D. Bergmann, *Tetrahedron*, **25**, 3919 (1969).

(3) F. Tutin, *J. Chem. Soc.*, **97**, 2495 (1910).

The structure of **4a** was elucidated from its spectral properties. The ir showed no carbonyl absorption and the nmr exhibited one vinylic proton and a characteristic low-field resonance at δ 8.22. The latter was a multiplet of 1 H, ortho to the fluorine (J_{HF} = 9 Hz), and further coupled with meta aromatic protons only. It was shown to be H-8 by the absence of this strong deshielding effect in other derivatives, such as **7a** and **b**, but not in **4b**. This deshielding must result from the long-range electrical effect of the chlorine atom.[4] A similar deshielding effect has been observed recently, though not confirmed, in α-chloro- and α-bromo-9-anisilidenefluorene.[5] These observations indicated the structure of **4a**, further confirmed by the analysis and the mass spectrum, which disclosed the presence of one chlorine atom and verified the molecular weight. The mass spectrum of **4a** exhibited a very intense peak corresponding to $(M - CClO)^+$. Its direct formation from the molecular ion was shown by an appropriate metastable transition. The elimination of CClO· as one entity from chlorinated aromatic ethers is known for some time.[6] However, until now the chlorine was directly attached to the aromatic ring.

The characteristic uv band of **4a** in EtOH appeared at 338 nm and was not shifted in cyclohexane. This, and the absence of the 338-nm band in the xanthene itself, suggested that the latter band is due to the $\pi \rightarrow \pi^*$ transition connected with the extended conjugation in 9-methylenexanthene derivatives as compared with xanthene. The methylenexanthene skeleton of **4a** was established by its oxidation with potassium permanganate to 2,7-difluoroxanthen-9-one (**5**). This compound was identical with a sample prepared as in eq 2.[7] Decarbonylation of oxalyl chloride during



5 (2)

Friedel–Crafts reactions with aluminum chloride is well known.[8] Thus, two one-step syntheses of 2,7-difluoroxanthene derivatives were achieved.

The reaction described by eq 1 was markedly influenced by the substituent R. When R = H, the intermediate **3a** was very reactive, not allowing its isolation under the reaction conditions. When R = Me, **3b** was not cyclized by aluminum chloride in boiling carbon disulfide, thus enabling its isolation and characterization by nmr. (See Experimental Section.) Crude **3b** gave eventually **4b** upon heating on a water bath with little methanol and a trace of hydrochloric acid. However, no **4** (R = C_6H_5) was isolated from the reaction of **1** and **2** (R = C_6H_5), which yielded unidentified oil.[9] The introduction of an α-methyl group in **4a**,

(4) R. F. Zürcher in "Nuclear Magnetic Resonance in Chemistry," B. Pesce, Ed., Academic Press, New York, N. Y., 1965, p 45.

(5) Z. Rappoport and A. Gal, *J. Org. Chem.*, **37**, 1174 (1972).

(6) I. Granoth and J. B. Levy, *J. Chem. Soc. B*, 2391 (1971).

(7) J. W. Cusic and R. A. Robinson, U. S. Patent 2,776,299 (1957); *Chem. Abstr.*, **51**, 8146 (1957).

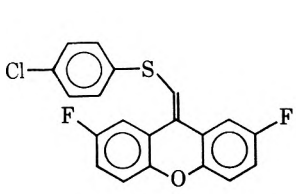
(8) P. E. Sokol, *Org. Syn.*, **44**, 69 (1964).

(9) A study of the scope and mechanisms of the reactions outlined by eq 1 and 3 is now in progress, including reactions of other aromatics with various α-substituted acid halides.

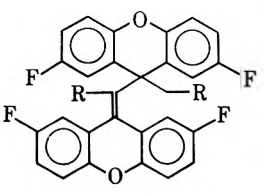
e.g., **4b**, produced a hypsochromic shift of the characteristic uv band by 16 nm to 322 nm.

Reactivity.—**4a** was inert toward sodium ethoxide in boiling ethanol, but with sodium *p*-chlorothiophenoxide under the same conditions gave **6**. Nucleophiles such as dibenzylamine (in boiling toluene) and methylmagnesium iodide (in ether) did not react with **4a**, which was recovered unchanged.

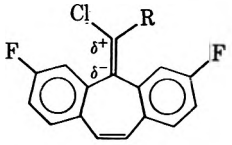
The compounds **4a** and **b** are isoelectronic[10] with the unknown heptafulvenes **8**.[11] Ordinary heptafulvenes have a polar exocyclic double bond, the terminal carbon being negative.[11] In the fulvenes,[11] and in those heptafulvenes bearing an electronegative substituent on the terminal carbon,[12] the exocyclic double bond is also polar, but the terminal carbon is positive. We suggest that, similarly to the latter, the terminal carbon of the exocyclic double bond in **4a** and **b** is positive. This would explain the formation of **7a** and **b** as the sole products of the $LiAlH_4$ reduction of **4a** and **b**.



6

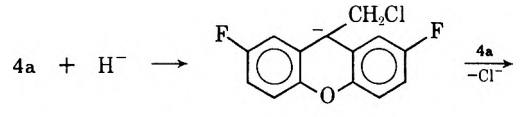


7a, R = H
b, R = Me



8

A vinylic chlorine is known[13] not to be hydrogenolyzed by $LiAlH_4$ under our reaction conditions. Taking into account that the reaction of **4a** with $LiAlH_4$ was exothermal, we assumed that the latter reaction proceeded as in eq 3.



