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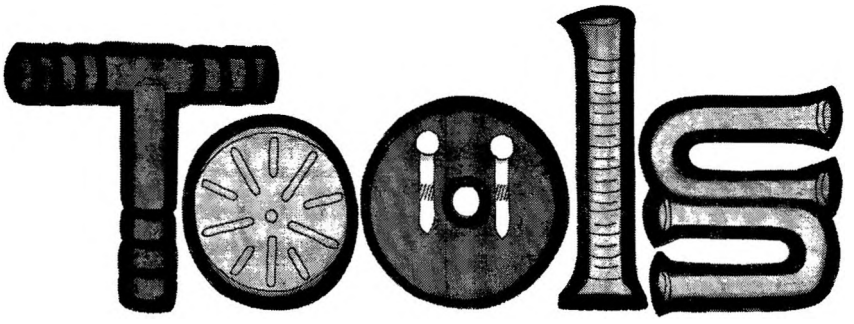

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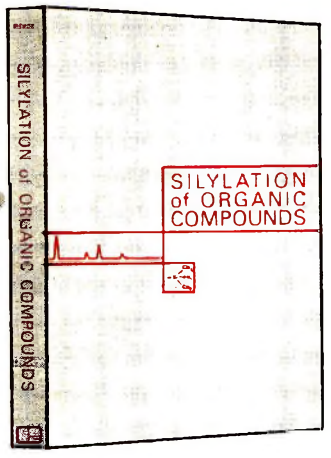

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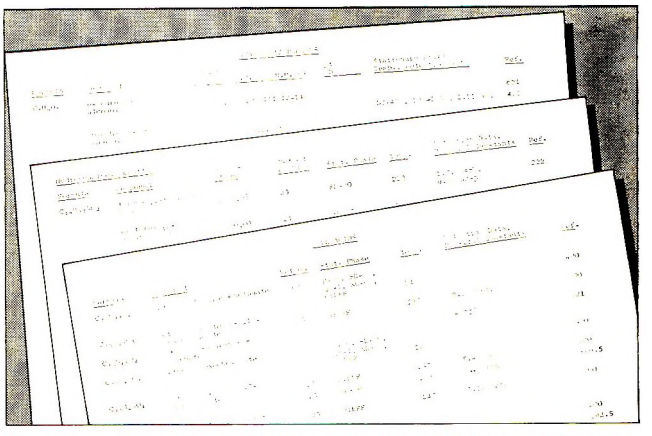

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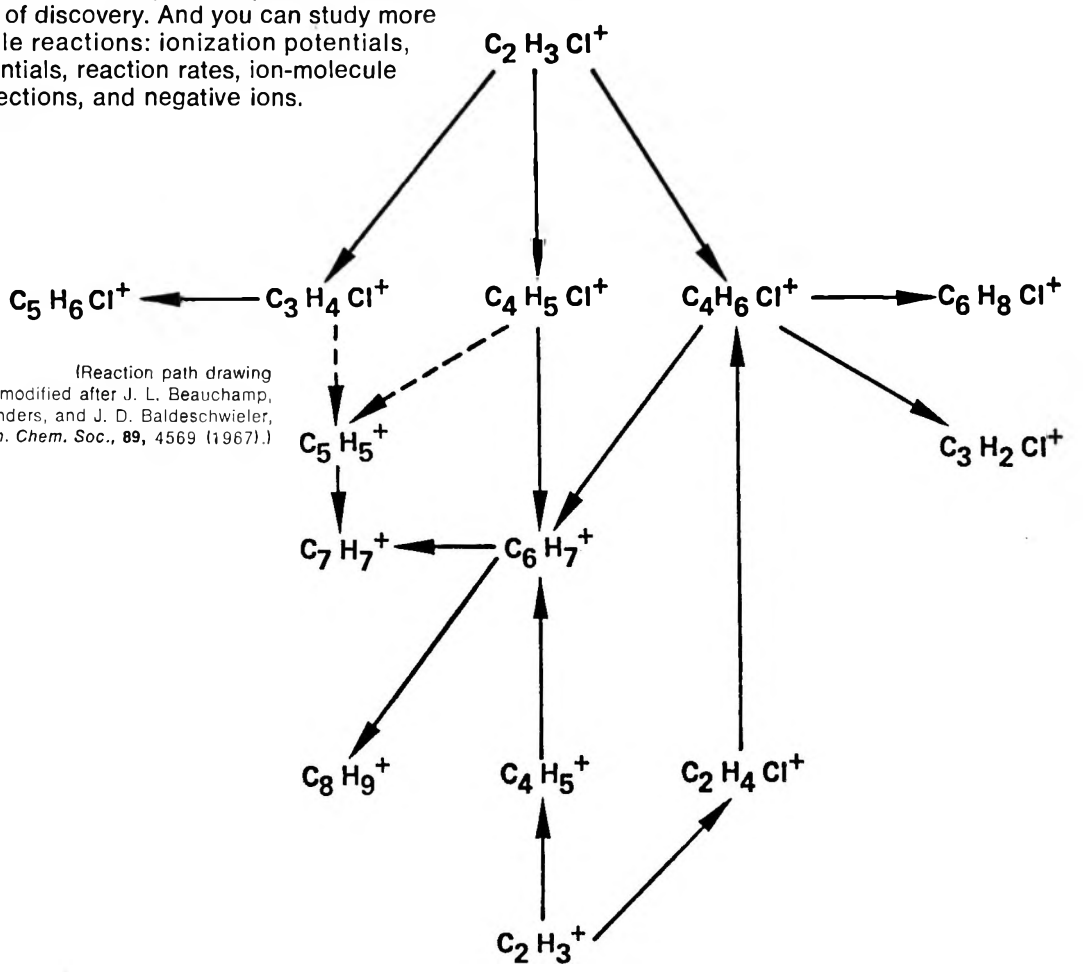

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The Photocycloaddition of Various Ketones and Aldehydes to Vinyl Ethers and Ketene Diethyl Acetal[1]

SIEGFRIED H. SCHROETER AND CHARLES M. ORLANDO, JR.

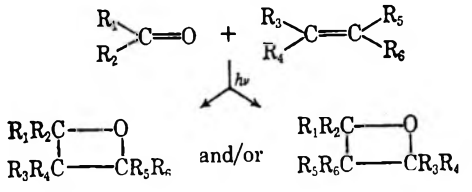
General Electric Research and Development Center, Schenectady, New York

Received September 3, 1968

Photoaddition of acetone to ethyl, *n*-butyl, and isobutyl vinyl ether and of propionaldehyde, cyclohexanone, benzaldehyde, and benzophenone to ethyl vinyl ether gives the corresponding 2- and 3-alkoxyoxetanes in ratios of (25 ± 5):75 independent of solvent. Acetone, cyclohexanone, and benzophenone also add to ketene diethyl acetal to give 2,2- and 3,3-diethoxyoxetanes in analogous ratios. Only 3,3-dialkoxyoxetanes were obtained from the photochemical reaction of ketene diethyl acetal with propion- and benzaldehyde. Selective transformations of 2-alkoxy- and 2,2-dialkoxyoxetanes with water, alcohols, or lithium aluminum hydride are used as a means of analyzing the reaction mixtures. The directions of the cycloadditions are compared with those of radical additions to vinyl ethers and ketene acetals. It is concluded that the isomer ratios in the cycloadditions cannot simply be predicted from the energy differences of the possible intermediates.

The Paterno–Büchi reaction, *i.e.*, the photocycloaddition of ketones and aldehydes to olefins, has recently been the subject of considerable study. Preparative work has been concerned with variations of the carbonyl[2-4] as well as of the olefinic[5,6] components. Mechanistic studies have shown that the cycloaddition to electron-rich olefins occurs *via* the n–π^* triplet state of the carbonyl compounds[7-9] and that the addition follows a two-step mechanism, *cis* and *trans* olefins giving the same mixtures of stereoisomeric oxetanes.[10] Rationalization of the mode of cycloaddition to unsymmetrical substituted olefins[11] has also led to the postulation of a nonconcerted mechanism; the predominant isomer formed is correctly predicted from consideration of the more stable biradical (ground state) intermediate, formed by addition of the carbonyl oxygen to the carbon–carbon double bond[11] (Scheme I).

SCHEME I



This paper describes the photocycloaddition of carbonyl compounds to vinyl ethers and to ketene diethyl acetal. The reaction represents a facile synthesis of mono- and dialkoxyoxetanes—compounds of considerable synthetic interest.[12] The quantitative determination of the isomer ratios formed from both vinyl ethers and ketene acetal has permitted a comparison of the direction of addition in both systems. The results show that product ratios are not always simply predicted from the stability of the intermediate radicals.

Results

Vinyl Ethers.—Acetone, propionaldehyde and cyclohexanone, when irradiated in the n–π^* region of the

(1) Presented at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968.

(2) (a) Y. Shigemitsu, Y. Odaira, and S. Tsutsumi, *Tetrahedron Lett.*, 55 (1967); (b) M. Hara, Y. Odaira, and S. Tsutsumi, *ibid.*, 2981 (1967); (c) Y. Odaira, T. Shimodaira, and S. Tsutsumi, *Chem. Commun.*, 757 (1967); (d) T. Tominaga, Y. Odaira, and S. Tsutsumi, *Bull. Chem. Soc. Jap.*, **40**, 2451 (1967).

(3) (a) D. Bryce-Smith, A. Gilbert, and M. G. Johnson, *J. Chem. Soc., C*, 383 (1967); (b) J. A. Barltrop and B. Hesp, *ibid.*, 1625 (1967); (c) R. C. Cookson, J. J. Frankel, and J. Hudec, *Chem. Commun.*, 16 (1965).

(4) (a) S. Farid and K.-H. Scholz, *ibid.*, 412 (1968); (b) S. Farid, D. Hess, and C. H. Krauch, *Chem. Ber.*, **100**, 3266 (1967); (c) C. H. Krauch and S. Farid, *ibid.*, **100**, 1685 (1967); (d) C. H. Krauch, S. Farid, and G. O. Schenck, *ibid.*, **98**, 3102 (1965); (e) C. H. Krauch and S. Farid, *Tetrahedron Lett.*, 4783 (1966).

(5) (a) D. R. Arnold and A. H. Glick, *Chem. Commun.*, 813 (1966); (b) H. Gotthardt, R. Steinmetz, and G. S. Hammond, *ibid.*, 480 (1967); *J. Org. Chem.*, **33**, 2774 (1968).

(6) (a) S. Toki and H. Sukurai, *Tetrahedron Lett.*, 4119 (1967); (b) G. R. Evanega and E. B. Whipple, *ibid.*, 2163 (1967); (c) J. Leitich, *ibid.*, 1937 (1967); (d) M. Ogata, H. Watanabe, and H. Kano, *ibid.*, 533 (1967); (e) C. Rivas and E. Payo, *J. Org. Chem.*, **32**, 2918 (1967).

(7) N. C. Yang, R. Loeschen, and D. Mitchell, *J. Amer. Chem. Soc.*, **89**, 5465 (1967).

(8) L. A. Singer and G. A. Davis, *ibid.*, **89**, 598, 158 (1967).

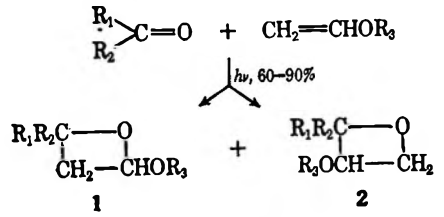
(9) D. R. Arnold, R. L. Hinman, and A. H. Glick, *Tetrahedron Lett.*, 1425 (1964).

(10) N. J. Turro, P. Wriede, J. C. Dalton, D. Arnold, and A. Glick, *J. Amer. Chem. Soc.*, **89**, 3950 (1967).

(11) G. Büchi, C. G. Inman, and E. S. Lipinsky, *ibid.*, **76**, 4327 (1954).

(12) S. H. Schroeter, *J. Org. Chem.*, **34**, 1188 1969).

SCHEME II



carbonyl group, readily added to vinyl ethers to afford mixtures of 2- and 3-alkoxyoxetanes (1 and 2, respectively) in high conversions and good yields (50–70%). With a 450-W medium-pressure mercury lamp, 50–60 g of oxetanes could be prepared within 24 hr. Similar high conversions and even better yields (80–90%) were obtained from the irradiation of benzaldehyde and benzophenone with vinyl ethers (Scheme II).

In many cases, the ratio of 2- to 3-alkoxyoxetanes could be determined by nmr spectroscopy. 2-Alkoxyoxetanes such as 1 show an ABX spectrum for their ring protons; the signal for the proton α to the ring oxygen (X part) appears around τ 4.8, those for the β protons (AB part) appear at *ca.* τ 7.5. 3-Alkoxyoxetanes, on the other hand, display an ABC pattern around τ 5.5. Integration over these signals gave the relative amounts of isomers. In addition, gas chromatographic analysis of the reaction mixtures was also possible in many cases. Results obtained from the gas chromatographic and nmr analyses were usually in good agreement (Table I). The mixtures obtained from the addition of benzaldehyde or benzophenone to ethyl vinyl ether and butyl vinyl ether could not be analyzed in the described manner because of overlap of nmr signals and decomposition of the compounds on vpc analysis. It was possible, however, to determine the isomer ratios in an indirect way *via* selective chemical transformations of the 2-alkoxy isomers. As described in detail in an accompanying paper,[12] 2-alkoxyoxetanes were found to react quantitatively with water, alcohols, phenols, Grignard reagents and lithium aluminum hydride under conditions where 3-alkoxyoxetanes are inert (Scheme III). Vpc analysis of these reaction mixtures permitted an indirect determination of the original product compositions. The isomer ratios obtained in all these additions are collected in Table I.

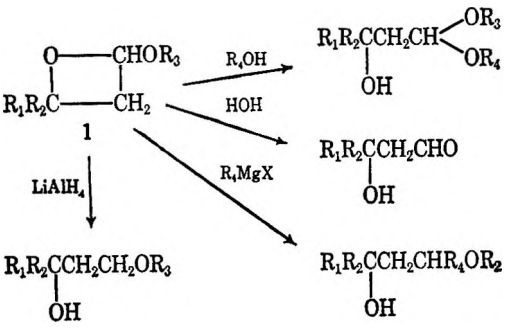
TABLE I

PRODUCT COMPOSITION OF ALKOXYOXETANES FROM THE PHOTOCHEMICAL CYCLOADDITION OF CARBONYL COMPOUNDS TO VINYL ETHERS[a]

Carbonyl compound	Ether	Yield,[b] %	2:3[d] Vpc	2:3[d] Nmr
Acetone	Ethyl vinyl	60–70[c]	30:70	25:75
Acetone	*n*-Butyl vinyl	60	25:75	25:75
Acetone	Isobutyl vinyl		25:75	
Propionaldehyde	Ethyl vinyl	49	19:81[e]	16:84
Cyclohexanone	Ethyl vinyl	50	30:70	30:70
Benzaldehyde	Ethyl vinyl	85	30:70[e]	
Benzophenone	Ethyl vinyl	99	25:75[e]	

[a] Irradiations in excess vinyl ether as a solvent; for solvent effects, see Table IV. [b] Yields after distillation. [c] Based on consumed ethyl vinyl ether; if calculated for consumed acetone, yields are much higher. Yields depend on irradiation conditions, 60% were obtained with Vycor, 70% with Corex filters. [d] Isomer ratios accurate to within ±5%. [e] After alcoholysis, see text.

SCHEME III



The reaction of the carbonyl compounds with the vinyl ethers always gave higher boiling materials together with an undistillable residue as side products. The observed ratios of 3- to 2-alkoxyoxetanes will, of course, only represent the original compositions if these higher molecular weight products are not formed preferentially from one of the isomers. Since the same isomer ratio was observed in all cases, including those where little polymeric material was formed, it is felt that the ratios given in Table I do indeed represent the original compositions. Further support for this comes from the observation that the isomer ratio was found to be unchanged during irradiation and that it was the same regardless of whether quartz, Pyrex, or Corex vessels were employed. The use of different filters only effected the amount of higher molecular weight materials formed. These materials were shown to consist mainly of vinyl ether units.

No solvent effects have been observed in the cycloadditions. The ratio of isomers formed was virtually unchanged in either neat vinyl ether or in benzene, acetonitrile or *t*-butyl alcohol (Table II). Addition of piperylene resulted in a remarkable decrease in the rate of cycloaddition, but had no effect on the isomer ratios (Table II). These results suggest that the additions occur *via* one excited quenchable state, most likely the n–π^* triplet state, of the carbonyl compounds.[13]

TABLE II

PRODUCT COMPOSITIONS FROM THE PHOTOCYCLOADDITION IN DIFFERENT SOLVENTS

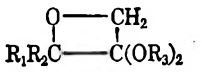
Carbonyl compound	Amt, mol/l.	Ether	Amt, mol/l.	Solvent	Quencher	2 isomer, %
Ph_2CO	0.1–0.3	EVE[a]	Neat			23 ± 3
Ph_2CO	0.1	EVE	1.0	C_6H_6		23 ± 3
Ph_2CO	0.2	EVE	1.3	CH_3CN[c]		27 + 3
Ph_2CO	0.2	EVE	1.3	*t*-BuOH		23 ± 3
Ph_2CO	0.1	EVE	0.3	C_6H_6	+*d*	22 ± 4
PhCHO	0.1	EVE	0.2	C_6H_6		27 ± 3
PhCHO	0.4	EVE	1.2	C_6H_6		30 ± 3
PhCHO	0.15	EVE	0.5	C_6H_6	+*e*	26 ± 4
Me_2CO	1–2	EVE	Neat			25 ± 3
Me_2CO	0.1	EVE	0.3	CH_3CN		25 ± 5
Me_2CO	0.4	EVE	2.0	CH_3CN		25 ± 3
Me_2CO	0.1	BVE[b]	0.3	CH_3CN		25 ± 2
Me_2CO	0.2	BVE	0.4	*t*-BuOH		31 ± 2

[a] Ethyl vinyl ether. [b] Butyl vinyl ether. [c] $CH_3CN:C_6H_6$ = 3:2. [d] Piperylene, *c* 0.2 mol/l. [e] Piperylene, *c* 0.35 mol/l.

Since 2- and 3-alkoxyoxetanes are virtually new types of compounds,[14-16] some of the isomers were separated for further characterization. 3-Alkoxyoxetanes show a characteristic infrared absorption around 980 cm^{-1}, already observed for other oxetanes.[9] In the 2-alkoxy isomers, this band was shifted toward longer wavelengths to 940–950 cm^{-1}. The nmr spectra of the isomers showed the characteristic differences in the shifts of the ring protons mentioned above. In addition, the signals corresponding to the protons in the alkoxy side chains were uniquely different in the isomers. In the 2-ethoxyoxetanes (**1**), the α-methylene protons (OCH_2CH_3) were nonequivalent and gave rise to complex splitting patterns (ABX_3 type) similar to other acetals, whereas these protons appeared as regular quartets in the 3-ethoxyoxetanes.

Separation of the 2 and 3 isomers was generally achieved by spinning-band distillation; isolation of pure 2-alkoxy isomers usually required refractionation of enriched samples. In cases where this seemed desirable, a quantitative isolation of the 3-alkoxyoxetanes from the reaction mixtures was readily achieved through the selective transformations of the 2-alkoxyoxetanes outlined in Scheme III. By proper choice of the reagents, the boiling points of the reaction products from the 2-alkoxy isomers could be selected in such a fashion that their separation from the unreacted 3-alkoxyoxetanes became quantitative. It was thus possible to study the composition of the isomeric 3-alkoxyoxetanes obtained from the cycloaddition of benzaldehyde to ethyl vinyl ether. The results showed that a 1:1 mixture of stereoisomers was formed (see Experimental Section). It is worth noting that in the oxetanes studied so far, the *cis*- and *trans*-geminal coupling constants were only slightly different. Similar effects have previously been observed in the cyclobutane series.[17] The isomer composition of the 2-phenyl-3-ethoxyoxetanes was confirmed by the results of their acid-catalyzed hydrolysis which led to a 1:1 mixture of diastereoisomeric 1-phenyl-3-ethoxypropane-1,3-diols.[12]

Ketene Acetals.—α,β-Unsaturated ketones have been found to react with ketene acetals under irradiation to give dialkoxycyclobutanes as the major[18,19] or the only[19,20] products, 3,3-dialkoxyoxetanes being side products in some cases.[18,19] Our results obtained from the cycloaddition of saturated carbonyl compounds to vinyl ethers prompted an extension of the studies to ketene acetals. Acetone, cyclohexanone, propionaldehyde, benzaldehyde and benzophenone all added readily to ketene diethyl acetal. Pure 3,3-dialkoxyoxetanes (**3**) could be isolated from the reaction mixtures by distillation and/or crystallization. The



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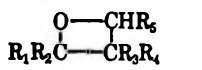
nmr and infrared spectra of these compounds showed the same characteristic absorption bands observed for the 3-alkoxyoxetanes. Further analogy between the 3-alkoxy and 3,3-dialkoxy compounds was found in the patterns of their respective mass spectra. These did not show molecular ion peaks, but fragments derived from the loss of formaldehyde from the oxetane (Table III).

TABLE III

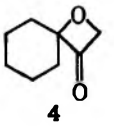
MASS SPECTRAL DATA FOR 3-ALKOXY- AND 3,3-DIALKOXYOXETANES



R_1	R_2	R_3	R_4	R_5	Mol wt	Highest mass fragment
CH_3	CH_3	H	OC_2H_5	H	130	100[a]
CH_3	CH_3	OC_2H_5	OC_2H_5	H	174	144[a]
CH_3	CH_3	OC_2H_5	OC_2H_5	CH_3	188	144[b]
						130[c]
C_2H_5	H	H	OC_2H_5	H	132	102[a]
C_2H_5	H	OC_2H_5	OC_2H_5	H	174	144[a]
$(CH_2)_5$		H	OC_2H_5	H	170	140[a]
$(CH_2)_5$		OC_2H_5	OC_2H_5	H	214	184[a]
C_6H_5	C_6H_5	OC_2H_5	OC_2H_5	H	298	268[a]

[a] $M^+ - CH_2O$. [b] $M^+ - CH_3CHO$. [c] $M^+ - (CH_3)_2CO$.

Hydrolysis of the cyclohexanone–ketene diethyl acetal adduct gave a moderate yield of 1-oxaspiro[3.5]-nonan-3-one (**4**) which had data in good agreement



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with those previously reported.[21] The structural assignment was further supported by the ir spectrum of the ketone which showed a carbonyl absorption at 1815 cm^{-1}, characteristic[22] for 3-oxetanones, as well as by its nmr spectrum which consisted of a singlet at τ 4.93 and a multiplet at *ca.* τ 8.3.

2,2-Dialkoxyoxetanes have not yet been reported in the literature. The nmr spectra of the reaction mixtures from the irradiation of acetone and cyclohexanone with ketene diethyl acetal showed singlets at τ 7.64 and 7.76, respectively, signals expected for 2,2-dialkoxyoxetanes. Distillation of these mixtures afforded fractions enriched in the 2,2-dialkoxy isomers, but isolation in a high state of purity could not be achieved. The oxetanes were therefore characterized

(13) NOTE ADDED IN PROOF.—It has meanwhile been shown in a study of the photocycloaddition of acetone to methyl β-ethylvinyl ether that such additions may occur both through the singlet and/or the triplet state, depending on experimental conditions [N. J. Turro and P. Wriede, *J. Amer. Chem. Soc.*, **90**, 6863, (1968)]. Addition of quenchers in this system also did not effect the ratio of 2- to 3-alkoxyoxetanes; *i.e.*, both excited states lead to the same ratio of 2 to 3 isomers.

(14) The preparation of some 2- and 3-alkoxyoxetanes by nonphotochemical routes has recently been reported; *cf.* ref 15 and 16.

(15) (a) F. Nerdel, D. Frank, H.-J. Lengert, and P. Weyerstahl, *Chem. Ber.*, **101**, 1850 (1968); (b) J. Jančulev, F. Nerdel, D. Frank, and G. Barth, *ibid.*, **100**, 715 (1967); (c) F. Nerdel and H. Kressin, *Ann.*, **707**, 706 (1967).

(16) N. P. Gambaryan, L. A. Simonyan, and P. V. Petrovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 918 (1967). R. J. Polak, J. A. Wojtowicz, and J. A. Zaslowsky, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p Q43.

(17) R. Steinmetz, W. Hartmann, and G. O. Schenck, *Chem. Ber.*, **98**, 3854 (1965), and references cited therein.

(18) O. L. Chapman, T. H. Koch, F. Klein, P. J. Nelson, and E. L. Brown, *J. Amer. Chem. Soc.*, **90**, 1657 (1968).

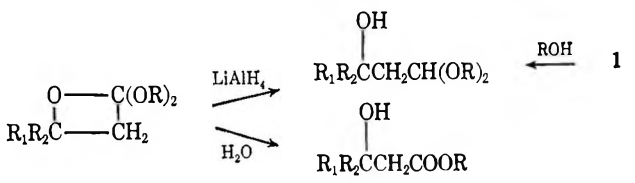
(19) (a) N. C. Yang, *Pure Appl. Chem.*, **9**, 591 (1964); (b) J. W. Hanifin and E. Cohen, *Tetrahedron Lett.*, 5421 (1966).

(20) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964).

(21) J. R. Marshall and J. Walker, *J. Chem. Soc.*, 467 (1952).

(22) (a) S. Searles, Jr., in "Heterocyclic Compounds," Vol. II/2, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1964, p 983; (b) G. Dittus in Houben Weyl's "Methoden der organischen Chemie," Vol. VI/3, Georg Thieme Verlag, Stuttgart, 1963, p 515.

SCHEME IV



via their transformation products (Scheme IV). In general, a similar difference in reactivity was observed between 2,2- and 3,3-dialkoxy isomers as was found between 2- and 3-dialkoxyoxetanes. Treatment of the mixtures of the isomeric oxetanes with excess lithium aluminum hydride in refluxing diethyl ether resulted in complete, selective conversion of the 2,2 isomers into the corresponding 3-hydroxy acetals. These acetals were readily separated from the unreacted 3,3-dialkoxyoxetanes by preparative vpc. They were identified by comparison with the compounds independently prepared by alcoholysis of the corresponding 2-alkoxyoxetanes.[12] Likewise, mixtures of 2,2- and 3,3-dialkoxyoxetanes, when treated with water, gave mixtures of unreacted 3,3-dialkoxy isomers and 3-hydroxy esters (for details, see Experimental Section). The presence of 2,2-dialkoxyoxetanes in the irradiation mixtures from acetone and cyclohexanone was thus unequivocally established.

Irradiation of benzophenone with ketene diethyl acetal also leads to a considerable amount of the 2,2-dialkoxyoxetane. This was demonstrated by isolating 3,3-diphenyl-3-hydroxypropionaldehyde diethyl acetal after $LiAlH_4$ reduction of the irradiation mixtures. Despite several attempts, no 2,2-dialkoxyoxetanes could be detected in the irradiation mixtures from benzaldehyde and propionaldehyde with ketene diethyl acetal. In these irradiations, the disappearance of the acetal and the carbonyl compounds were much faster than in other cases. Further, the reaction mixtures contained very large amounts of high molecular weight materials, even after short irradiation times. It seems likely, therefore, that in analogy to all the other cases, 2,2-dialkoxyoxetanes are also formed with these aldehydes, but that they are destroyed subsequently. The results from the addition to ketene diethyl acetal are summarized in Table IV.

TABLE IV

PRODUCT COMPOSITION OF DIALKOXYOXETANES FROM THE PHOTOCHEMICAL CYCLOADDITION OF CARBONYL COMPOUNDS TO KETENE DIETHYL ACETAL

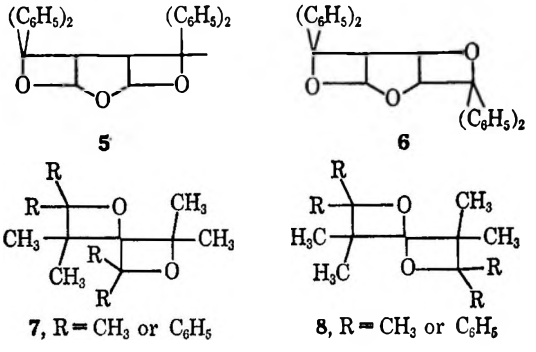
Carbonyl compound	Solvent	2,2-Dialkoxyoxetane,[a] %	Method of identification[b]
Acetone	Acetone	30 ± 5	Nmr, hydrolysis, $LiAlH_4$ reduction
Cyclohexanone	Cyclohexanone	30 ± 5	Nmr, hydrolysis, $LiAlH_4$ reduction
	t-BuOH[c]	30 ± 5	Nmr
	CH_3CN[c]	30 ± 5	Nmr
Benzophenone	Benzene	21 ± 5	$LiAlH_4$ reduction
Propionaldehyde	Pentane	None	$LiAlH_4$ reduction
Benzaldehyde	Benzene	None	$LiAlH_4$ reduction

[a] 2,2-Dialkoxy + 3,3-dialkoxyoxetane = 100%. [b] Identification of the 2,2-dialkoxyoxetane. [c] [Cyclohexanone] = 0.1 mol/l.; [ketene diethyl acetal] = 0.4 mol/l.

Discussion

Products.—A striking feature in the photocycloaddition to the vinyl ethers is the good yields obtained with aliphatic and alicyclic ketones. Whereas oxetanes are usually quite readily available from the reaction of aromatic ketones with olefins,[23] the addition of aliphatic ketones generally does not represent a useful synthetic method.[10,22-24] Because of the high energy levels of the excited states of such aldehydes and ketones, hydrogen abstraction and/or energy transfer (leading to dimerization of the olefin) often compete with oxetane formation.[9] Oxetanes are useful intermediates; they react with a large variety of reagents under ring opening to give 3-substituted hydroxy compounds or derivatives thereof.[22] So far, these reactions have been of theoretical rather than of practical interest, since oxetanes have generally been prepared by ring closure of such difunctional compounds.[22]

Mechanism.—Cycloadditions to vinyl ether systems have recently been reported in a few special cases. In the second addition of carbonyl compounds to allenes[5] or furans,[6] the unsaturated system is a vinyl ether. The mode of addition of carbonyl compounds to the systems studied in this paper is not predictable from these results, however. In the case of the second addition of benzophenone to furan, more of the 2-alkoxy isomer **5** (as compared with **6**) was formed,[6b,d] whereas addition of benzophenone and acetone to tetramethylallene[5] has been reported[5a] to give more of the 3-alkoxy isomer **7** than of the 2 isomer **8**. It has



been pointed out[5b] that, in the latter reactions, methyleneoxetanes might not be representative examples of acyclic vinyl ethers.

The isomer ratios given in Tables I, II, and IV show that the addition of the carbonyl compounds to both vinyl ethers and ketene acetals occurs preferentially, though by no means exclusively, in an anti-Markovnikov fashion with regard to ground-state polarizations. Anti-Markovnikov addition would be predicted by the biradical mechanism discussed above since the stabilizing effect of alkoxy substituents is well known from the radical addition reactions to vinyl

(23) L. L. Muller and J. Hamer in "1,2-Cycloaddition Reactions," Interscience Publishers, New York, N. Y., 1967, Chapter III.

(24) (a) J. S. Bradshaw, *J. Org. Chem.*, **31**, 237 (1966); (b) P. DeMayo, J. B. Stothers, and W. Templeton, *Can. J. Chem.*, **39**, 488 (1961).

ethers and ketene acetals.[25,26] However, the formation of a large proportion of 2-alkoxyoxetanes in the photoadditions to vinyl ethers indicates that factors other than the stability of the intermediate biradicals must play an important role in determining the mode of photocycloaddition. Otherwise, one would expect similar orientational specificity in the photocycloaddition reaction in comparison to the free radical additions where anti-Markovnikov additions are exclusively observed.[25,26]

Even more surprising is the fact that relatively large proportions of 2,2-alkoxyoxetanes are found in the photoadditions to ketene acetals. If radical stability of the intermediates were the only determining factor in the cycloaddition reaction, one would expect the isomer ratio to change considerably in changing from vinyl ethers to ketene acetals—which is not the case.

At this time, we can only speculate on the various factors that determine the addition. One might expect that the rate of formation of the intermediates may depend on electronic as well as on steric factors. The actual polarization of the carbonyl group in the excited state (as yet unknown) will certainly play an important role in the addition to such highly polarized molecules as vinyl ethers or ketene acetals. The formation of the intermediate may be reversible[27] owing to a second energy barrier separating intermediates and products (Figure 1). Further work designed to understand more fully the mechanism, of these photoreactions is currently in progress in this laboratory.

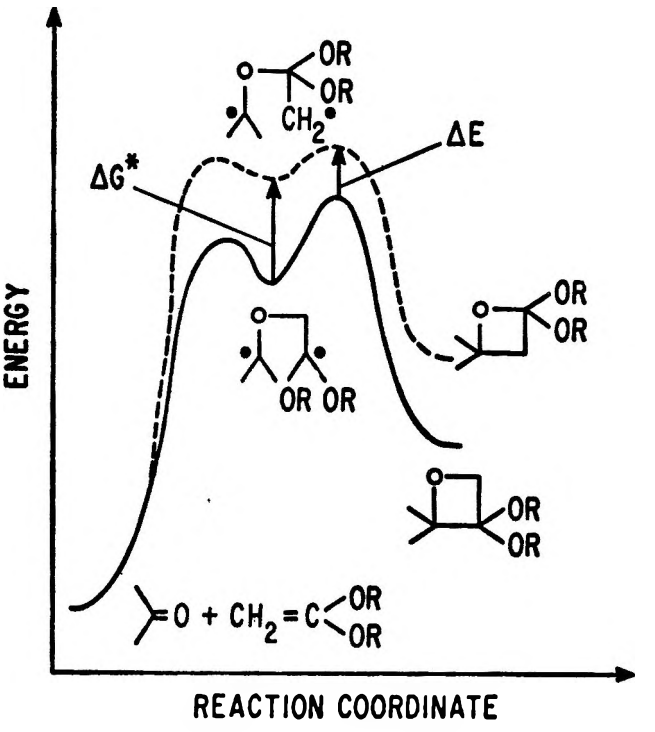


Figure 1.