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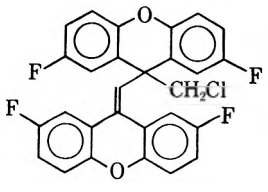
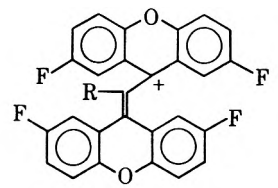


10

The hydride addition to **4a** is not unusual, but the nucleophilic attack of the hindered carbanion **9** on **4a** seems to be quite remarkable. The final hydrogenolysis of the chlorine in **10** could be expected, once **10** was obtained in the presence of $LiAlH_4$. The structures of **7a** and **b** were deduced from their nmr and mass spectra. (See also Experimental Section).

The only intense peaks in the mass spectra of **7a** and **7b** were $M\cdot^+$, $M - RCH_2^+$ (**11**), and **12**. This is attributed to the high stability of the ions **11** and **12**, which may be stabilized by resonance with, *e.g.*, **13**. Another characteristic ion in the latter two spectra was **14** (*m/e* 217), which is typical of xanthene derivatives.



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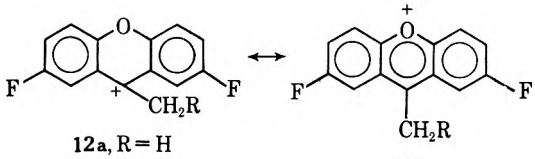
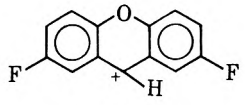


12a, R = H
b, R = Me

13



14

The nmr spectrum of **7b** displayed, *inter alia*, δ 0.47 (3 H, t, aliphatic Me) and 5.95 (1 H, dd, H-1). The latter was assigned to H-1 since it showed $J_{HF} = 9$ Hz and further coupling with a meta proton. These are considerable shielding effects of H-1 and the aliphatic Me which are brought toward the influence of the diamagnetic-ring current,[14] owing to the crowding near the ethyl substituent in **7b**. The uv spectrum of **7b** showed a blue shift of 29 nm, as compared with **7a**. Assuming that the α-Me in **7b** contributed a shift of 16 nm (as in **4b** above), it might be concluded that the additional 13-nm shift was due to the increased distortion of coplanarity of the two aromatic systems in **7b**, resulting from the crowding in this compound.

Experimental Section

Melting points are uncorrected. Proton nmr spectra were recorded in $CDCl_3$ with a JEOL 60 HL instrument, and are given in δ units downfield from internal TMS. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU6 mass spectrometer at 70 eV using the direct insertion probe, and source temperature 150–200°. Peaks of intensity greater than 20% of the base peak are given and isotope peaks are excluded. The uv spectra were measured on a Bausch & Lomb 505 spectrometer.

2,7-Difluoro-9-chloromethylenexanthene (4a).—Chloroacetyl chloride (12.4 g, 0.11 mol) was added rapidly to a mechanically stirred mixture of carbon disulfide (300 ml), 4,4′-difluorodiphenyl ether (**1**) (20.6 g, 0.1 mol), and aluminum chloride (17.3 g, 0.13 mol). The mixture was refluxed for 5 hr and cooled, and the solvent was decanted. The solid residue was decomposed with ice–water and extracted with chloroform, affording the

(10) For a recent improvement of the basic isoelectronic principle, see J. F. Liebman, *J. Chem. Educ.*, **48**, 188 (1971). One of the authors (I. G.) and J. F. Liebman are currently investigating further modifications of the isoelectronic principle.

(11) E. D. Bergmann, *Chem. Rev.*, **68**, 41 (1968).

(12) T. Asao, N. Morita, and Y. Kitahara, *J. Amer. Chem. Soc.*, **94**, 3655 (1972).

(13) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience, New York, N. Y., 1956, p 902.

(14) L. M. Jackman and S. Sternhell, "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969 p, 94.

crude product after evaporation. Crystallization from ethyl acetate–ethanol gave 15.8 g (60%) of **4a**, mp 147°.

Anal. Calcd for $C_{14}H_7ClF_2O$: C, 63.5; H, 2.6; Cl, 13.4. Found: C, 63.7; H, 2.4; Cl, 13.4. Spectra: nmr ($CDCl_3$) δ 6.54 (1 H, s, H-α), 7.15 (5 H, m, Ar), 8.22 (1 H, m, H-8); mass spectrum *m/e* (rel intensity) 264 (100, $M\cdot^+$), 201 (51, M − $CClO^+$); λ_{max} (EtOH) 240 nm (sh, ε 10,900), 258 (sh, 5100), 290 (sh, 3200), 338 (8400).