Experimental Section

Ethyl vinyl, *n*-butyl vinyl and isobutyl vinyl ether were obtained from commercial sources, dried, and fractionated over sodium. Acetone was dried over calcium chloride and fractionated over potassium permanganate. Irradiations were carried out under nitrogen in internally water-cooled reactors at 15–25° with a 450-W medium-pressure mercury lamp. For reactions with aliphatic ketones and aldehydes, a quartz reactor was used in combination with a Vycor 7910 glass filter to eliminate wavelengths below 2500 Å. Irradiations with aromatic aldehydes, aryl alkyl ketones and diaryl ketones were carried out in Pyrex vessels. Care was taken to protect the reaction mixtures from moisture since 2-alkoxyoxetanes and ketene acetals react with water at room temperature. Most gas chromatographic analyses were carried out on a 3-ft Apiezon L column on a dual column, temperature-programmed 5750 F & M research chromatograph. 2-Alkoxyoxetanes were found to be unstable on virtually all other columns. Nmr spectra were recorded on a Varian A-60 and ir spectra on a Perkin-Elmer Model 337 spectrometer. Coupling constants are approximate values (±1 cps). Elemental analyses and molecular weight determinations were obtained from Galbraith and Schwarzkopf Microanalytical Laboratories. The substituted alkoxy and dialkoxyoxetanes are consistently named in such a fashion that they appear either as 2- or 3-alkoxyoxetanes (or 2,2- and 3,3-dialkoxyoxetanes, respectively).

Acetone–Ethyl Vinyl Ether.—A solution of 43.5 g (0.75 mol) of acetone in 300 ml of ethyl vinyl ether was irradiated for 50 hr. Excess ethyl vinyl ether was carefully removed at 50 mm and the residue distilled to afford 59 g (60.5%) of a mixture of alkoxyoxetanes, bp 60–80° (70 mm). Vpc analysis on a 2-ft Apiezon column showed this to be a 25:75 mixture of isomers. Comparison of the nmr signals at τ 4.8, 5.8 and 7.8 gave a 30:70 ratio of 4,4-dimethyl-2-ethoxy- to 2,2-dimethyl-3-ethoxyoxetane. Distillation through an 80-cm spinning-band column afforded 35 g of **2,2-dimethyl-3-ethoxyoxetane**, bp 67–68° (65 mm), n^{20}D 1.4103, which was shown to be free from its isomer by nmr and vpc analysis: ir (neat, cm^{-1}) 890 vs, 960 vs; nmr (neat) τ 5.50–6.12 (m, 3, eight-line spectrum), 6.62 (q, 2), 8.69 (s) and 8.87 (t) of 9-H.

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84; mol wt, 130.18. Found: C, 64.58; H, 10.85; mol wt, 174.

4,4-Dimethyl-2-ethoxyoxetane [bp 54° (62 mm), n^{20}D 1.4002] was obtained by careful fractionation of enriched samples. It was shown to be free of its 3 isomer by vpc and nmr analysis: ir (CCl_4, cm^{-1}) 980 w, 940 vs; nmr (neat) τ 4.69 (s), 4.76 (s), 4.78 (s) and 4.75 (s) of 2-H, *ca.* 6.5 (14-line spectrum, 2-H), 7.33–7.99 (eight-line spectrum, 2-H), 8.61 (s), 8.64 (s) and 8.83 (t) of 9-H.

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.74; H, 10.74.

Acetone–*n*-Butyl Vinyl Ether.—A solution of 100 g of *n*-butyl vinyl ether in 200 ml of acetone was irradiated for 22 hr. Distillation gave 156 g of an azeotropic mixture of acetone and *n*-butyl vinyl ether, bp 55–95°, containing 24 g of the vinyl ether (*via* vpc), 8 g of *n*-butyl vinyl ether [bp 65° (95 mm)], and 60 g (60%) of a 75:25 mixture (*via* vpc and nmr) of 2,2-dimethyl-3-*n*-butoxy- and 4,4-dimethyl-2-*n*-butoxyoxetane. This mixture was fractionated through an 80-cm spinning-band column to afford 21.2 g of pure (>99% by vpc) **2,2-dimethyl-3-*n*-butoxyoxetane**: bp 70° (16 mm); n^{20}D 1.4200; ir (neat, cm^{-1}) 980 vs, 960 vs; nmr (neat) τ 5.5–6.12 (m, 3, ABC spectrum), 6.69 (m, 2), 8.3–8.7 (m, 11) with 8.68 (s), 9.08 (m, 3).

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47; mol wt, 158.23. Found: C, 68.12; H, 11.55; mol wt, 175.

4,4-Dimethyl-2-*n*-butoxyoxetane [bp 66° (18 mm), n^{20}D 1.4125] was obtained by careful fractionation of enriched samples. It was shown to contain less than 3% of its isomer by vpc analysis: ir (neat, cm^{-1}) no OH or C=O absorption, 990 vw, 940 vs, 845 vs; nmr (neat) τ 4.72, 4.77, 4.81, 4.86 (singlets, 1, X part of ABX), 6.15–6.92 (m, 2), 7.34–7.93 (eight lines, 2, AB part), *ca.* 8.5 (m, 10) with 8.61 (s) and 8.65 (s), *ca.* 9.0 (m, 3) with 9.08 (s).

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47; mol wt, 158.23. Found: C, 68.49; H, 11.49; mol wt, 161.

Acetone–Isobutyl Vinyl Ether.—A solution of 69 g isobutyl vinyl ether in 250 ml of acetone was irradiated for 20 hr. Work-up from two such irradiations gave unreacted acetone and vinyl

(25) (a) E. S. Huyser and L. Kim, *J. Org. Chem.*, **33**, 94 (1968); (b) C. Walling and E. S. Huyser, *Org. Reactions*, **13**, 91 (1963); (c) F. W. Stacey and J. F. Harris, *ibid.*, **13**, 150 (1963); (d) A. N. Nesmeyanov, R. Kh. Freidlina, and L. I. Zakharkin, *Dokl. Akad. Nauk SSSR*, **97**, 91 (1954); *cf. Chem. Abstr.*, **49**, 8793 (1955); (e) A. V. Bogdanova and M. F. Shostakovskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 224 (1957); *Chem. Abstr.*, **51**, 10361 (1957).

(26) E. S. Huyser, R. M. Kellogg, and D. T. Wang, *J. Org. Chem.*, **30**, 4377 (1965).

(27) N. C. Yang, J. I. Cohen, and A. Shani, *J. Amer. Chem. Soc.*, **90**, 3266 (1968).

ether and 100 g (46%) of a 75:25 mixture of the 3- and 2-isobutyoxyoxetane (*via* nmr), 19.8 g of a fraction [bp 60–100° (0.1 mm)] and 13.9 g of residue. Fractionation of the isomer mixture afforded 44.2 g of isomer-free (*via* vpc and nmr) **2,2-dimethyl-3-isobutoxyoxetane**: bp 65° (17 mm); n^{20}D 1.4163; ir (neat, cm^{-1}) 980 vs, 963 vs; nmr (neat) τ 5.48–6.12 (m, 3), 6.92 (d, 2), 7.88–8.53 (m, 1), 8.68 (s, 6) and 9.07 (d, 6).

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47; mol wt, 158.23. Found: C, 68.5; H, 11.6; mol wt, 165.

The enriched 2-isobutoxy isomer was converted into **β-methyl-β-hydroxybutyraldehyde diisobutyl acetal**. A 45:55 mixture (30.0 g) of the 2- and 3-alkoxyoxetanes was refluxed in dry isobutyl alcohol for 16 hr and the product was fractionated to afford 18.62 g (97%) of the acetal: bp 60° (0.05 mm); n^{20}D 1.4274; purity 99% by vpc; ir (CCl_4, cm^{-1}) 3530 vs, 1120 vs, 1042 vs; nmr (neat) τ 5.27 (t, 1), *ca.* 5.5 (m, 5), 8.22 (d, superimposed on m) and 8.81 (s) with total of 6-H, 9.02 (s) and 9.12 (s), total of 12-H.

Anal. Calcd for $C_{13}H_{28}O_3$: C, 67.19; H, 12.15; mol wt, 232.35. Found: C, 67.27; H, 11.93; mol wt, 230.

Propionaldehyde–Ethyl Vinyl Ether.—A solution of 60 g of freshly distilled propionaldehyde in 250 ml of ethyl vinyl ether was irradiated for 26 hr. Evaporation of excess vinyl ether *in vacuo* and distillation afforded 65 g (49%) of a 19:81 mixture (*via* nmr) of 2- and 3-alkoxyoxetanes. Vpc analysis showed two peaks in a ratio of 16:84. The oxetane mixture (60 g) was refluxed with absolute ethanol for 10 hr. Vpc analysis now showed 81% of oxetanes (one peak) and 19% of a compound of higher retention time. Spinning-band distillation gave 43 g of **2-ethyl-3-ethoxyoxetanes** (mixture of *cis* and *trans*): bp 63–65° (28 mm); n^{20}D 1.4173; ir (CCl_4, cm^{-1}) 970 vs; nmr (neat) τ 5.25–6.15 (m, 4), 6.62 (q, 2), 8.48 (m, 2), 8.88 (t, 3) and 9.13 (t, split further, 3).

Anal. Calcd for $C_7H_{14}O_2$: C, 64.58; H, 10.84; mol wt, 130.18. Found: C, 64.61; H, 10.98; mol wt, 132.

The second fraction consisted of pure (98% by vpc) **β-hydroxy-n-valeraldehyde diethyl acetal**: bp 42° (0.05 mm); n^{20}D 1.4242 [lit.[28] bp 88–90 (8–9 mm), n^{18}D 1.4262]; ir (CCl_4, cm^{-1}) 3630 w, 3503 vs, 1125 vs, 1065 vs; nmr (neat) τ 5.28 (t, 1), 6.1–6.7 (m, 6) and 8.1–9.1 (m, 13) with 8.83 (t).

Anal. Calcd for $C_9H_{20}O_3$: C, 61.33, H, 11.44; mol wt, 176.25. Found: C, 61.12; H, 11.41; mol wt, 180.

Cyclohexanone–Ethyl Vinyl Ether.—A solution of 100 g of cyclohexanone in 200 ml of ethyl vinyl ether was irradiated for 22 hr. Work-up gave 43 g of unreacted cyclohexanone, 51 g (50% based on consumed ketone) of a mixture of oxetanes and 62 g of polymeric residue. As judged by the relative intensities of the signals at τ 4.8 and 5.8, the mixture consisted of a 30:70 ratio of the 2- and the 3-ethoxy isomer. Vpc analysis also gave a 30:70 ratio. Spinning-band distillation afforded 31.5 g of pure (>99% by vpc) **3-ethoxy-1-oxaspiro[3.5]nonane**: bp 72° (3.8 mm); n^{20}D 1.4555; ir (neat, cm^{-1}) 975 vs, 940 vs, 925 m, 910 vs; nmr (neat) τ 5.49–6.20 (nine lines, 3, ABC spectrum), 6.70 (q, 2), 8.0–8.8 (m, 13), maxima at 8.47 and 8.88.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66; mol wt, 170.24. Found: C, 70.58; H, 10.57; mol wt, 174.

2-Ethoxy-1-oxaspiro[3.5]nonane, which contained <2% of its isomer (*via* vpc), bp 56.5 (2.5 mm), n^{20}D 1.4502, was obtained by fractionation of enriched samples. In contrast to its 3 isomer, it had a pleasant, acetal-like odor: ir (neat, cm^{-1}) no OH or C=O adsorption, 950 vs, 928 vs, 908 vs; nmr (neat) τ 4.67, 4.74, 4.77, 4.83 (singlets, 1), *ca.* 6.47 (14 lines, 2, X part of ABX), 7.53–8.18 (eight lines, 2, AB part,) *ca.* 8.3 (m, 13) with 8.83 (t).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66; mol wt, 170.24. Found: C, 70.50; H, 10.52; mol wt, 175.

Benzaldehyde–Ethyl Vinyl Ether.—A solution of 53 g of freshly distilled benzaldehyde in 300 ml of ethyl vinyl ether was irradiated for 30 hr until all the benzaldehyde had disappeared. Vpc analysis of the crude mixture gave no separation of isomers. Distillation afforded 75.05 g (85%) of oxetanes and 6 g of undistillable residue. Spinning-band distillation led to enrichment of the isomers. Two fractions of bp 65° (0.2 mm) (no. 1) and bp 75° (0.4 mm) (no. 2) showed different ir intensities [no. 1 (CCl_4, cm^{-1}) 930 vs, 980 w; no. 2, 930 w, 980 vs], but had virtually the same nmr spectrum.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; mol wt, 178.22. Found: (no. 1, no. 2): C, 74.03, 74.33; H, 8.05, 8.14; mol wt, 179, 180.

A distilled mixture of oxetanes (73 g) was therefore refluxed with absolute ethanol. Vpc analysis then showed 75% of oxetanes and 25% of a compound of higher retention time. Distillation of this mixture afforded 63.8 g of a 47:53 mixture of *cis*- and *trans*-2-phenyl-3-ethoxyoxetanes: bp 50° (0.05 mm); nmr (neat), isomer A, τ 2.7 (m), 4.32 (d, J = ~5 cps), 5.5 (m), 6.74 (m), 8.93 (t), and isomer B, τ 2.7 (m), 4.43 (d, J = ~5 cps), 5.5 (m), 7.10 (m), 9.28 (t).

Anal. Found: C, 74.07; H, 7.94; mol wt, 178.

The second fraction consisted of 17.8 g (97%) of **β-phenyl-β-hydroxypropionaldehyde diethyl acetal**: bp 86° (0.04 mm); n^{20}D 1.4934; ir (CCl_4, cm^{-1}) 3615 m, 3510 vs, 3030 m, 1600 w, 1495 s, 695 vs (phenyl), 1120 vs, 1060 vs; nmr (CCl_4) τ 2.78 (s, 5), *ca.* 5.4 (m, 2), *ca.* 6.5 (m, 5), *ca.* 8.2 (m, 2) and 8.88 (t, 6).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.91; H, 8.99; mol wt, 224.29. Found: C, 69.79; H, 9.10; mol wt, 226.

Benzophenone–Ethyl Vinyl Ether.—A solution of 20 g of benzophenone in 300 ml of ethyl vinyl ether was irradiated for 48 hr. Evaporation of excess ether and distillation afforded 26.0 g (99%) of a mixture of oxetanes, bp *ca.* 110° (0.1 mm), that was heated in 125 ml of absolute ethanol for 12 hr. Vpc analysis of the heated mixture showed two major components in a ratio of 73:23. These were separated by spinning-band distillation. **2,2-Diphenyl-3-ethoxyoxetane** had bp 118° (0.25 mm); ir (CCl_4, cm^{-1}) 1600 w, 1495 s, 1450 s, 1175 and 1130 vs, 980 vs, 695 vs; nmr (CCl_4) τ 2.8 (m, 10), *ca.* 5.4 (m, 3), 6.75 (q, 2) and 9.12 (t, 3).

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13; mol wt, 254.31. Found: C, 80.25; H, 7.36; mol wt, 242.

The second fraction consisted of **β,β-diphenyl-β-hydroxypropionaldehyde diethyl acetal**: bp 133° (0.3 mm); ir (CCl_4, cm^{-1}) 3480 vs, 1600 w, 1495 s, 1450 s, 1175 s, 1120 vs, 1060 vs, 700 vs; nmr (CCl_4) τ 2.5–2.9 (m, 10), 5.25 (s, 1, OH), 5.57 (t, 1, $CH(OR)_2$), 5.59 (m, 4), 7.56 (d, 2, J = 6 cps), 8.94 (t, 6).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05; mol wt, 300.38. Found: C, 75.84; H, 7.93; mol wt, 299.

Acetone–Ketene Diethyl Acetal.—A solution of 59 g of ketene diethyl acetal[29] in 300 ml of dry acetone was irradiated for 22 hr. Excess acetone was evaporated *in vacuo* and the residue was distilled to give a major fraction (43.6 g) of bp 60–90° (14 mm), one (3.8 g) of bp 65–100° (0.3 mm) and 1.8 g of a polymeric residue. The major fraction was shown to be a 73:27 mixture of 2,2-dimethyl-3,3-diethoxy- and 4,4-dimethyl-2,2-diethoxyoxetane by measuring the relative intensities of the nmr signals at τ 5.78 (s) and 7.64 (s). Fractionation of the major fraction through an 80-cm spinning-band column gave 20.1 g (23%) of the pure **2,2-dimethyl-3,3-diethoxyoxetane**: bp 85–86° (12 mm); ir (neat, cm^{-1}) 1195, 1177, 1068, 1050, 985 (all vs), 960 s, 943 s, no carbonyl absorption; nmr (neat) τ 5.78 (s, 1), *ca.* 6.6 (m, 2), 8.68 (s) and 8.83 (t) of 6-H.