α-Chloro-2,7-difluoro-9-ethylidenexanthene (4b).—α-Chloropropionyl chloride (13.9 g, 0.11 mol), **1** (20.6 g, 0.1 mol), and aluminum chloride (17.3 g, 0.13 mol) were refluxed for 5 hr in carbon disulfide (300 ml) with agitation. Decantation of the solvent, hydrolysis, and chloroform extraction gave an impure oil, shown by nmr to contain mainly **3b**, nmr δ 1.37 (3 H, d, Me), 4.23 (1 H, q, CHCl), 6.92 (7 H, m, Ar). The above oil and 100 ml of methanol were refluxed for 10 min and heated in a rotovaporator for 1 hr on a steam bath. The residue solidified upon trituration with hexane, and was crystallized from cyclohexane giving 4.5 g (16%) of **4b**, mp 162°.

Anal. Calcd for $C_{15}H_9ClF_2O$: C, 64.6; H, 2.8; Cl, 12.7; F, 13.6. Found: C, 64.2; H, 3.1; Cl, 13.1; F, 13.7. Spectra: nmr ($CDCl_3$) δ 2.55 (3 H, s, Me), 7.16 (5 H, m, Ar), 7.86 (1 H, m, H-8); mass spectrum *m/e* (rel intensity) 278 (100, $M\cdot^+$), 243 (58, M − $Cl\cdot^+$), 242 (45, M − $HCl\cdot^+$), 241 (74, M − H_2Cl^+), 214 (22, M − $CHClO^+$); λ_{max} (EtOH) 238 nm (sh, ε 10,100), 253 (sh, 8800), 288 (3200), 322 (9100).

2,7-Difluoroxanthen-9-one (5). A.—Potassium permanganate (8 g) was added in four portions during 10 min to a stirred solution of **4a** (5.3 g, 0.02 mol) in 85% aqueous pyridine (100 ml). When the exothermal reaction slowed down, the mixture was heated to the boiling point and filtered hot. Dilution of the filtrate with water precipitated **5**, which was collected and crystallized from ethanol, giving 3.0 g (65%), mp 170°.

Anal. Calcd for $C_{13}H_6F_2O_2$: C, 67.2; H, 2.6; F, 16.4. Found: C, 67.2; H, 2.7; F, 16.7. Spectra: nmr ($CDCl_3$) δ 7.45 (4 H, m, Ar), 7.83 (2 H, m, H-1, 8, J_{HF} = 9 Hz); mass spectrum *m/e* (rel intensity) 232 (100, $M\cdot^+$), 204 (40, M − $CO\cdot^+$), 176 (28, M − $2CO\cdot^+$); λ_{max} (EtOH) 230 nm (ε 39,400), 257 (sh, 14,900), 294 (5500), 355 (9100).

B.—**1** (10.3 g, 0.05 mol), aluminum chloride (10.0 g, 0.075 mol), oxalyl chloride (9.5 g, 0.075 mol), and carbon disulfide (150 ml) were refluxed for 7 hr, cooled, and treated with ice water. The organic layer was evaporated and the residue gave 4.1 g (35%) of **5** upon crystallization from ethanol, mp and mmp 170°. This sample was identical with the one obtained by method A.

α-*p*-Chlorophenylthio-2,7-difluoro-9-methylenexanthene (6).—Sodium hydride (0.12 g, 5 mmol), *p*-chlorothiophenol (0.73 g, 5 mmol), and **4a** (1.32 g, 5 mmol) were added in turn to absolute ethanol (100 ml) and the mixture was refluxed for 5 hr. The yellow precipitate (**6**) was filtered and crystallized from ethanol, giving 1.7 g (91%), mp 156°.

Anal. Calcd for $C_{20}H_{11}ClF_2OS$: C, 64.4; H, 3.0; Cl, 9.5; F, 10.2; S, 8.6. Found: C, 64.1; H, 2.8; Cl, 10.0; F, 10.4; S, 9.0. Spectra: nmr ($CDCl_3$) δ 6.61 (1 H, s, H-α), 7.15 (5 H, m, Ar), 7.43 (4 H, s, Ar S), 7.66 (1 H, m, H-8); λ_{max} (dioxane) 255 nm (ε 9100), 295 (10,100), 368 (21,700).

2,7-Difluoro-9-(2′,7′-difluoro-9′-methyl)xanthylmethylenexanthene (7a).—Lithium aluminum hydride (1.1 g, 0.03 mol) was added to a solution of **4a** (5.3 g, 0.02 mol) in dry THF (100 ml). The mixture was refluxed for 1 hr, cooled, and decomposed with 5 ml of dilute hydrochloric acid. The organic layer was evaporated and the residue was crystallized from ethanol, thus giving 3.0 g (65%) of **7a**, mp 165°.

Anal. Calcd for $C_{28}H_{16}F_4O_2$: C, 73.0; H, 3.5; F, 16.5. Found: C, 73.1; H, 3.5; F, 17.1. Spectra: nmr ($CDCl_3$) δ 1.70 (3 H, s, Me), 6.17 (1 H, s, H-α), 6.07–7.20 (12 H, m, Ar); mass spectrum *m/e* (rel intensity) 460 (30, $M\cdot^+$), 445 (100, M − Me^+), 231 (42, **12a**); λ_{max} (EtOH) 240 nm (sh, ε 23,700); 260 (sh, 10,300), 291 (8500), 336 (11,900).