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41; mol wt, 174.23. Found: C, 62.05; H, 10.51; mol wt, 180.

In another preparation, irradiation was carried out with a Corex filter until half of the ketene acetal had been consumed and the mixture of oxetanes was distilled at 40–60° (6 mm), bath temperature ≤80°. This fraction (B) showed 30 ± 5% 2 isomer by nmr analysis.

Hydrolysis of 4,4-Dimethyl-2,2-diethoxyoxetane.—A mixture consisting of both isomeric dimethyldialkoxyoxetanes (fraction B) was dissolved in acetone and water was added until the solution became cloudy. This mixture was allowed to stand at room temperature for 10 hr. Vpc analysis now showed unreacted 2,2-dimethyl-3,3-diethoxyoxetane (75.5%) together with **ethyl 3-methyl-3-hydroxybutyrate** (24.5%). The ester was isolated by preparative vpc: ir (neat, cm^{-1}) 3450, 1725, 1250, 1035, 910; nmr (CCl_4) τ 8.78 (s) and 8.73 (t) of 9-H, 7.6 (s, 2), 6.78 (s, 1), 5.83 (q, 2).

Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65; mol wt, 146.18. Found: C, 57.72; H, 9.81; mol wt, 150.

$LiAlH_4$ Reduction of 4,4-Dimethyl-2,2-diethoxyoxetane.—An ether solution containing both isomeric dimethyldiethoxyoxetanes (fraction B) was added to excess $LiAlH_4$ and the mixture was refluxed for 30 min. Work-up with acetone and water gave a mixture consisting of unreacted 2,2-dimethyl-3,3-diethoxyoxetane (71%) and of **3-methyl-3-hydroxybutyraldehyde diethyl**

(28) L. A. Yanovskaya, V. F. Kucherov, and B. G. Kovalev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 647 (1962); *Chem. Abstr.*, **57**, 16379c (1962).

(29) S. M. McElvain and D. Kundiger, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 501.

acetal (29%) which was identified by comparison of its spectra with those of an authentic[12] sample.

Cyclohexanone–Ketene Diethyl Acetal.—A solution of 50 g of ketene diethyl acetal[29] in 200 ml of freshly distilled cyclohexanone was irradiated for 19.5 hr. Excess cyclohexanone was removed at 20 mm through a spinning-band column and the residue was distilled to afford 60 g of a fraction of bp 65–105° (0.5 mm) and 16.0 g of undistillable residue. Nmr intensities of the signals at τ 5.79 (s) and 7.76 (s) showed the major fraction to consist of a 70:30 mixture of the 3- and the 2-dialkoxy isomers. Fractionation afforded 22.2 g (24%) of pure **3,3-diethoxy-1-oxaspiro[3.5]nonane**: bp 85–86° (2.0 mm); ir (neat, cm^{-1}) 1200 vs, 1068 vs, 1058 vs, 990 vs; nmr (neat) τ 5.80 (s, 2), 6.58 (q, 4), *ca.* 8.55 (m, 9) with 8.83 (t).

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35; mol wt, 214.30. Found: C, 67.15; H, 10.43; mol wt, 214.

Hydrolysis of 2,2-Dialkoxy-1-oxaspiro[3.5]nonane.—A mixture consisting of both isomeric dialkoxyoxaspironanes was dissolved in acetone, water was added until the mixture was almost cloudy and the solution was allowed to stand at room temperature for 12 hr. Vpc analysis showed two major components that were separated by preparative vpc and identified as unreacted 3,3-diethoxy-1-oxaspiro[3.5]nonane and as **ethyl 1-hydroxycyclohexylacetate**: ir (CCl_4, cm^{-1}) 3530 vs, 1720 vs, 1175 vs; nmr (neat) τ 5.86 (q, 2), 6.53 (s, 1, OH), 7.60 (s, 2, CH_2), 8.48 (m) and 8.79 (t) of 13-H.

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74; mol wt, 186.24. Found: C, 64.64; H, 9.85; mol wt, 190.

$LiAlH_4$ Reduction of 2,2-Diethoxy-1-oxaspiro[3.5]nonane.—A mixture containing both isomeric dialkoxyoxaspirononanes was dissolved in ether and added to excess $LiAlH_4$. The mixture was refluxed for 1 hr and decomposed with acetone and water. Vpc analysis showed two major components that were isolated by preparative vpc and identified as unreacted 3,3-diethoxy-1-oxaspiro[3.5]nonane and as **1-hydroxycyclohexyl acetaldehyde diethyl acetal**: ir (CCl_4, cm^{-1}) 3564 vs, 1125 vs, 1050 vs; nmr (neat) τ 5.27 (t, 1), 6.45 (m) and 6.6 (s, OH) of 5-H, 8.28 (d), 8.52 (m) and 8.84 (t) of 18-H. The ir and nmr spectra were identical with those of the acetal prepared by ethanolysis of 2-ethoxy-1-oxaspiro[3.5]nonane.[12]

Hydrolysis of 3,3-Diethoxy-1-oxaspiro[3.5]nonane.—A mixture of 21 g of 3,3-diethoxy-1-oxaspiro[3.5]nonane, 500 ml of benzene, 5 ml of water and 2 g of *p*-toluenesulfonic acid monohydrate was refluxed for 4 hr. Most of the benzene was then slowly distilled off and the residual solution was extracted with sodium bicarbonate solution and brine and dried ($MgSO_4$). Vpc analysis of this mixture indicated it to consist of a complex mixture, containing about 30% 1-oxaspiro[3.5]nonan-3-one which showed the lowest retention time. The products from two such preparations were combined and the mixture was distilled on a spinning-band column to afford 4.75 g (20%) of 1-oxaspiro[3.5]nonan-3-one: bp 67° (18 mm); $n^{20}D$ 1.4642; λ_{max} (hexane) 290 mμ (log ϵ 1.8) [lit.[21] bp 86° (28 mm), $n^{18}D$ 1.4631, λ_{max} (hexane) 290 mμ (log ϵ 1.4)]; ir (CCl_4, cm^{-1}) 1815; nmr (neat) τ 4.93 (s, 2), 8.0–8.5 (m, 11). The mass spectrum showed no molecular ion peak; the highest mass peak appeared at 112 (molecular weight − CO). The **semicarbazone** had mp 194° (from ethanol) (lit.[21] mp 194°)].

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63; mol wt, 140.18. Found: C, 68.74; H, 8.63; mol wt, 145.

The higher boiling fractions consisted of saturated and unsaturated carbonyl compounds, as indicated by ir and nmr.

Propionaldehyde–Ketene Diethyl Acetal.—A solution of 30 g of freshly distilled propionaldehyde and 60 g of ketene diethyl acetal[29] in 250 ml of dry pentane was irradiated for 24 hr. The pentane was removed through a small Vigreux column and the residue distilled *in vacuo* to afford (a) 8.02 g of a mixture consisting of ketene acetal and ortho ester [bp 60–70° (97 mm)]; (b) 5.52 g of a fraction of bp 70–80° (97 mm); (c) 34.52 g (38.4%) of oxetane [bp 70–90° (18 mm)]; (d) 16.2 g of a fraction of bp 90–110° (18–0.1 mm); and (e) 6.5 g of undistillable residue. No 4-ethyl-2,2-diethoxyoxetane could be detected. Reduction of the crude reaction mixture with $LiAlH_4$ did not give any 3-hydroxyvaleraldehyde diethyl acetal. Pure **2-ethyl-3,3-diethoxyoxetane** of bp 74.5° (13 mm) was obtained by spinning-band distillation of fraction c: ir (neat, cm^{-1}) 985 vs and 950 vs; nmr (neat) τ 5.57 (t) and 5.68 (s) of 3-H, 6.59 (q, 4), 8.38 (m), 8.83 (t) and 9.12 (t) of 11-H.

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41; mol wt, 174.23. Found: C, 62.0; H, 10.6; mol wt, 178.

Benzaldehyde–Ketene Diethyl Acetal.—A solution of 31.8 g (0.03 mol) of freshly distilled benzaldehyde and 38.5 g (0.03 mol) of ketene diethyl acetal[29] in 400 ml of dry benzene was irradiated for 20 hr. During this time, the solution turned intense yellow. Evaporation of the benzene *in vacuo* left a residue that gave (a) 15.8 g of unreacted aldehyde, (b) 17.44 g (39.5% based on consumed aldehyde) of crude oxetane, bp 110–140° (0.1 mm), and (c) 16 g of undistillable residue. No 4-phenyl-2,2-diethoxyoxetane could be detected; reduction of the crude reaction mixture with excess $LiAlH_4$ failed to produce any 3-phenyl-3-hydroxypropionaldehyde diethyl acetal. Distillation of fraction b over a 60-cm spinning-band column afforded **2-phenyl-3,3-diethoxyoxetane**: bp 85° (0.3 mm); ir (neat, cm^{-1}) 985 vs, 950 s, weak absorption at 1715; nmr (neat) τ 2.7 (m), 4.47 (s), 5.43 (s, ?), 6.37–7.23 (m), 8.79 (t) and 9.21 (t).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16; mol wt, 222.24. Found: C, 70.34; H, 8.19; mol wt, 213.

Benzophenone–Ketene Diethyl Acetal.—A solution of 15 g (82 mmol) of benzophenone and 10.4 g (90 mmol) of ketene diethyl acetal[29] in 220 ml of dry benzene was irradiated for 13 hr. The light yellow solution was concentrated *in vacuo* to leave 25.0 g of a yellow liquid. Vacuum distillation gave (a) 10.34 g of a colorless liquid, bp 120° (0.01 mm), which was shown to be a 40:60 mixture of benzophenone and 2,2-diphenyl-3,3-diethoxyoxetane by vpc analysis, and (b) a second fraction, 2.33 g, which solidified on standing (12.67 g = 52.1%). Fraction a gave 5.68 g of oxetane upon cooling its hexane solution. The solids from fractions a and b were shown to be identical by nmr and vpc analysis. They were combined and recrystallized from hexane to give **2,2-diphenyl-3,3-diethoxyoxetane** as colorless plates: mp 68–70°; ir (KBr, cm^{-1}) 1206, 1180, 1120, 1050, 985 (all vs); nmr (CCl_4) τ 2.68 (m, 5), 5.45 (s, 1), 6.79 (m, 2), 9.15 (t, 3).

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43; mol wt, 298.33. Found: C, 76.48; H, 7.54; mol wt, 296.

Reduction of the crude reaction mixture by $LiAlH_4$ in refluxing ether gave a mixture consisting of unreacted 2,2-diphenyl-3,3-diethoxyoxetane (79%) and of **β,β-diphenyl-β-hydroxypropionaldehyde diethyl acetal** (21%) which were separated by preparative vpc. The acetal was identified by comparison with the authentic sample obtained from 4,4-diphenyl-2-ethoxyoxetane (see above) and by its analysis.

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.27; H, 8.74.

Registry No.—2,2-Dimethyl-3-ethoxyoxetane, 18267-24-8; 4,4-dimethyl-2-ethoxyoxetane, 18267-25-9; 2,2-dimethyl-3-*n*-butoxyoxetane, 18267-26-0; 4,4-dimethyl-2-*n*-butoxyoxetane, 18267-27-1; 2,2-dimethyl-3-isobutoxyoxetane, 18267-28-2; β-methyl-β-hydroxybutyraldehyde diisobutyl acetal, 18267-29-3; 2-ethyl-3-ethoxyoxetane (*cis*), 18267-45-3; 2-ethyl-3-ethoxyoxetane (*trans*), 18267-49-7; β-hydroxy-*n*-valeraldehyde diethyl acetal, 18267-30-6; 3-ethoxy-1-oxaspiro[3.5]-nonane, 18267-31-7; 2-ethoxy-1-oxaspiro[3.5]nonane, 18320-75-7; 2-phenyl-3-ethoxyoxetane (*cis*), 18267-46-4; 2-phenyl-3-ethoxyoxetane (*trans*), 18267-47-5; β-phenyl-β-hydroxypropionaldehyde diethyl acetal, 18267-32-8; 2,2-diphenyl-3-ethoxyoxetane, 18267-33-9; β,β-diphenyl-β-hydroxypropionaldehyde diethyl acetal, 18267-34-0; 2,2-dimethyl-3,3-diethoxyoxetane, 18267-35-1; ethyl 3-methyl-3-hydroxybutyrate, 18267-36-2; 3,3-diethoxy-1-oxaspiro[3.5]nonane, 18267-37-3; ethyl 1-hydroxycyclohexylacetate, 5326-50-1; 1-hydroxycyclohexyl acetaldehyde diethyl acetal, 18267-39-5; 1-oxaspiro[3.5]non-3-one, 18267-40-8; 2-ethyl-3,-3-diethoxyoxetane, 18267-41-9; 2-phenyl-3,3-diethoxyoxetane, 18267-42-0; 2,2-diphenyl-3,3-diethoxyoxetane, 18267-43-1; ketene diethyl acetal, 2678-54-8.

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The Synthesis of 3-Hydroxyaldehydes, 3-Hydroxy Acetals, and 3-Hydroxy Ethers from 2-Alkoxyoxetanes[1]

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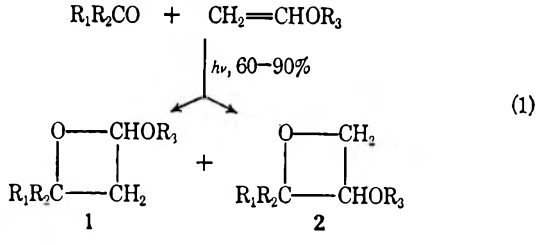
2-Alkoxyoxetanes have been found to react quantitatively under mild conditions with water to give 3-hydroxyaldehydes, with primary, secondary, or tertiary alcohols or phenols to give 3-hydroxy acetals, and with Grignard reagents and lithium aluminum hydride to yield 3-hydroxy ethers. These reactions may be carried out selectively in the presence of the isomeric 3-alkoxyoxetanes which are obtained together with 2-alkoxyoxetanes from the photochemical cycloaddition of carbonyl compounds to vinyl ethers. Hydrolysis of some 3-alkoxyoxetanes to substituted glycerine α-monoethers is also described.

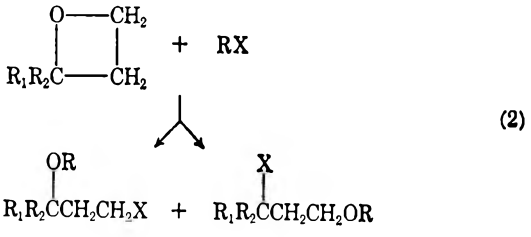
Previously, an efficient photochemical synthesis of 2- and 3-alkoxyoxetanes (**1** and **2**, respectively) from aliphatic and aromatic aldehydes and ketones and vinyl ethers was reported[2] (eq 1). In most cases, the ratio



(1)

of isomers present in the reaction mixtures could be determined by nuclear magnetic resonance or gas chromatographic analysis. These techniques failed, however, in a number of important cases. It was therefore desirable to develop chemical methods that would permit the determination of the isomer ratios.

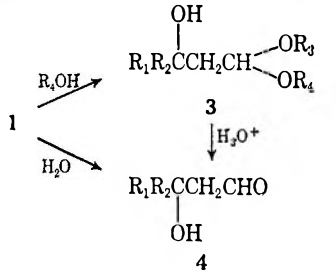
Oxetanes have been shown[3] to react with a large number of compounds such as water, acids, alcohols, etc., to give ring-opened products. Usually, both carbon–oxygen bonds are cleaved in these reactions with subsequent formation of isomeric 3-substituted hydroxy compounds (or derivatives thereof) in moderate to good yields (eq 2). Ring opening of oxetanes



(2)

generally occurs *via* a carbonium ion mechanism, the rate-determining step being the reaction of the conjugate acid of the oxetane to the final product.[4] Oxetanes with alkoxy groups β to the ring oxygen might therefore be expected to show the same reactivity as the alkyl- and aryl-substituted oxetanes studied earlier. On the other hand, 2-alkoxyoxetanes (four-membered cyclic acetals) would be expected to be much more reactive. A 2-alkoxy substituent will decrease the stability of the conjugate acid with regard to bond breaking since the developing carbonium ion will be stabilized by the alkoxy group. Hopefully, selective reactions of 2-alkoxyoxetanes in the presence of their 3-alkoxy isomers would thus permit an indirect determination of the isomer ratios in the photoproducts. At the same time, selective reactivity would make 2-alkyoxyoxetanes (though minor components in the photomixtures) useful materials for the synthesis of a variety of classes of compounds. Mixtures of the isomeric alkoxyoxetanes from the photoreactions (eq 1) could directly be used for transformation of the 2-alkoxy compounds without prior separation, and isolation of the reaction products from the unreacted 3-alkoxyoxetanes often would be quite simple. These expectations have indeed been found to be fulfilled by experimental evidence and selective transformations of 2-alkoxyoxetanes are described in this paper.