2,7-Difluoro-α-9-(2′,7′-difluoro-9′-ethyl)xanthylethylidenexanthene (7b).—The procedure for **7a** was repeated with $LiAlH_4$ (0.38 g, 10 mmol), **4b** (1.4 g, 5 mmol), and THF (50 ml). Trituration with ethanol yielded 0.3 g of **4b** (recovered from the ethanol), and 0.4 g (42%) of **7b**, mp 247°.

Anal. Calcd for $C_{30}H_{20}F_4O_2$: C, 73.8; H, 4.1; F, 15.6. Found: C, 73.5; H, 4.2; F, 15.7. Spectra: nmr ($CDCl_3$) δ 0.47 (3 H, t, $MeCH_2$), 2.06 (2 H, q, CH_2), 2.59 (3 H, s, Me-α), 5.95 (1 H, dd, H-1, J_{HF} = 10 Hz), 7.00 (11 H, m, Ar); mass spectrum *m/e* (rel intensity) 488 (7, $M\cdot^+$), 459 (20, M − Et^+), 245 (100, **12b**); λ_{max} (EtOH) 248 nm (ε 18,900), 288 (7900), 307 (12,300).

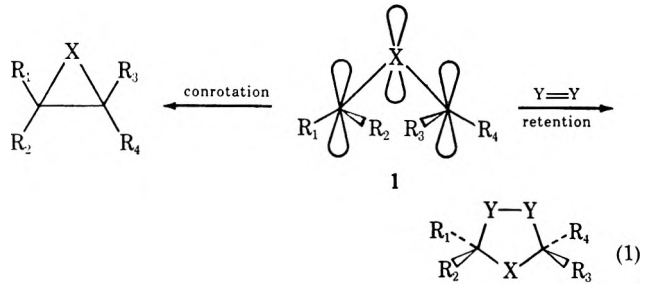
Registry No.—**1**, 330-938; **4a**, 37611-30-6; **4b**, 37611-31-7; **5**, 37611-32-8; **6**, 37611-33-9; **7a**, 37735-74-3; **7b**, 37611-34-0; chloroacetyl chloride, 79-04-9; α-chloropropionyl chloride, 7623-09-8.

See Editorial, *J. Org. Chem.*, **37**, No. 19, 4A (1972).

Reaction of Thiocarbonyl Ylides with Diphenylketene. Stereochemistry of 1,3 Addition

Summary: *trans*-Thiocarbonyl ylides add suprafacially in a 1,3 manner over the carbonyl function of diphenylketene affording *trans*-2,4-disubstituted 5-diphenylmethylene-1,3-oxathiolanes.

Sir: The reactive intermediates **1** (X = NR, S, O), which embody an obvious potential for stereochemical labeling, have been useful in substantiating theoretical predictions made by Woodward and Hoffmann[1] for cyclization processes (eq 1). Huisgen and co-

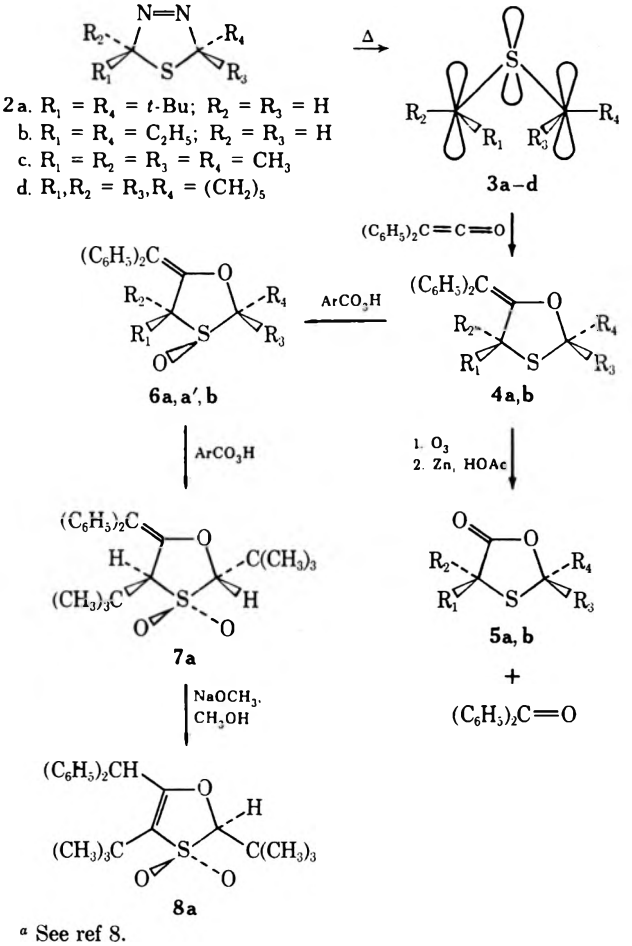


workers,[2,3] working with azomethine ylides (**1**, X = NR) first succeeded in this type of endeavor; similar demonstrations for thiocarbonyl ylides (**1**, X = S)[4] and carbonyl ylides (**1**, X = O)[5] followed.[6]

This is a report on the use of stereochemically labeled thiocarbonyl ylides to probe into the geometrical aspects of an unusual cycloaddition with diphenylketene.[7]