Alcohols and Phenols.—2-Alkoxyoxetanes react readily with primary, secondary or tertiary alcohols upon heating to give acetals of substituted β-hydroxypropionaldehydes (eq 3). Reaction with phenols



(3)

takes place without heating. By using an alcohol with an alkyl group R_4 different from that present in the alkoxy group OR_3 of the oxetane, mixed acetals can be prepared. Reaction of **1** ($R_1 = R_2 = CH_3$, $R_3 = C_2H_5$) with *n*-butyl alcohol or of **1** ($R_1 = R_2 = CH_3$, $R_3 = n$-C_4H_9) with ethanol gives the same mixed acetal. Mixed acetals are the only products, since exchange of alcohol groups does not occur without an acidic catalyst. 3-Alkoxyoxetanes are completely stable under these conditions. Mixtures of 2- and 3-alkoxyoxetanes from the photochemical reactions were therefore used directly in the alcoholysis. The boiling points of the

(1) S. H. Schroeter and C. M. Orlando, Jr., presented at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, Abstracts, ORGN 15.

(2) S. H. Schroeter and C. M. Orlando, Jr., *J. Org. Chem.*, **34**, 1181 (1969).

(3) For pertinent literature, see S. Searles, Jr., in "Heterocyclic Compounds," A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1964, p 983, and G. Dittus in Houben-Weyl's, "Methoden der organischen Chemie," Vol. VI, 4th ed Georg Thieme Verlag, Stuttgart, 1965, pp 508–515

(4) (a) F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Amer. Chem. Soc.*, **79**, 2362 (1957); (b) J. G. Pritchard and F. A. Long, *ibid.*, **80**, 4162 (1958).

TABLE I.—ACETALS $R_1R_2C(OH)CH_2CH(OR_3)(OR_4)$ FROM THE ALCOHOLYSIS OF 2-ALKOXYOXETANES 1[a]

No.	R_1	R_2	R_3	R_4	Bp, °C (mm)	$n^{20}D$	Yield after distn, %	Formula	Calcd Mol wt	Calcd % C	Calcd % H	Found Mol wt	Found % C	Found % H
1	CH_3	CH_3	C_2H_5	C_2H_5	72 (7)	1.4195[b]	96	$C_9H_{20}O_2$	176.25	61.33	11.44	180	61.35	11.65
2	CH_3	CH_3	n-C_4H_9	n-C_4H_9	61 (0.05)	1.4305	82	$C_{13}H_{28}O_2$	232.35	67.19	12.15	240	67.5	12.2
3	CH_3	CH_3	i-C_4H_9	i-C_4H_9	60 (0.05)	1.4774	97	$C_{13}H_{28}O_2$	232.35	67.19	12.15	230	67.27	11.93
4	H	C_2H_5	C_2H_5	C_2H_5	42 (0.05)	1.4242[c]	98	$C_9H_{20}O_2$	176.25	61.33	11.44	180	61.12	11.41
5	$(CH_2)_5$		C_2H_5	C_2H_5	56.5 (0.05)	1.4522	96	$C_{12}H_{24}O_2$	216.31	66.63	11.18	210	66.8	11.3
6	H	C_6H_5	C_2H_5	C_2H_5	86 (0.04)	1.4934	97	$C_{13}H_{20}O_2$	224.29	69.91	8.99	226	69.79	9.10
7	CH_3	CH_3	C_2H_5	n-C_4H_9	53 (0.2)	1.4257[d]	87	$C_{11}H_{24}O_2$	204.30	64.66	11.84	206	64.79	11.92
	CH_3	CH_3	C_2H_5	n-C_4H_9	51 (0.1)	1.4257[e]	71	$C_{11}H_{24}O_2$	204.30	64.66	11.84	196	64.42	11.62
8	CH_3	CH_3	C_2H_5	t-C_4H_9	41 (0.1)	1.4245	87	$C_{11}H_{24}O_2$	204.30	64.66	11.84	204	64.71	11.84
9	CH_3	CH_3	C_2H_5	C_6H_5	97 (0.3)	1.4546	75	$C_{13}H_{20}O_2$	224.29	69.61	8.99	228	69.85	9.17
10	C_6H_5	C_6H_5	C_2H_5	C_2H_5	135 (0.5)		90	$C_{19}H_{24}O_2$	300.38	75.97	8.05	299	76.27	7.84

[a] Purity of acetals was generally greater than 99%, as indicated by vpc and nmr analysis. All compounds had spectral data consistent with the structures given. [b] Prepared earlier [N. L. Wendler and H. L. Slates, *J. Amer. Chem. Soc.*, **72**, 5341 (1950)], but not characterized. [c] Lit. bp 88–90° (8–9 mm), $n^{15}D$ 1.4262 [L. A. Yanovskaya, V. F. Kucherov, and B. G. Kovalev, *Izv. Akad. Nauk SSSR, Ser. Kim.*, 674 (1962); *Chem. Abstr.*, **57**, 16379c (1962)]. [d] From 4,4-dimethyl-2-ethoxyoxetane. [e] From 4,4-dimethyl-2-*n*-butoxyoxetane.

acetals differ markedly from those of the alkoxyoxetanes so that a clean and almost quantitative separation is possible. Results are listed in Table I. Most of the compounds have hitherto been unknown, only a few have been prepared, generally by more difficult routes. 3-Hydroxy acetals can be converted either into the corresponding β-hydroxy[5,6] or α,β-unsaturated[6–8] carbonyl compounds by known methods. The reaction sequence expressed in eq 1 and 3 therefore represents a new synthesis of such aldehydes.

β-Hydroxycarbonyl compounds such as **4** formally represent aldol condensation products of carbonyl compounds R_1R_2CO with acetaldehyde. However, aldol condensation often does not lead to the desired products because of self-condensation of the more reactive carbonyl compounds.[9] Only recently has a modified aldol condensation been developed[6,10] which utilizes metalated Schiff bases of the aldehydes and ketones. It was found that this condensation does not take place with more substituted acetaldehydes. The Schiff base from cyclohexylamine and α,α-diethylacetaldehyde, for example, did not react with benzophenone. No such limitations have yet been found during preparation and alcoholysis of more highly substituted alkoxyoxetanes.[11]

Water.—β-Hydroxyaldehydes can directly be prepared from 2-alkoxyoxetanes by reaction with water (eq 3). Ring opening occurs exothermally upon mixing the reagents at room temperature. The known[7] 3-methyl-3-hydroxybutyraldehyde, **4** ($R_1 = R_2 = CH_3$), was thus obtained from 4,4-dimethyl-2-alkoxyoxetanes. It was isolated as its crystalline dimer which had spectral data consistent with the proposed[7] 1,3-dioxane structure **5**. Pure 3-alkoxyoxetanes do not react with

5

water, even at reflux temperature. It was found, however, that prolonged contact of mixtures of 2- and 3-alkoxyoxetanes with water eventually leads to ring opening of the 3 isomers as well, probably through the catalytic effect of traces of acid formed by autoxidation of the aldehydes. Ring opening of 3-alkoxyoxetanes occurs readily in the presence of dilute acids in the cold or upon treatment with dilute ammonium chloride solution at reflux temperature to give glycerine monoethers in 50–70% yield. Some of the ethers prepared are listed in Table II. The modest yields observed may be due to the fact that oxetanes also undergo acid-

(5) M. J. van Dam, *Rec. Trav. Chim. Pays-Bas*, **81**, 435 (1962).
(6) G. Wittig and H. Reiff, *Angew. Chem.*, **80**, 8 (1968).
(7) F. G. Fischer, *Chem. Ber.*, **76**, 734 (1943).
(8) See Table I, footnote *b*.
(9) Houben-Weyl, "Methoden der organischen Chemie," 4th ed, Georg Thieme Verlag, Stuttgart 1954, Vol. VII, 1, p 76.
(10) (a) G. Wittig, W. Stilz, and H. Pommer, French Patent 1,391,323, (March 5, 1965); *Chem. Abstr.*, **63**, P1739c (1965); (b) G. Wittig and H. D Frommeld, *Chem. Ber.* **97**, 3541 (1964); (c) G. Wittig and P. Suchanek, *Tetrahedron Suppl.*, **8**, 347 (1966).
(11) S. H. Schroeter, unpublished data.

TABLE II.—SUBSTITUTED GLYCERINE α-MONOETHERS [$R_1R_2C(OH)CH(OR_3)CH_2OH$] FROM THE HYDROLYSIS OF 3-ALKOXYOXETANES 2

No.	R_1	R_2	R_3	Mp or bp, °C (mm)	Yield, %	Formula	Calcd Mol wt	Calcd %C	Calcd %H	Found Mol wt	Found %C	Found %H
1	CH_3	CH_3	C_2H_5	54 (0.4)	70	$C_7H_{16}O_3$	148.20	56.73	10.88	157	56.88	10.91
2	CH_3	CH_3	*n*-C_4H_9	80 (0.6)	60	$C_9H_{20}O_3$	176.25	61.33	11.44	180	61.33	11.41
3	CH_3	CH_3	*i*-C_4H_9	60 (0.6)	55	$C_9H_{20}O_3$	176.25	61.33	11.44	179	61.15	11.60
4	C_6H_5	H	C_2H_5	135 (0.2)[a]	67	$C_{11}H_{16}O_3$	196.24	67.32	8.22	194	67.38	8.27
5				74–75		$C_8H_{16}O_3$	160.21	59.98	10.07	166	60.12	10.18

[a] Mixture of diastereoisomers; nmr showed two triplets in a ratio of 1:1 at τ 8.98 and 9.09. [b] Isolated by preparative vpc; all other compounds isolated by spinning-band distillation; purity generally greater than 98% *via* vpc.

TABLE III.—3-HYDROXY ETHERS [$R_1R_2C(OH)CH_2CHR_4OR_3$] FROM THE REACTION OF 2-ALKOXYOXETANES 1 WITH GRIGNARD REAGENTS R_4MgX 1–4 AND WITH $LiAlH_4$ 5–8

No.	3-Hydroxy ether R_1	R_2	R_3	R_4	Bp, °C (mm)	$n^{20}D$	Formula	Calcd Mol wt	Calcd %C	Calcd %H	Found Mol wt	Found %C	Found %H
1	CH_3	CH_3	*n*-C_4H_9	CH_3	75 (5)	1.4218	$C_{10}H_{22}O_2$	174.28	68.91	12.72	177	68.75	12.85
2	$(CH_2)_5$		C_2H_5	CH_3	76 (2.2)	1.4526	$C_{11}H_{22}O_2$	186.29	70.92	11.90	190	70.75	11.77
3	C_6H_5	H	C_2H_5	CH_3	80 (0.1)	1.5000	$C_{12}H_{18}O_2$	194.26	74.19	9.34	193	74.38	9.37
4	CH_3	CH_3	C_2H_5	C_6H_5	57 (0.05)	1.4900	$C_{13}H_{20}O_2$	208.92	74.96	9.68	213	75.15	9.74
5	CH_3	CH_3	C_2H_5	H	74.5 (19)	1.4172	$C_9H_{16}O_2$	132.20	63.59	12.20	139	63.44	12.40
6	CH_3	CH_3	*n*-C_4H_9	H	60 (2.8)	1.4243	$C_9H_{20}O_2$	160.25	67.45	12.58	165	67.32	12.33
7	$(CH_2)_5$		C_2H_5	H	52 (0.2)	1.4588	$C_{10}H_{20}O_2$	168.28	71.37	11.98	169	69.91	11.59
8	C_6H_5	H	C_2H_5	H	76 (0.2)	1.5072	$C_{11}H_{16}O_2$	180.24	73.30	8.95	178	73.23	9.07

catalyzed ring cleavage to carbonyl compounds and olefins.[12]

Grignard Reagents.—When a mixture of 2- and 3-alkoxyoxetanes is added to excess Grignard reagent, the 2-alkoxy isomer reacts exothermally to give, after hydrolysis, 3-hydroxy ethers **6** (eq 4). Vpc analysis

$$\mathbf{1} \xrightarrow[\text{in refluxing } Et_2O]{R_4MgX \text{ or } LiAlH_4} \underset{\underset{OH}{|}}{R_1R_2CCH_2CHROR_3} \quad (4)$$

6

shows that conversion of the 2-alkoxy isomers is quantitative after 15 min of refluxing in diethyl ether, while 3-alkoxyoxetanes remain unchanged even after prolonged refluxing. The yield of isolated hydroxy ethers depends solely on the skill with which the ethers are separated from the unreacted 3-alkoxyoxetanes. In the examples studied (Table III, entries 1–4), separation was essentially quantitative in cases where $R_3 > CH_3$ and about 60–80% where $R_3 = CH_3$. Alkyl- and aryl-substituted oxetanes have been found to undergo ring opening with Grignard reagents in moderate yields only upon prolonged treatment at higher temperatures, *e.g.*, in refluxing benzene.[13]

Lithium Aluminum Hydride.—2-Alkoxyoxetanes react selectively when a mixture of 2- and 3-alkoxyoxetanes is treated with excess lithium aluminum hydride in refluxing diethyl ether. Sodium and potassium borohydride proved to be ineffective. The 3-hydroxy ethers prepared are listed in Table III, entries 5–8. Reductive ring opening of the 2-alkoxyoxetanes by lithium aluminum hydride in diethyl ether usually required longer refluxing than did the opening with Grignard reagents. Complexing of the oxetane oxygen with the metal apparently plays an important role. Searles[13a] reported that oxetane itself forms a complex with magnesium bromide, from which 3-bromopropanol-1 is isolated upon hydrolysis. Alkyl- and aryl-substituted oxetanes have been found to react with lithium aluminum hydride only at higher temperatures.[14] With some oxetanes a detectable reaction did not take place even at 140°.[2] However, reduction of oxetanes can be carried out in refluxing diethyl ether with the stronger complexing reagent "mixed hydride."[15]

Experimental Section

Mixtures of 2- and 3-alkoxyoxetanes were prepared as previously reported.[2] Gas chromatographic analyses were performed on a 3-ft Apiezon column on a dual column, temperature-programmed F & M 5750 research chromatograph. Nmr spectra were recorded on a Varian A-60, and ir spectra on a Perkin-Elmer Model 337 spectrometer. Elemental analysis and molecular weight determinations were performed by Galbraith Microanalytical Laboratories. The following examples illustrate the preparation of the compounds listed in Tables I–III.

3-Methyl-3-hydroxybutyraldehyde Diethyl Acetal.—A 60-g sample of a mixture consisting of 24% 4,4-dimethyl-2-ethoxyoxetane and 76% 2,2-dimethyl-3-ethoxyoxetane was refluxed in

(12) G. Büchi, C. G. Inman, and E. S. Lipinsky, *J. Amer. Chem. Soc.*, **76**, 4327 (1954).

(13) (a) S. Searles, *ibid.*, **73**, 124 (1951); (b) T. Cuvigny and H. Normant, *C. R. Acad. Sci., Paris*, **254**, 316 (1962).

(14) S. Searles, K. A. Pollart, and E. F. Lutz, *J. Amer. Chem. Soc.*, **79**, 948 (1957).

(15) C. Schaal and J. Seyden-Penne, *C. R. Acad. Sci., Paris, C.*, **266**, (3), 217 (1968).

250 ml of absolute ethanol for 24 hr. Vpc analysis showed that all 2-alkoxyoxetane had been converted into a compound of higher retention time (31%) whereas the 3-alkoxy isomer had remained unchanged. The ethanol was removed through a spinning-band column at 100-mm pressure and the residue fractionated to give two major fractions—30.0 g (84%) of 2,2-dimethyl-3-ethoxyoxetane [bp 65° (60 mm); n^{20}D 1.4102] and 19.08 g (97.5% yield) of the acetal [bp 72° (7 mm); n^{20}D 1.4195; ir (CCl_4, cm^{-1}) 3530 vs, 1125 vs, 1057 vs; nmr (neat, τ) 5.25 (t, 1), *ca.* 6.45 (m, 5, OCH_2, OH), 8.22 (d, 2), 8.80 (s), and 8.82 (t, 12)]. See Table I, entry 1, for analysis. No acetal was obtained when the mixture of oxetanes was refluxed in ethanol containing small amounts of potassium *t*-butoxide.

Hydrolysis.—A 9.0-g sample of the acetal was treated with 40 ml of dilute hydrochloric acid (1:100). The mixture which became homogeneous shortly after mixing was allowed to stand at room temperature for 1 hr, neutralized with potassium carbonate and evaporated *in vacuo*. The residue was treated with ether to yield 3.41 g (69%) of 3-methyl-3-hydroxybutyraldehyde, identical with the compound the preparation of which is described below.