Pyrolysis of thiocarbonyl ylide precursors **2a,b** in hydrocarbon solvents (5 hr, 100° for **2a**, 45° for **2b**) in the presence of an equimolar amount of diphenylketene led to the formation of cycloadducts in 85–94% isolated yields (Scheme I[8]).[9] Elemental analyses and mass spectral data established that **4a,b** were 1:1 adducts of thiocarbonyl ylides **3a,b** with diphenylketene. The sharpness of the nmr spectra as well as

SCHEME I[a]



[a] See ref 8.

their simplicity suggested the formation of a single isomer; no unassignable peaks were present in the nmr spectra of crude reaction mixtures before work-up. Monitoring the progress of the reaction by nmr spectroscopy failed to reveal the presence of intermediates. Lack of carbonyl absorption in **4a,b** suggested unusual, but not unprecedented,[10] 1,3 addition over the carbonyl function. The strongest evidence in favor of this structural assignment is provided by ozonization results. Cleavage of either **4a** or **4b** (ozonization of **4a** was very sluggish but clean) gave nearly quantitative yields of benzophenone and the lactones **5a,b** (ir 1770 cm^{-1}, other expected spectral features).[11]

Oxidation of **4a** with 1 equiv of *m*-chloroperbenzoic acid ($ArCO_3H$) gave two isomeric sulfoxides **6a,a′**; further oxidation of this mixture gave sulfone **7a**. A single sulfoxide, **6b**, was obtained from **4b**; the sulfone could not be obtained crystalline. The anticipated exocyclic–endocyclic shift of the double bond in **7a** took place on treatment with base. Raney

(1) R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969).

(2) See, for example, R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.*, **89**, 1753 (1967), and references compiled in ref 4c.

(3) For review and comment on these types of reactions, see (a) R. Huisgen, *Angew. Chem.*, **75**, 604 (1963); (b) R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968).

(4) (a) R. M. Kellogg and S. Wassenaar, *Tetrahedron Lett.*, 1987 (1970); (b) R. M. Kellogg, S. Wassenaar, and J. Buter, *ibid.*, 4689 (1970); (c) J. Buter, S. Wassenaar, and R. M. Kellogg, *J. Org. Chem.*, **37**, 4045 (1972).

(5) See references compiled in ref 4c.

(6) Similar demonstrations are also available for allyl anions: (a) P. Eberhard and R. Huisgen, *J. Amer. Chem. Soc.*, **94**, 1346 (1972); (b) R. Huisgen and P. Eberhard, *ibid.*, **94**, 1346 (1972); (c) G. Boche and D. Martens, *Angew. Chem.*, **84**, 768 (1972).

(7) Review of ketene chemistry: H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, New York, N. Y., 1967, p 38.

(8) Racemic mixture; no absolute configuration implied. Stereochemical assignments for **5a,b** and **7a** made by analogy (see text).

(9) The experimental portion of this paper will appear following these pages in the microfilm edition of the Journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-73-844. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

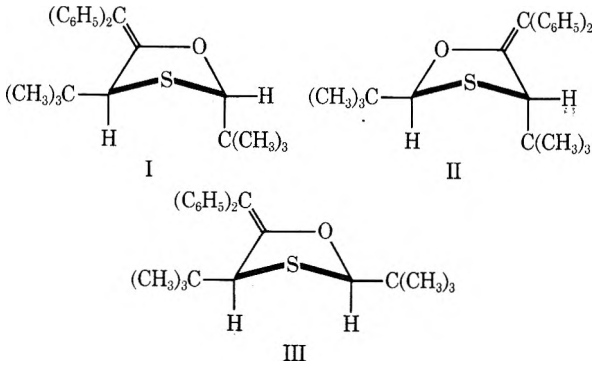
(10) (a) H. Staudinger and T. Reber, *Helv. Chim. Acta*, **4**, 3 (1921); (b) W. Kirmse, *Ber.*, **93**, 2357 (1960).

(11) See, for leading references, D. H. R. Barton and B. J. Willis, *J. Chem. Soc., Perkin Trans. 1*, 305 (1972).

nickel desulfurization failed with highly hindered **4a**; with **4b** a mixture of products was obtained.

No characterizable products were obtained from reactions of thiocarbonyl ylide precursors **2c,d** with diphenylketene. The cis isomer of **2a**, which is only moderately stable in solution,[4c] failed to give any characterizable product besides *trans*-2,3-di-*tert*-butyl episulfide.[4c] Attempts to add **3a,b** to phenyl isocyanate failed.

Two lines of evidence indicate that configuration has been maintained during cycloaddition; that is, *trans*-thiocarbonyl ylides **3a,b** give trans adducts **4a,b**. The most definitive arguments can be advanced for **4a**. If trans, **4a** should tend toward conformations I and II; if cis, III should approximate a preferred