3-Methyl-3-hydroxybutyraldehyde Ethyl Phenyl Acetal.—A solution of 20 g of phenol and 65 g of a mixture consisting of 20% 4,4-dimethyl-2-ethoxyoxetane and 80% 2,2-dimethyl-3-ethoxyoxetane in 250 ml of ether was refluxed for 8 hr. Vpc analysis now showed a mixture consisting of 75% unreacted 3 isomer and 25% of a compound of higher retention time. The solution was extracted several times with 10% sodium hydroxide solution and brine and dried ($MgSO_4$). Distillation through a spinning-band column afforded 54.3 g of material, including 30.0 g of the 3-ethoxyoxetane and 17.16 g (75%) of the acetal: bp 97° (0.3 mm); n^{20}D 1.4546; ir (CCl_4) 3615 s, 3550 vs, 3040 m, 3030 m, 1595 vs, 1490 vs, 1375, 1215, 1190–1170, 1140, 1025, 1000, 965, 960 (all vs); nmr (CCl_4, τ) 2.9 (m, 5), 4.53 (t, 1, J = ~6 cps), 6.46 (q, 3, J = ~7 cps), 8.05 (d, 2, J = ~6 cps), 8.78 (s) and 8.89 (t, 9, J = ~7 cps). See Table I, entry 9, for analysis.

Hydrolysis of 4,4-Dimethyl-2-ethoxyoxetane.—A 60-g sample of a mixture containing 20% 4,4-dimethyl-2-ethoxyoxetane and 80% 2,2-dimethyl-3-ethoxyoxetane was shaken with 200 ml of water for 15 min. The mixture warmed considerably during this period. The organic phase was taken up with little ether. Vpc analysis indicated that most of the 2-ethoxyoxetane had reacted and was present in the aqueous layer. This was evaporated *in vacuo* to afford, after distillation, 4.0 g of 3-methyl-3-hydroxybutyraldehyde, bp *ca.* 50° (5 mm), which crystallized upon standing. The organic layer was distilled through a short Vigreux column to afford the unreacted 3-alkoxyoxetane and another 0.6 g of aldehyde (4.6 g, 55%) which also crystallized. When the mixture of alkoxyoxetanes and water was shaken for a longer period, or heated, the 3-alkoxy isomer also underwent ring opening and a mixture of 3-methyl-3-hydroxybutyraldehyde and 3-methyl-2-ethoxy-butane-1,3-diol was obtained. The dimer of 3-methyl-3-hydroxybutyraldehyde had mp 81° [from ether–petroleum ether (bp 30–60°)] (lit.[5] mp 91°); ir (CCl_4, cm^{-1}) no carbonyl, 3580 m and 3480 vs, br (OH), 1368, 1150, 1125, 1105 and 1003, all vs; nmr (CCl_4, τ) 4.90 (t, 2), 5.3 (s, OH, 2), 8.03–8.43 (m), 8.50 (s), 8.67 (s) and 8.72 (s), total of 16 H.

Hydrolysis of 2,2-Dimethyl-3-ethoxyoxetane. A.—A 10.0-g sample of the oxetane was shaken with 60 ml of dilute hydrochloric acid (1:100); the mixture warmed and became homogeneous. The solution was allowed to stand at room temperature for 4 hr, was made slightly alkaline with sodium carbonate and evaporated *in vacuo*. The residue was taken up in ether which was dried ($MgSO_4$) and evaporated, to afford, after distillation, 7.91 g (70%) of 3-methyl-2-ethoxy-butane-1,3-diol, which was shown to be 95% pure by vpc.

B.—A mixture of 10 g of the oxetane, 20 ml of water and four drops of acetic acid was shaken at room temperature but no reaction occurred. The mixture was then refluxed for 1.5 hr and the homogeneous solution was worked up as above to afford 4.0 g (35%) of pure diol (*via* vpc).

C.—A 15-g sample of oxetane, 60 ml of water and 3 g of ammonium chloride were refluxed for 12 hr. Evaporation of the aqueous layer and distillation gave 9.6 g (57%) of diol. The combined products from A, B and C were redistilled through a spinning-band column to afford a diol of 99% purity as indicated by vpc. See Table II, entry 1, for analysis. The other compounds listed in Table II were prepared either by method B or C.

2-Methyl-4-*n*-butoxy-2-butanol.—A solution of 10 g of 4,4-dimethyl-2-*n*-butoxyoxetane in 50 ml of ether was slowly added to excess methylmagnesium iodide (prepared from 17.7 g of methyl iodide and 3.0 g of magnesium in 120 ml of ether) at such a rate that the ether solution was kept at gentle reflux. It was then refluxed for an additional 30 min, cooled, and decomposed with ice water and dilute hydrochloric acid. The aqueous layer was twice extracted with ether and the combined ethereal layers were shaken with sodium bicarbonate solution and brine and dried ($MgSO_4$). Distillation afforded 9.07 g (83%) of 2-methyl-4-*n*-butoxy-2-butanol: bp 75° (5 mm); n^{20}D 1.4218; vpc analysis showed only one peak; ir (CCl_4, cm^{-1}) 1180, 1152, 1128, 1082 (all vs); nmr (CCl_4, τ) *ca.* 6.5 (m, 2), 8.3–9.3 (m, 9), with 8.82 (s) and 8.92 (d, J = 2 cps). See Table III, entry 1, for analysis. The isomeric 2,2-dimethyl-3-*n*-butoxyoxetane did not react under these conditions.

1-Ethoxy-1-phenyl-2-methyl-2-butanol.—A 60-g sample of a mixture consisting of 28% 4,4-dimethyl-2-ethoxyoxetane and 72% 2,2-dimethyl-3-ethoxyoxetane in 150 ml of ethyl ether was added to excess phenylmagnesium bromide (prepared from 5.0 g magnesium and 32.0 g bromobenzene in 220 ml of ether) and the resulting mixture was refluxed for 30 min, cooled and decomposed with ice and dilute hydrochloric acid. The ethereal layer was extracted with sodium bicarbonate solution and brine and dried ($MgSO_4$). Vpc analysis of the ethereal solution showed a mixture consisting of 65% of the unreacted 3-ethoxyoxetane and 35% of a compound of higher retention time. Distillation afforded 30.2 g of 2,2-dimethyl-3-ethoxyoxetane, bp 69° (66 mm), and 22.6 g (84%) of 1-ethoxy-1-phenyl-2-methyl-2-butanol: bp 57° (0.05 mm), n^{20}D 1.4900; ir (CCl_4, cm^{-1}) 3610 w, 3510 vs, 1600 w, 1495 s, 1115 vs, 1085 vs, 795 vs; nmr (CCl_4, τ) 2.75 (s, 5), 5.30, 5.35, 5.48, 5.53 (all s, 1, X part of ABX), 6.22 (s, 1, OH), 6.67 (q, 2, J = ~7 cps), 7.78, 7.97, 8.03, 8.19, 8.32, 8.37, 8.55, 8.61 (all s, 9, AB part) 8.70 (s), 8.82 (s), 8.87 (t, J = ~7 cps). See Table III, entry 4, for analysis.

2-Methyl-4-*n*-butoxy-2-butanol.—A solution of 10 g of 4,4-dimethyl-2-*n*-butoxyoxetane in 40 ml of dry ether was added to 2.0 g of lithium aluminum hydride in 100 ml of diethyl ether and the resulting mixture was gently refluxed for 5 hr. Excess hydride was destroyed by acetone, methanol, and water and the ethereal solution was dried ($MgSO_4$). Vacuum distillation afforded 8.0 g (80%) of 2-methyl-4-*n*-butoxy-2-butanol [bp 60° (2.8 mm), n^{20}D 1.4243], which was purified from traces of higher and lower boiling materials by spinning-band distillation: ir (CCl_4, cm^{-1}) 3520 vs, 1105 vs; nmr (CCl_4, τ) 6.42 (t, J = ~6 cps), 6.59 (t), 6.80 (s, OH) and 8.32 (t, J = ~6.5 cps), 8.50 (m), 8.83 (s), 9.07 (m) of relative areas 1:3. Under the same conditions 2,2-dimethyl-3-*n*-butoxyoxetane was not reduced. See Table III, entry 6, for analysis.

Registry No.—Table I—1, 19768-99-1; 2, 19769-00-7; 3, 18267-29-3; 4, 18267-30-6; 5, 18267-39-5; 6, 18267-32-8; 7, 19769-05-2; 8, 19769-06-3; 9, 19769-07-4; 10, 18267-34-0. Table II—1, 19769-09-6; 2, 19769-10-9; 3, 19769-11-0; 4, 19769-12-1; 5, 19769-13-2. Table III—1, 19769-14-3; 2, 19769-15-4; 3, 19769-16-5; 4, 19769-17-6; 5, 19769-18-7; 6, 19769-19-8; 7, 19769-20-1; 8, 18776-18-6.

Structural Factors Influencing Rotational Isomerism and Alkylation Properties in Some α-Haloacetanilides[1a]

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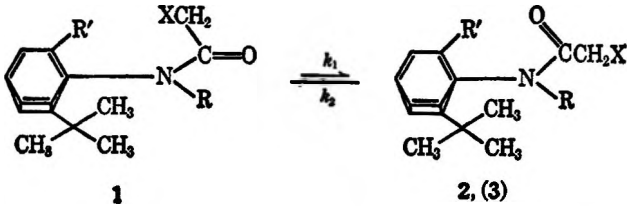
Widely divergent rotational and alkylation properties recently reported for *ortho*-substituted α-halo-N-methylacetanilides and their N-hydrogen homologs prompted further investigation of higher N-substituted 2-halo-6′-*t*-butyl-*o*-acetotoluidides. The relationship between alkylation and rotational isomerism has been verified; alkylation conditions are defined that coincide with conversion of the major isomer **1** to the reactive minor isomer **2**. From direct nmr measurements and the more precise and convenient alkylation technique developed, kinetic and thermodynamic values for isomer interconversion were determined for a series of homologous N-alkyl and other N-substituted anilides. Results and rationales for the measured equilibrium constants, rates, and thermodynamics found for the different series are discussed, and compared to current knowledge on the subject.

A recent study[1b] of α-halo-N-methyl-2′-*t*-butyl-6′-alkylacetanilides derived from 2-*t*-butyl-6-methyl- or -6-ethylaniline revealed that they exist in two separable rotomeric forms, **1** and **2**, with major isomer **1** having the halomethylene group *cis* and orthogonal to the anilide ring. In this spatial arrangement the halogen was shown to be unreactive toward usual nucleophilic displacement. Alkylation by anilide **1** proceeded by prior isomerization to **2**, the latter possessing a much more labile halogen. It was further found that the corresponding secondary anilides displayed quite different properties from the N-methyl compounds, the former apparently exhibiting no isomerism and having a spatial arrangement and alkylating ability akin to **2**.

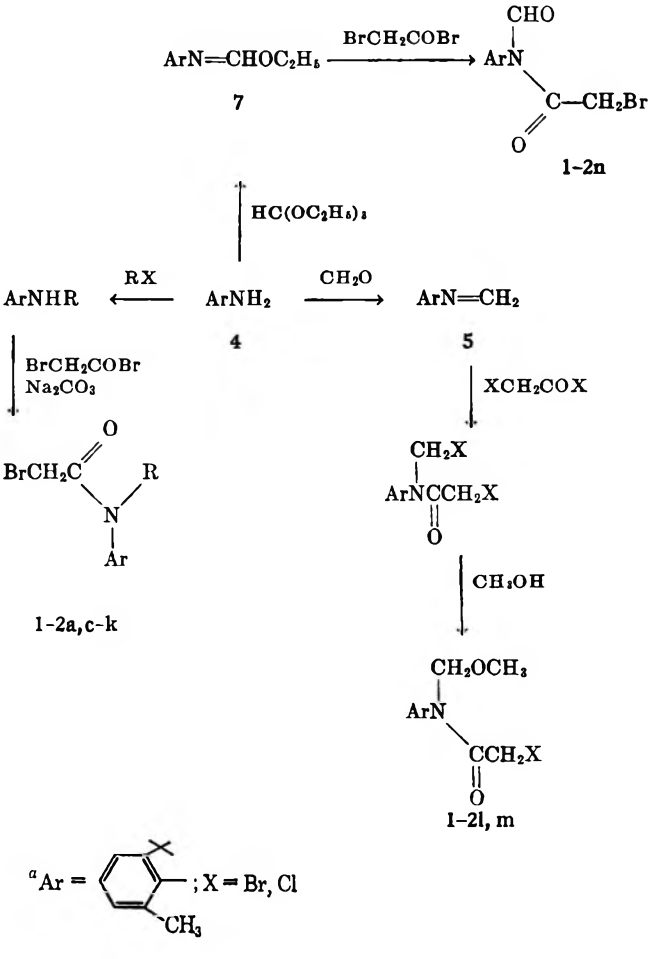
In view of the significant contrast found between N-methyl and N-hydrogen α-haloacetanilides, it became of interest to study the interconversion properties of other N-substituted α-haloacetanilides within the same *ortho*-substituted series so that structural factors influencing the kind and degree of rotational isomerism could be more fully delineated. This is all the more important when it is appreciated that rotational isomerism in these biologically active materials can greatly influence alkylation rates; indeed, under favorable circumstances, the latter can be made to coincide with isomer equilibration kinetics. As pointed out earlier[1b] from studies of N-methylanilides, a fair approximation of k_1 (defined in Table I) may be measured where first-order kinetics control alkylation in suitably hindered tertiary anilides. From k_1 and the equilibrium constant K, interconversion kinetics could thereby be obtained solely from **1** or even an equilibrium mixture containing predominately this isomer. It was therefore of added interest to confirm and utilize this rule in the study of higher N-substituted α-haloacetanilides.



1 **2, (3)** (A)

(1) (a) Presented at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, Abstract ORGN-144. (b) J. P. Chupp and J. F. Olin, *J. Org. Chem.*, **33**, 2297 (1967).

SCHEME I[a]



[a]Ar = ; X = Br, Cl

Results

Synthesis and Spectral Characteristics.—Synthesis of the requisite anilides (Scheme I and Table I) features 6-*t*-butyl-*o*-toluidine (**4**) as the starting amine. Materials **1-2a,b,d-k** were prepared by alkylating **4** with the corresponding alkyl halide, followed by reaction of the secondary amine with bromoacetyl bromide. Of interest is the synthesis of **1-2l,m** from azomethine **5**. The latter material is monomeric and appears to possess a stable shelf life; refractive index and spectra of the purified monomer remain unchanged over a prolonged period, thus surpassing the stability of the azomethine from *t*-butylamine, which slowly poly-

TABLE I
α-HALOACETANILIDES[a]

Material	R'	X	R	Mp, °C	Nmr (CCl4), ppm XCH2	Nmr (CCl4), ppm ArCH3	Formula	Calcd, % N	Calcd, % X	Found, % N	Found, % X
1a	CH_3	Br	CH_3	59–61	3.54	2.28	$C_{14}H_{20}BrNO$	4.70	26.80	4.79	27.07
2a	CH_3	Br	CH_3	90.5–91.5	3.85	2.13	$C_{14}H_{20}BrNO$	4.70	26.80	4.63	26.71
1b	CH_3	Br	$(CH_3)_2CH$	85–86	3.50	2.35	$C_{15}H_{24}BrNO$	4.29	24.49	4.22	24.74
1c	H	Br	$(CH_3)_3C$	97–98			$C_{15}H_{24}BrNO$	4.29	24.49	4.35	24.35
1d	CH_3	Br	C_2H_5	58–60	3.58	2.30	$C_{15}H_{22}BrNO$	4.49	25.59	4.56	26.13
1e	CH_3	Br	n-C_3H_7	70–71	3.54	2.29	$C_{15}H_{24}BrNO$	4.29	24.49	4.40	24.59
1f	CH_3	Br	n-C_4H_9	76–78.5	3.52	2.28	$C_{17}H_{28}BrNO$	4.12	23.48	4.12	23.18
1g	CH_3	Br	CH_2=$CHCH_2$	92–93	3.52	2.23	$C_{15}H_{22}BrNO$	4.32	24.65	4.42	25.14
1h	CH_3	Br	$HC{\equiv}CCH_2$	75–78	3.52	2.30	$C_{15}H_{20}BrNO$	4.35	24.80	4.24	24.05
1i	CH_3	Br	$NCCH_2$	116–118	3.61	2.36	$C_{15}H_{19}BrN_2O$	8.67	24.72	8.43	25.06
1j	CH_3	Br	$CH_3O(CH_2)_2$	74–75	3.51	2.28	$C_{17}H_{26}BrNO_2$	3.93	22.43	3.98	22.43
1k	CH_3	Br	$CH_3O(CH_2)_3$	69–70	3.58	2.29	$C_{18}H_{24}BrNO_2$	4.09	23.35	4.23	23.48
1l	CH_3	Br	CH_3OCH_2	51.5–52	3.58	2.32	$C_{15}H_{22}BrNO_2$	4.27	24.35	4.32	24.02
2l	CH_3	Br	CH_3OCH_2		4.04	2.19					
1m	CH_3	Cl	CH_3OCH_2		3.64	2.28					
2m	CH_3	Cl	CH_3OCH_2	78–79	4.18	2.16	$C_{15}H_{22}ClNO_2$	4.94	12.49	5.00	12.43
3	CH_3	Br	H	120.5–121.5	4.07[b]	2.21[b]	$C_9H_{18}BrNO$	4.93	28.12	4.82	28.04
1–2n	CH_3	Br	CHO	116–117	3.90[b]	2.12[b]	$C_{14}H_{18}BrNO_2$	4.49	25.60	4.26	25.69

[a] See eq A in text for position of R, R', and X. [b] Nmr measured in $CDCl_3$.

merized on standing.[2] **1–2n** was prepared by reaction of imidate **7** with bromoacetyl bromide. Unhindered N-formylated acetanilides made in this fashion are notoriously unstable, giving secondary anilides upon thermal treatment.[3] **1–2n** will convert into **3** only upon prolonged heating.

With some exceptions it is not immediately obvious that the tertiary anilides listed in Table I are capable of existing in both rotational forms **1** and **2.** When purified by simple recrystallization, the materials give pure isomer **1.** Thus the nmr spectra for materials **1b–l** display the XCH_2 group as a singlet at *ca.* 3.5 ppm, upfield from the usual position for this group in **2** or **3.** Similarly the aryl methyl in **1** shows the characteristic singlet at *ca.* 2.23–2.36 ppm, while spectra of authentic samples of **3, 2a,** and **2m** in chlorinated or aqueous acetone solvents display this group at slightly higher field. Further structure proof for isomer **1** rests on the observed alkylation properties discussed below.

With the exception of **1–2a,k,l,m,** casual examination of the nmr spectra from aged solutions of **1** fails to reveal immediately the presence of **2.** This is due to the complex spectra displayed by anilides containing an N substituent higher than methyl. Thus **1d–m** possess an $N\text{-}CH_2$ group with the methylene hydrogens nonequivalent to each other, displaying an AB-type resonance. This arises from assymmetry in these anilides caused by restricted rotation about the Ar–N bond, and is identical with well-known methylene proton nonequivalence first observed in assymmetric ethers,[4] and later in anilides.[5,6] Moreover, most of the methylene protons are further spin coupled with protons on neighboring carbon atoms, making the absorption complex in the 3–5-ppm region. Thus, if the equilibrium amount of **2** is small, the N substituent and halomethylene group of this isomer can be quite obscured. A further complication is the capability of the XCH_2 from **2** to exist also in certain solvents as an AB pair.

To determine whether in fact **2** existed in equilibrium with **1,** it was necessary to examine the resonance of the aryl methyl and aryl *t*-butyl. The latter proved to be more insensitive, usually displaying a single singlet even for equilibrium amounts of **1–2a** in chlorinated solvents. More reliable is the aryl methyl resonance at 2–3 ppm. By examination with 100-cps scans, the emergence with time of a singlet for the aryl methyl group from **2** was readily apparent.

Of interest is **1–2n.** Temperature studies reveal $BrCH_2$ and CHO to have single, broadened resonances at room temperature, becoming sharp and narrow at higher temperature (60°). At −40° two distinct nonequivalent resonances emerge for both groups at *ca.* 3.8, 4.2 and 9.7, 9.5 ppm, respectively. It is apparent then that **1–2n** represents a rapidly interconverting system at room temperature.

Some attempts were made actually to isolate pure **2,** to further characterize this isomer. However, only **2a** and **2m** were isolated in pure crystalline form. Although it is tempting to blame unfavorable stabilities

(2) Brochure on *t*-Alkyl Primary Amines (Rohm and Haas), CP-558/61, p 35.
(3) H. L. Wheeler and P. T. Walden, *Amer. Chem. J.*, **19**, 129 (1897).
(4) F. Kaplan and J. D. Roberts, *J. Amer. Chem. Soc.*, **83**, 4666 (1961).
(5) B. J. Price, J. A. Eggleston, and I. O. Sutherland, *J. Chem. Soc., B* 922 (1967).
(6) T. H. Siddall, III, *J. Org. Chem.*, **28**, 1296 (1963).

TABLE II

EQUILIBRIUM AND EQUILIBRATION RATE CONSTANTS AS DETERMINED BY NMR IN AQUEOUS ACETONE

Material	K	$k_1 \times 10^7$, sec^{-1}	$k_2 \times 10^7$, sec^{-1}	Correlation coeff r[a]
2a	0.16	4.5	28	0.9978
1d	0.12	18	150	0.9490
1e	0.12	19	160	0.9861
1f	0.12	49	400	0.9853
1g	0.10	60	590	0.9326
1h	0.09	82	890	0.9770
1j	0.10	46	480	0.9950
1k	0.21	190	910	0.9957
1l	0.35	680	1900	0.9912
2m	0.31	750	2400	0.9980

[a] As determined from average seven points; see Experimental Section.

and/or equilibrium constants for failure, it is possible that success in separating isomers is largely determined by a fortuitous combination of favorable melting point and solubility. Thus equilibrium constant and isomer stability are approximately the same for **1-2l,m**; yet it was not possible to isolate **2l** in the purification of **1l**, although attempts were made to do so. On the other hand, the oily equilibrium mixture of **1-2m** deposits an enriched mixture of **2m** from which by simple recrystallization this isomer is obtained pure, while **1m** (never obtained pure) probably is an oil or low-melting solid. Hence large amounts of the otherwise minor isomer **2m** can easily be obtained by utilizing the shift in equilibrium as this isomer crystallizes from an oily mixture originally rich in **1m.**

Rate Determinations.—In order to validate the alkylation method as feasible for measuring equilibration kinetics, it was first necessary to obtain direct nmr rate data, however approximate, for comparison. Equilibration kinetics were followed by measuring the increasing intensity ratio (**2**:**1**) of the aryl methyl resonance as a function of time. Equilibrium constant K was then the value of this ratio after at least ten half-lives. From these data k_1 and k_2 could be calculated as before.[1b] It is apparent from linear correlation constants, r given in Table II, that straight-line plots necessary to determine kinetics are less reliable as the amount of **2** in equilibrium with **1** decreases. As noted earlier,[1b] the best determinations by nmr are from measurements initiated with **2.**

In order to take advantage of alkylation rates as an aid in determining equilibration characteristics it is necessary that the system follow fairly "pure" kinetics. Without recourse to steady-state approximations and other manipulations, eq 1, 2, and 3 serve to illustrate the relationships between the observed pseudo-first-order rate constant, $k_{\psi obsd}$, obtained by measuring bromide ion formation, and the previously defined equilibration rate constants, k_1 and k_2.

nucleophile dependent alkylation for **2** (or **3**)

$$\text{alkylation rate} = k_{\psi obsd}([2^0] - [Br^-]) \cong k_{\psi obsd}[2] = k_\psi[2] \quad (1)$$

([2^0] = initial concentration of **2**; k_ψ[7a] $\gg k_1$ and k_2)

nucleophile independent alkylation for **1**

$$\text{alkylation rate} = k_{\psi obsd}([1^0] - [Br^-]) \cong k_{\psi obsd}[1] \cong k_1[1] \quad (2)$$

([1^0] = initial concentration of **1**; $k_\psi \gg k_1$ and k_2)

nucleophile dependent alkylation for **1**[8]

$$\text{alkylation rate} = k_{\psi obsd}([1^0] - [Br^-]) \cong k_\psi[2eq] < k_1[1] \quad (3a)$$

$$K = [2eq]/[1eq]$$

$$k_\psi[2eq] = k_{\psi obsd}([1eq] + [2eq]) \quad (3b)$$

$$K = k_{\psi obsd}/(k_\psi - k_{\psi obsd})$$

([**1**eq] and [**2**eq] are equilibrium concentration)

Equation 1 represents alkylation kinetics initiated with reactive isomer **2.** For the pseudo-first-order rate constant k_ψ[7a] to be equivalent to $k_{\psi obsd}$ it is necessary that **2** react more quickly with piperidine than its transformation to **1**, (*i.e.*, $k_\psi \gg k_1$ or k_2). That **2** (or **3**) does in fact react very fast with excess piperidine *via* a classical SN2 process has been verified previously[1b] and is also shown in several examples contained in Table III (**3**, **2a**, **2l**, **1-2n**). The fast interconversion between **1n** and **2n** observed at room temperature by nmr serves to explain the fast second-order kinetics although undoubtedly additional electronic factors[7b] operate to make this anilide the most potent alkylator listed in Table III.

For the alkylation rate initiated with **1** to be truly nucleophile independent and equal to its equilibration rate as given in eq 2 ($k_{\psi obsd} = k_1$), it is necessary for **2** to react with piperidine nearly as fast as it is formed (in the slow step) from **1.** Then the rate of bromide ion formation will be equivalent to disappearance of **1.** If **2** does not react in this fashion, either because k_ψ or [**2**] is too small, the alkylation of piperidine starts to

TABLE III

OBSERVED PSEUDO-FIRST-ORDER RATE CONSTANTS FROM ALKYLATION IN THE PRESENCE OF EXCESS PIPERIDINE

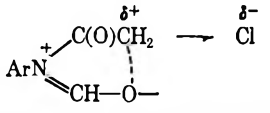
Material	$k^1\psi_{obsd} \times 10^7$ sec^{-1} (amine/amide 50:1)	$k^2\psi_{obsd} \times 10^7$ sec^{-1} (amine/amide 20:1)	Approx % SN2[a]
1a	7.6	6.4	10
1b	13	5.0	100
1c	18	6.5	80
1d	29	26	10
1e	29	26	10
1f	31	28	10
1g	50	43	10
1h	73	64	10
1i	130	63	70
1j	28	25	10
1k	140	120	10
1l	470	420	10
3	16,500	6,300	100
2l	18,400	9,200	70
2a	32,200	12,100	100
1-2n	36,000	14,000	100

[a] See Experimental Section for calculation.

(7) (a) The constant k_ψ is defined as follows.

$$\mathbf{2} + \text{excess piperidine} \xrightarrow{k_\psi} \text{alkylation product}$$

(b) Anchimeric assistance by the formyl oxygen in promoting lability of the halogen is a possibility.



(8) The other possibility, that isomer in configuration **1** reacts directly *via* SN2 kinetics with piperidine to give alkylation product, is minimized by the fact that **1a**, the least hindered and most stable tertiary anilide under study, gives little or no evidence of such reaction. The other bulkier and shorter lived tertiary anilides in this configuration would be expected to be even less susceptible to this form of alkylation.

TABLE IV
ACTIVATION PARAMETERS FOR CONVERSION 1 → 2 FROM TEMPERATURE-DEPENDENT STUDY OF $k^2\psi_{obsd}$

Material	E_a, kcal	Log A, sec^{-1}	$\Delta S^\ddagger$ (25°), eu	Correlation coeff r^a
1a	25.1	12.2	−4.5	0.9996
1d	23.7	11.8	−6.5	0.9998
1e	23.1	11.3	−8.5	0.9995
1f	23.1	11.4	−8.5	0.9990
1g	21.9	10.7	−11.5	0.9984
1k	21.4	10.8	−11.0	0.9991
1l	21.5	11.4	−8.5	0.9988

[a] As determined from four points on plots of log $k^2\psi_{obsd}$ *vs.* $1/T$ between 25 and 40° (±0.02°).

become the slow rate-determining step, and the reaction becomes nucleophile dependent.

It is for this reason that k_ψ has been kept as large as possible by choosing for alkylation studies high concentrations of reactive piperidine with the α-bromo- rather than α-chloroacetanilides. Nevertheless if the equilibrium concentration of **2** as derived from **1** is small enough, the low effective concentration of **2** will slow its reaction with piperidine sufficiently to allow the equilibration to exceed the alkylation rate. Equation 3 is useful to explain apparent anomalies (**1b,c,i**) in Table III. With fast equilibration, compared with alkylation, the observed rates approach dependence on the equilibrium concentrations, [1eq] and [2eq]. Equation 3 gives the relationship between $k_{\psi obsd}$, k_ψ, and K. Thus if $k^1\psi$ for **2b** is assumed to have an appreciable value, approaching that for **2a** (*i.e.*, *ca.* 10^{-3} sec^{-1}) and inserting the value for $k^1\psi_{obsd}$ from **1b** of 1.3×10^{-6} sec^{-1}, K is calculated at 1.3×10^{-3}. This small value of K gives an equilibrium concentration of only *ca.* 0.1% **2b**, and explains the failure to observe this isomer by nmr. Similarly, **1c** and **1i** give "mixed" kinetics between eq 1 and eq 3 because of a low equilibrium constant. Spectrally, an aged solution of **1c** shows no **2c**, while **1i** gives only 2% **2i**.

Since **2l** could not be isolated in pure form, the alkylation kinetics for it are derived from data plotted in Figure 1; the plot further serves to confirm the

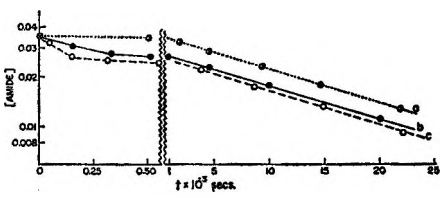


Figure 1.—Log [amide] *vs.* *t*, with initial concentration of amide at 0.0358 *M*. Dotted lines (a) represent plot from piperidine/**1l** of 50:1 without prior equilibration. Solid lines (b) and dashed lines (c) represent, respectively, initial piperidine/**1–2l** at 20:1 and 50:1, both with prior equilibration. The two time scales used as the abcissa are designed to show the early differences and later equality in slopes between a, b, and c. Estimated $k_{\psi obsd}$ in Table III for **2l** are from the slopes of b and c given by the first three points.

dependence of alkylation on rotational isomerism. Thus alkylation by **1l** without prior equilibration gives the usual slow amine independent reaction reflecting the rate-determining conversion of **1l** to isomer **2l**. Prior equilibration to give an approximately 25–30% equilibrion concentration of reactive isomer **2l** causes the subsequent alkylation reaction to be initially fast and piperidine dependent, followed by slow amine independent kinetics equal to that shown by pure **1l**. The small divergence of the kinetics from SN2 for **2l** is due not only to error in obtaining true values of $k^1\psi_{obsd}$ and $k^2\psi_{obsd}$ from the slopes of the lines b and c in Figure 1, but also comes from the significant contribution of k_2 [**2l**] in this rather rapidly equilibrating system, such that eq 1 does not strictly apply.

The relationship between equilibration and alkylation discussed earlier is confirmed. Thus k_1, extending in value over two orders of magnitude, when approximately measured from direct equilibration experiments by nmr (Table II) is in substantial agreement with values of $k_{\psi obsd}$ calculated from alkylations *governed primarily by first-order kinetics* (Table III).[9] Advantage was taken of this more convenient and precise alkylation method for measuring equilibration to calculate the thermodynamics for conversion of **1** → **2** by temperature-dependent studies of $k^2\psi_{obsd}$ (Table IV).

Discussion

Previous studies[10] regarding tertiary amides indicate that the more abundant rotational isomer be sterically favored, minimizing nonbonded interactions by having the larger groups attached *trans* to each other. If the same steric explanation applied to the tertiary anilides in Table I, then apparently the halomethylene and N-alkyl substituent, structured *trans* in the predominate isomer **1**, are the two larger groups. The trigonal nature of the aromatic carbon, coupled with orthogonal positioning to the amide moiety of the otherwise bulky aryl group, presumably minimizes this group's steric requirements in the ground state. The steric explanation is at least consistent with the observation that secondary acetanilides also have the two smallest groups *trans* (O and H)[1,11] while, with higher N-alkyl substitution than N-methyl, the amount of the more abundant isomer increases, becoming nearly 100% with N-isopropyl and *t*-butyl. It is obvious however that the steric explanation is only partially successful in predicting isomer distribution. The amount of **2** found in rotomeric systems possessing N-methoxyalkyl substituents increases with increasing proximity of the ether to the carbonyl oxygen (compare K in **1–2j,k,l**). This indicates perhaps an unfavorable dipole–dipole interaction operable between the *cis*-oriented oxygen atoms. On the other hand the electronic rationale for the small amount of **2i** observed in not clearly understood.

Rotational isomerism as observed in amides has traditionally been explained as arising from the interaction of the unshared pair of electrons on nitrogen with the carbonyl oxygen, giving rise to a rigid polar resonance form, $-OC{=}N^+-$—consequently the greater the resonance interaction, the more the energy barrier to isomerization. The resonance contribution is also important in anilides studied here, even though bulky

(9) The discrepancies noted between k_1 and $k_{\psi obsd}$ are not only due to experimental error, but to the necessarily somewhat different concentrations and solvent systems employed in the two different types of measurement.

(10) L. A. LaPlanche and M. J. Rogers, *J. Amer. Chem. Soc.*, **85**, 3728 (1963).