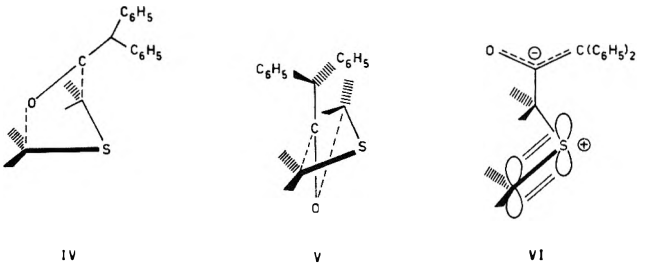


conformation. As anticipated, nuclear Overhauser effects (NOE) are found between the *tert*-butyl groups and the methine protons.[12] Saturation of a *tert*-butyl group at δ 0.78 results in a 24 ± 3% intensity increase of a methine proton at δ 5.11 and a 8 ± 3% increase of the other methine proton at δ 4.26. Saturation of a *tert*-butyl group at δ 0.83 results in 11 ± 3% and 24 ± 3% increases for the same two methine protons, respectively. No NOE is found between the two methine protons. These observations rhyme only with expected interactions from conformations I and II from the trans isomer of **4b**, that is, 1,3 interactions over the ring as well as interactions with the methine proton on the carbon atom to which the *tert*-butyl group is bonded. For the cis isomer of **4b** there is no obvious mechanism by which a *tert*-butyl group can cause an NOE with more than one proton, namely the proton on the carbon to which the *tert*-butyl group is bonded.[13]

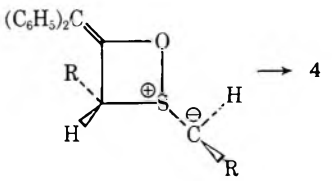
A second line of evidence is derived from the sulfoxides **6a,a′** obtained from **4a**. These are formed in about 90:10 ratio. The major isomer (**6a**), mp 175–176°, and the minor isomer (**6a′**), concentrated by repeated recovery of the mother liquors to a 60:40 mixture with **6a**, both have a single *tert*-butyl absorption shifted downfield 0.19 to 0.29 ppm relative to **4a**; in sulfone **7a** (single isomer) both *tert*-butyl groups are shifted downfield. Upfield shifts of a single methine proton also are apparent in **6a,a′**, although the effect is less clear-cut. Such behavior is not expected for the cis isomer of **4a** where shielding effects should affect either *both* methine protons or *both* *tert*-butyl groups.[14]

Only one isomer of sulfoxide **6b** was formed, apparently owing to a greater selectivity of oxidation of **4b**. As expected, one methine proton is shifted upfield and only one methylene group downfield consistent with trans stereochemistry.

Investigations of the stereochemistry of the cycloadditions of ketenes with alkenes have revealed that the alkenic component retains configuration (reacts suprafacially) during cycloaddition,[15,16] but theory demands,[1] and stereochemical arguments are not inconsistent with,[15] *antarafacial* participation of the ketene. However, the present example is unique because, if cycloaddition is concerted and if **4a** and **4b** are truly kinetically controlled products, then in an "allowed" reaction the thiocarbonyl ylide and diphenylketene must *both* participate suprafacially [$4_s + 2_s$] as in IV or *both* antarafacially [$4_a + 2_a$] as in V. Providing that the foregoing "if's" are valid, then the present results indicate that IV best approximates the geometry of the transition state for cycloaddition.



Alternatives to the above argumentation, which presumes that there is no *a priori* electronic bias against suprafacial participation of the ketene, include the intervention of dipolar species such as VI. Also, there is precedent in sulfur diimide[17] chemistry for intermediates such as **9** (eq 2), which, if short lived under



(2)

(12) (a) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect. Chemical Applications," Wiley-Interscience, New York, N. Y., 1971; (b) G. E. Bachers and T. Schaefer, *Chem. Rev.*, **71**, 617 (1971); (c) P. D. Kennewell, *J. Chem. Educ.*, **47**, 278 (1970); (d) M. C. Woods, I. Miura, Y. Nakadaira, A. Terahara, M. Maruyamo, and K. Nakanishi, *Tetrahedron Lett.*, 321 (1967).

(13) The small separation (3 Hz) of the *tert*-butyl peaks in **4a** makes selective excitation difficult thereby raising in principle the possibility that a single *tert*-butyl group does not cause NOE's on both methine protons but rather that both *tert*-butyl groups are being excited simultaneously. However, in sulfoxide **6a**, where the *tert*-butyl groups are better separated (8 Hz), saturation of a *tert*-butyl group at δ 0.78 caused 21 ± 3% and 7 ± 3% increases in methine protons at δ 5.11 and δ 4.26, respectively. Saturation of a *tert*-butyl group at δ 0.83 resulted in 15 ± 3% and 0 ± 3% increases, respectively. Sulfoxide **6a** is likely more rigid than **4a** causing one conformation to predominate. That *tert*-butyl group in a pseudoaxial orientation produces two NOE effects, again consistent only with trans stereochemistry.

(14) Similar effects are found for *trans*-2,5-di-*tert*-butyl-2,5-dihydrothiophenes on oxidation to the sulfoxides.[4c]

(15) See, for example, (a) R. Huisgen and P. Otto, *Tetrahedron Lett.*, 4491 (1968); (b) G. Binsch, L. A. Feiler, and R. Huisgen, *ibid.*, 4497 (1968); (c) L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde, and P. Mollet, *Tetrahedron*, **27**, 615 (1971); (d) R. Sustmann, A. Ansmann, and F. Vahrenholt, *J. Amer. Chem. Soc.*, **94**, 8099 (1972); (e) M. Rey, S. Roberts, A. Dieffenbacher, and A. S. Dreiding, *Helv. Chim. Acta*, **53**, 417 (1970).

(16) Similar considerations should apply also in [2 + 6] cycloadditions for which the thus far described examples involve cyclic 6-π-electron systems also forced to react suprafacially: O. S. Rothenberger, R. T. Taylor, D. L. Dalrymple, and J. A. Moore, *J. Org. Chem.*, **37**, 2640 (1972).

(17) H. Grill and G. Kresze, *Tetrahedron Lett.*, 1427 (1970)

the reaction conditions, would escape detection. One certainly should not construe the failure to detect as proof of failure to exist.

Acknowledgment.—All NOE experiments were expertly carried out by Dr. J. de Wit of this department, to whom I am also indebted for advice.

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RECEIVED NOVEMBER 20, 1972

Orientation in Base-Promoted β Elimination from 2-Butyltrimethylammonium *p*-Toluenesulfonate. The Absence of a Base Association Effect

Summary: Orientation in β eliminations from 2-butyltrimethylammonium *p*-toluenesulfonate promoted by *t*-BuOK in *t*-BuOH is not influenced by base association.

Sir: Base association in solvents of low polarity, such as *t*-BuOH, has very recently been shown to profoundly affect positional and geometrical orientation[1] in base-promoted β eliminations from 2-alkyl halides and *p*-toluenesulfonates.[2,3] Investigation of a possible effect of base association upon orientation in eliminations of a charged "onium" leaving group seemed warranted.

Relative olefinic proportions from reactions of 2-butyltrimethylammonium *p*-toluenesulfonate with *t*-BuOK–*t*-BuOH are recorded in Table I. The 2-butyltrimethylammonium ion was chosen because of the absence of significant amounts of syn elimination for this substrate.[4]

TABLE I
OLEFINIC PRODUCTS FROM REACTIONS[a] OF 2-BUTYLTRIMETHYLAMMONIUM *p*-TOLUENESULFONATE[b] WITH *t*-BuOK–*t*-BuOH AT 85°

Expt	[*t*-BuOK]	% 1-butene	*trans*-2-Butene/*cis*-2-butene
1	0.10	90.6 ± 0.5[c]	0.42 ± 0.01
2	0.25[d]	91.6 ± 0.2	0.43 ± 0.03
3	0.50	91.1 ± 0.2	0.44 ± 0.04
4	0.25[e,f]	91.7 ± 0.8	0.46 ± 0.02

[a] Ampoule technique: R. A. Bartsch, *J. Org. Chem.*, **35**, 1334 (1970). [b] [2-BuNMe$_3$OTs], 0.10 *M*. [c] Standard deviation from repetitive analysis of reaction mixture. [d] Reference 4 reports a *trans*-2-butene/*cis*-2-butene ratio of 0.42 for reaction of 2-butyltrimethylammonium iodide with 0.2–0.3 *M* *t*-BuOK–*t*-BuOH. [e] With 0.25–0.30 *M* dicyclohexyl-18-crown-6 present. [f] Average of two runs.

From the results in Table I it is clearly evident that in reactions of 2-butyltrimethylammonium ion with *t*-BuOK–*t*-BuOH positional and geometrical orientation are insensitive to changes in the base concentration (expt 1–3) or to the addition of the potassium ion complexing reagent[5] dicyclohexyl-18-crown-6[6] (expt 4). These results are in sharp contrast to those reported for eliminations from 2-butyl bromide and *p*-toluenesulfonate.[2,3] Apparently, eliminations from the 2-butyltrimethylammonium ion are being induced by *dissociated tert*-butoxide base species produced through interaction of the tetraalkylammonium salt with *t*-BuOK.[7] Base association is therefore judged to be unimportant in determining orientation for anti eliminations from "onium" compounds.

(1) In eliminations from a 2-substituted alkane, positional orientation refers to the relative proportions of 1- and 2-alkenes which are formed, whereas geometrical orientation compares the relative amounts of *trans*-2-alkene and *cis*-2-alkene which are produced.

(2) R. A. Bartsch, G. M. Pruss, R. L. Buswell, and B. A. Bushaw, *Tetrahedron Lett.*, 2621 (1972).

(3) R. A. Bartsch, G. M. Pruss, D. M. Cook. R. L. Buswell, B. A. Bushaw, and K. E. Wiegers, *J. Amer. Chem. Soc.*, submitted for publication.

(4) D. S. Bailey, F. C. Montgomery, G. W. Chodak, and W. H. Saunders, Jr., *ibid.*, **92**, 6911 (1970).

(5) C. J. Pederson, *ibid.*, **89**, 7017 (1967); **92**, 391 (1970).

(6) Trivial name for 2,5,8,15,18,21-hexaoxatricyclo[20.4.0.0^{9,14}]hexacosane.

(7) Benzyltrimethylammonium *tert*-butoxide is dissociated to a much greater extent than *t*-BuOK in *t*-BuOH: D. Bethell and A. F. Cockerill, *J. Chem. Soc. B*, 913 (1966).

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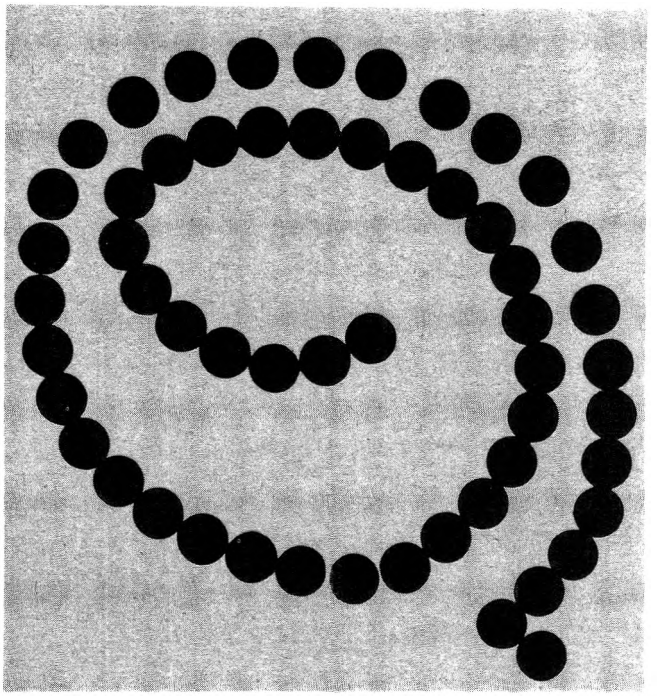
RECEIVED DECEMBER 19, 1972

Bioinorganic Chemistry



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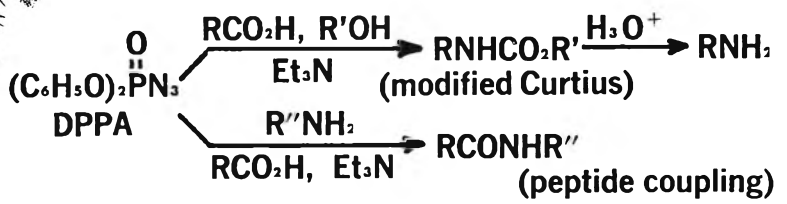
ALDRICH Shows the Way to Avoid Explosions!

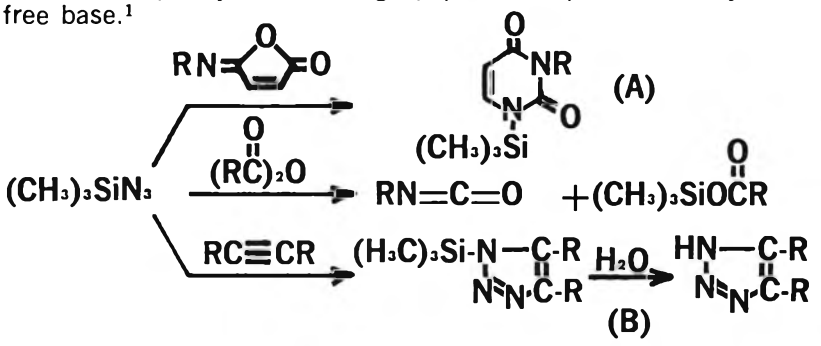
Diphenylphosphonic azide (DPPA)



DPPA, a stable and distillable liquid*, readily converts carboxylic acids to urethanes in the presence of triethylamine and a protic solvent[1], **via a modified Curtius** reaction. If the reaction is carried out in **tert**-butanol, a **tert**-butylurethane is obtained which can be hydrolyzed to the amine. This modified Curtius reaction is much simpler than the classical method, and requires neither the strong alkali of the Hofmann reaction nor the strong acid of the Schmidt rearrangement. Furthermore pyridine-2-carboxylic acid, which fails to undergo the Schmidt reaction, is smoothly converted by DPPA to **tert**-butyl N-(2-pyridyl)carbamate in 73% yield.[1]

DPPA is also a highly useful peptide reagent, capable of coupling peptides in good yield (69-95%) with practically no racemization.[1] The reaction is general and can tolerate a wide range of functionalities in both the carboxyl and the amino components.[1] The reaction is conveniently performed by adding DPPA (1.1-1.2 equiv) in dimethylformamide (DMF) to a stirred mixture of N-protected amino acid (1 equiv) and peptide ester (1.1-1.2 equiv) followed by triethylamine (2.1-2.2 equiv). The use of DMF widens the scope of this method to include poorly soluble large peptides. Peptide ester hydrochloride may be used as well as the free base.[1]

Azidotrimethylsilane (Trimethysilyl azide)



Azidotrimethylsilane, a stable liquid*, enables a simple conversion of isomaleimides to 3-substituted-1-trimethylsilyluracils (A) which are potentially useful in nucleoside synthesis.[2] Reaction of carboxylic anhydrides with azidotrimethylsilane affords isocyanates in good yield and provides a new route to amines.[2] Azidotrimethylsilane can be used in place of the explosive hydrazoic acid for the preparation of 1,2,3-triazoles (B) from acetylenes.[3]

*While both azides have been reported to be stable, and we have not encountered explosions in their manufacture, we would advise caution in handling them.

References:

1. T. Shioiri, K. Ninomiya and S. Yamada, **J. Amer. Chem. Soc., 94,** 6203 (1972).
2. S. Washburne, W. R. Peterson, Jr. and D. A. Berman, **J. Org. Chem., 37,** 1738 (1972).
3. (a) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, p 1236.
   (b) L. Birkofer and A. Ritter, **Angew. Chem., Internat. Ed., 4,** 417 (1965).

17,875-6	Diphenylphosphonic azide (DPPA)	25g-$14.00; 100g-$40.00
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