(11) H. Kessler and A. Rieker, *Z. Naturforsch*, **22b**, 446 (1967).

ortho substituents reinforce the energy barrier to rotation. Thus electron-withdrawing groups attached to nitrogen cause an increase in interconversion rate. The formyl group as expected is quite effective in this regard, while the methoxy group exerts its inductance most effectively in anilide **1-2l,** with a fall-off with increasing chain length (**1-2j,k**). Similarly, mild deactivators such as allyl and propargyl increase the interconversion rate moderately. Measurement of the destabilizing effect of an electron-withdrawing N substituent has been observed before, although not necessarily with such consistancy, especially with moieties several carbons distant. Thus lowered energy barriers were observed for some N-vinylformamides, but not for similarly substituted N-(2-chloroethyl)formamides.[12]

It becomes incumbent to reconcile the mild interconversion rate enhancement with ascending N-*n*-alkyl substitution (steric acceleration of rotational rates). In most systems the inductive electron-donating ability of ethyl and *n*-propyl groups is higher than methyl;[13] indeed studies of ^{14}N chemical shifts in simple ureas and amides have recently shown increasing electron delocalization of the nitrogen lone pair (*via* the stabilizing dipolar form) with increasing size of the N-alkyl substituent.[14] It might be expected then that ascending N-*n*-alkyl substitution would cause *decreases* in interconversion rates. The apparent anomaly observed here may be overcome by assuming an increasingly unfavorable steric interaction between the carbonyl oxygen and higher N-alkyl groups in the planar polar form, $^{-}OC{=}N^{+}$, accompanied perhaps by less solvation in the more bulky amides. These effects would tend to increase the relative energy in the ground state thus leading to lower energies of activation.

High collision frequencies (A) and small positive activation entropies are usually observed from accurately determined energy barriers in unhindered amides.[15] This is due to the change from a rigid, stabilizing dipolar amide form (solvated) in the ground state, to a less rigid, less polar form in the activated complex. However, it is not inconsistent to expect, as observed here, small negative activation entropies for conversion $1 \rightarrow 2$, increasing somewhat with higher N substitution. An appreciable portion of the energy barrier to rotation in the amides studied here is due to steric hindrance, and thus strains, with resultant loss of rotational freedom encountered in the transition state, are not surprising. Similar observations have been made in rotational studies of other sterically hindered systems including anilines.[16]

Experimental Section

N-2-Di-*t*-butylaniline.—To 8 mol of *o*-*t*-butylaniline was added 950 g (17 mol) of isobutene with 240 g of acid-treated clay. The mixture was heated in a 3-l. rocking autoclave for 212 hr at 100–120°. After filtration of the autoclave contents the material was distilled, and that collected at 117–137° (13 mm) was refractionated through a 4 ft × 16 mm packed column to give the pure aniline: bp 129–130° (14 mm); $n^{25}D$ 1.5145.

Anal. Calcd for $C_{14}H_{23}N$: C, 81.89; H, 11.29; N, 6.82. Found: C, 81.78; H, 11.29; N, 6.92.

6-*t*-Butyl-*o*-tolylglycinonitrile.—The procedure is similar to that used by Elliott.[17] To 200 ml of 50% (v/v) alcohol was added 163 g (1 mol) of 6-*t*-butyl-*o*-toluidine[1] (**4**) and the resulting mixture heated to reflux with stirring. Glycolonitrile (1 mol, 81 g of 70% solution in water) was added over 45 min with the mixture stirred at 90° for an additional 18 hr. Upon solvent removal under vacuum, the viscous oily residue was recrystallized from cold toluene to give, after a further wash with water and heptane, crystals, mp 84–86°.

Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97. Found: C, 77.17; H, 8.98.

6-*t*-Butyl-N-(3-methoxypropyl)-*o*-toluidine.—A mixture of 188 g of 3-chloropropyl methyl ether (3.2 mol), 522 g of **4** (3.2 mol), and 265 g of potassium iodide (1.6 mol) in 1 l. of methanol was heated with stirring in an autoclave at 110° for 16 hr. After cooling, the suspended salt was filtered, and the filtrate heated with 1 l. of 10% caustic. After drying, the organic portion was fractionated, bp 152–158° (8 mm), to give 153.5 g of product, $n^{25}D$ 1.5130.

Anal. Calcd for $C_{15}H_{25}NO$: N, 5.95. Found: N, 6.38.

6-*t*-Butyl-N-ethyl-*o*-toluidine.—To **4** (163 g, 1 mol) was added 200 g of acetonitrile and 175 g (1.12 mol) of ethyl iodide and the resulting mixture refluxed for 48 hr. The reaction mass was cooled, 100 ml of water added, and the excess ethyl iodide and solvent were removed under vacuum. After the residue was treated with 20% NaOH, the oily layer was separated, washed with water, then 170 g collected by fractional distillation, bp 110–119° (9.5 mm). This material was redistilled to give 143 g of product: bp 115–117° (9.5 mm); $n^{25}D$ 1.5186.

Anal. Calcd for $C_{13}H_{21}N$: N, 7.32. Found: N, 7.32.

6-*t*-Butyl-N-methylene-*o*-toluidine (5).—A mixture of 1 kg of **4** (6.12 mol), 240 g of paraformaldehyde, 10 g of 25% trimethylamine in methanol, and 500 ml of *n*-heptane was heated to reflux at 95°. By separation of the azeotrope, water was collected, and then the solvent removed by distillation to a pot temperature of 140°. After cooling, the reaction mass was filtered and the filtrate fractionated through a 16-in. packed column. Azomethine (1047 g, 97.5% yield) was collected: bp 114–116° (14 mm); $n^{25}D$ 1.5284. The refractive index remained unchanged on storage under nitrogen for over 6 months.

Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.79; N, 7.99. Found: C, 81.86; H, 9.85; N, 7.77.

6-*t*-Butyl-N-methyl-*o*-toluidine has been reported previously, prepared by methylation of **4**.[1b] An alternative procedure which gives a nearly quantitative yield of pure product involves the lithium aluminum hydride reduction of **5**. A 1-l. ethereal solution containing 430 g of **5** (2.46 mol) was added dropwise to 72 g of $LiAlH_4$ slurried in ether. The temperature was kept at reflux by suitable adjustment of the addition rate. Wet ether was then introduced, and the hydrolyzed reaction mixture filtered. After drying the ethereal solution over magnesium sulfate, solvent was removed to give 415.2 g of essentially pure 6-*t*-butyl-N-methyl-*o*-toluidine.

Ethyl N-(6-*t*-Butyl-*o*-tolyl)formimidate (7).—Ethyl orthoformate (233 g, 1.57 mol) and 245 g of **4** (1.5 mol) were heated together in a flask provided with a short vigreux column and distillation head. At a pot temperature of 130°, alcohol began to distil slowly. The reaction mixture was heated over 20 hr at 145–180°, with heating terminated after a further 0.5 hr at 198°. A total of 124 g of ethanol was removed. The residue was distilled to give 287 g, bp 125–125.5 (6.5 mm), $n^{25}D$ 1.5116. On standing, **7** solidified, mp 34–35°.

Anal. Calcd for $C_{14}H_{21}NO$: N, 6.39. Found: N, 6.32.

Preparation of N-Isopropyl, -propyl, -butyl, -allyl, -propargyl-6-*t*-butyl-*o*-toluidines.—These materials were made, respectively, from reaction of an equimolar or excess amount of alkyl bromide or iodide with **4**. The reactions were all carried out at reflux in acetonitrile at ordinary pressure for 24–48 hr. The cooled mixture was then vacuum treated to remove solvent and the residue treated with 10% NaOH, then extracted with ether. After drying over magnesium sulfate and ether evaporation, the

(12) D. G. Gehring, W. A. Mosher, and G. S. Reddy, *J. Org. Chem.*, **31**, 3436 (1966).

(13) J. F. Bunnett in "Rates and Mechanism of Reactions," S. L. Friess, E. S. Louis, and A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1956.

(14) P. Hampson and A. Mathias, *J. Chem. Soc., B*, 673 (1968).

(15) (a) R. C. Neuman and V. Jonas, *J. Amer. Chem. Soc.*, **90**, 1970 (1968), and previous papers. (b) A. Pines and M. Rabinovitz, *Tetrahedron Lett.*, 3529 (1968).

(16) B. J. Price, J. A. Eggleston, and I. O. Sutherland, *J. Chem. Soc., B*, 922 (1967).

(17) I. W. Elliott, Jr., *J. Amer. Chem. Soc.*, **77**, 4408 (1955).

residues were distilled through a 4 ft × 16 mm packed glass helice column. A cut, rich in the desired secondary aniline, was taken between 50 and 80° (*ca.* 0.3 mm). Assay of the desired aniline by glpc and nmr revealed contamination by **4** and the N,N-disubstituted 6-*t*-butyl-*o*-toluidine. Rather than attempt further purification of the secondary aniline, the distillate was converted directly into the α-haloacetanilide.

Preparation of α-Haloacetanilides (1a–k, 3).—These materials were prepared in essentially the same manner using Schotten–Bauman conditions. The preparation of **1j** is typical. 6-*t*-Butyl-N-(3-methoxypropyl)-*o*-toluidine (50 g, 0.212 mol), 20 g of sodium carbonate, 250 ml of water and 200 ml of benzene were mixed together. With agitation and external cooling a 10–20% molar excess of bromoacetyl bromide was added dropwise at 5–10°. After addition the external ice bath was removed and the stirred mixture allowed to reach room temperature. The organic phase was separated, washed with water and dried over magnesium sulfate. After solvent removal the material was purified by recrystallization from heptane to give 50 g of **1j**. Other solvents found acceptable for anilide purification were aqueous methanol, methylcyclohexane, and hexane. Although no attempt was made to optimize conditions, yields of recrystallized product were usually 50–80%. Physical constants and analyses are provided in Table I.

2-Bromo-6′-*t*-butyl-N-methoxymethyl-*o*-acetotoluidide (1–2l).—Azomethine **5** (130 g, 0.74 mol) was dissolved in 300 ml of toluene. With agitation 160 g (0.79 mol) of bromoacetyl bromide was added over 45 min with stirring, the temperature of the reaction mixture reaching 85°. The resulting turbid solution was transferred to a separatory funnel and added over 1 hr to 240 g (1 mol) of 25% trimethylamine in methanol, maintaining the temperature between 10 and 15° with external cooling. After addition the reaction mixture was stirred an additional 0.5 hr, then washed twice with water. After filtration and evaporation of toluene the product (155 g) was induced to crystallize. A final purification was performed by recrystallization from heptane to give pure **11**.

6′-*t*-Butyl-2-chloro-N-methoxymethyl-*o*-acetotoluidide (1–2m).—To chloroacetyl chloride (113 g, 1 mol) mixed with 250 ml of heptane was added 175 g (1 mol) of **5** over 20 min. During addition the temperature of the mixture reached 80°. The turbid solution was refluxed for 10 min whereupon it became clear. The mixture was cooled to 5° and a total of 221 g of solid was collected, most of it melting between 86 and 89°. A portion (20 g, 0.07 mol) of the crude 6′-*t*-butyl-2-chloro-N-chloromethyl-*o*-acetotoluidide was mixed with 100 ml of a 25% solution of trimethylamine in methanol. The methanol and excess trimethylamine were then evaporated, water added to the residue and the resulting oily layer extracted with hexane. When cooled the hexane solution deposited solid containing both **1** and **2m**. A further recrystallization from cold hexane gave pure **2m**. The oil (upon melting **2m**, *ca.* 70% **1m** formed), only slowly, over a period of days, deposited crystals rich in **2m**.

2-Bromo-6′-*t*-butyl-N-formyl-*o*-acetotoluidide (1–2n).—Bromoacetyl bromide (110 g, 0.55 mol) was mixed with 175 ml of heptane and to this solution was added dropwise 109.2 g of **7** (0.5 mol). The mixture was allowed to warm to 80–85°, with apparent reflux of ethyl bromide. After 0.5 hr at this temperature the reaction mixture was cooled to −15°, whereupon crystals formed. The solid was collected, washed twice with 100 ml of cold hexane to give 150.5 g of product. Small amounts of contaminating **3** could be removed by elution with chloroform through silicic acid to give **1–2n**.

Determination of Interconversion Rate (1 and 2).—The interconversion rate between **1–2a** and **1–2n** was determined by measuring the relative areas corresponding to the nuclear magnetic resonances of both XCH_2 and NCH_3, starting with pure isomer **2**. This method has been described previously.[1b] The other interconversion rates listed in Table II were determined by measuring the relative areas of the $ArCH_3$ group corresponding to **1** and **2**. At time zero, 0.13 g of pure crystalline **1** was dissolved in 1.0 g of a solution containing 85% acetone-d_6, 15% D_2O. The solution was then placed in a sealed nmr tube at 25 ± 1° and at intervals, momentarily inserted in the nmr probe. The Varian A-60 was adjusted to a 100-Hz scan. The Ar-CH_3 resonance from **1** was always downfield from that for **2**, as well as being downfield from the multiplet for acetone-d_6.[18] In certain instances the resonances furthest downfield in this nearly symmetrical five-peak multiplet coincided with the absorption singlet for $ArCH_3$ from **2**. In this event, to determine the relative amounts of **1** and **2** for time t, the area corresponding to $ArCH_3$ from **2** was calculated by subtracting from the total area of this singlet at time t a constant amount, equivalent to the area of the resonance peak for acetone-d_6 at highest field. Equilibrium constants K were determined after permitting the solution to stand for at least ten times the observed half-life of the reaction. From the above data, rate constants k_1 and k_2 could be calculated as before.[1] The data in Table II are derived from linear plots averaging seven points per line, with the correlation coefficients r calculated therefrom.

Determination of Nucleophilic Substitution Rate (1, 2, and 3).—The determination of observed pseudo-first-order rate constants, $k_{\psi obsd}$, by plotting log (initial[amide] − [Br^-]) *vs.* t, derived from potentiometric titrations for halide ion has been described before.[1] The rate constants $k^1_{\psi obsd}$ and $k^2_{\psi obsd}$ were obtained by employing an initial ratio of piperidine/amide concentration of 50:1 and 20:1, respectively. The approximate percentage of SN2 character was then estimated from the expression, $100[(k^1_{\psi obsd}/k^2_{\psi obsd}) - 1]/1.5$. Points making up the linear plots (average of seven per line) were obtained from determinations extending over at least two-thirds of the alkylation reaction. Correlation coefficients, r, calculated from all linear plots to determine $k_{\psi obsd}$ in Table III averaged 0.998 ± 0.002. Average deviation of $k_{\psi obsd}$ as determined from multiple determinations was ±2%. To obtain the data from **1–2** listed in Table III and necessary for preparing Figure 1, the following procedure was carried out. Pure **11** (0.2935 g, 0.000895 mol) was mixed with a solution containing 85 parts acetone and 15 parts water to a total volume of 10 ml. The amide was allowed to equilibrate by permitting the solution to stand 1 week. At time zero the solution was mixed with 85% aqueous acetone containing piperidine (3.80 and 1.52 g, respectively, at initial amine/amide ratios of 50:1 and 20:1), so that the total mixture including washings totaled 25 ml. At intervals of *ca.* 2.5 min thereafter, 0.5-ml aliquots of the solution were withdrawn at time t and pipeted into 50 ml of an acid solution (pH 2–3 with H_2SO_4) containing *ca.* 45 ml of acetone and 5 ml of water. After 7–15 min, longer time intervals were permitted between determinations of [Br^-]. The rate data derived for pure **11** was collected in identical fashion except no prior equilibration was permitted.

The determination of Arnhenius energies of activation, E_a, listed in Table III were calculated from the slopes of linear plots of log $k^2_{\psi obsd}$ *vs.* $1/T$. Four points at 5° intervals (±0.02°) between 25 and 40° make up each line. The essentially first-order character of the alkylations was assured by comparing $k^1_{\psi obsd}$ and $k^2_{\psi obsd}$ throughout this temperature range. In no case in the temperature-dependent studies was the percentage SN2 > 10%.

Registry No.—**1a**, 19298-40-9; **1b**, 19298-41-0; **1c**, 19298-42-1; **1d**, 19298-43-2; **1e**, 19298-44-3; **1f**, 19298-45-4; **1g**, 19298-46-5; **1h**, 19298-47-6; **1i**, 19298-48-7; **1j**, 19298-49-8; **1k**, 19298-50-1; **1l**, 2163-81-7; **1m**, 4212-91-3; **1n**, 4649-37-0; **3**, 6873-41-2; **5**, 2760-41-0; **7**, 4655-11-2; N,2-di-*t*-butylaniline, 19298-56-7; 6-*t*-butyl-*o*-tolylglycinonitrile, 19298-57-8; 6-*t*-butyl-N-(3-methoxypropyl)-*o*-toluidine, 19298-58-9; 6-*t*-butyl-N-ethyl-*o*-toluidine, 19298-59-0.

(18) NMR Spectra Catalog II (Varian Associates), 1963 p 388.

Quinone Dehydrogenation. III.[1] The Oxidation of 2,4-Di-*t*-butylphenol

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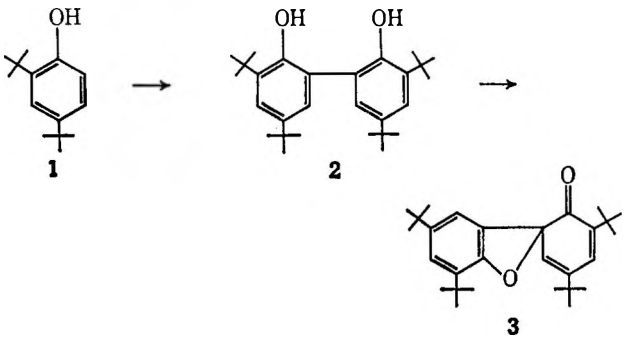
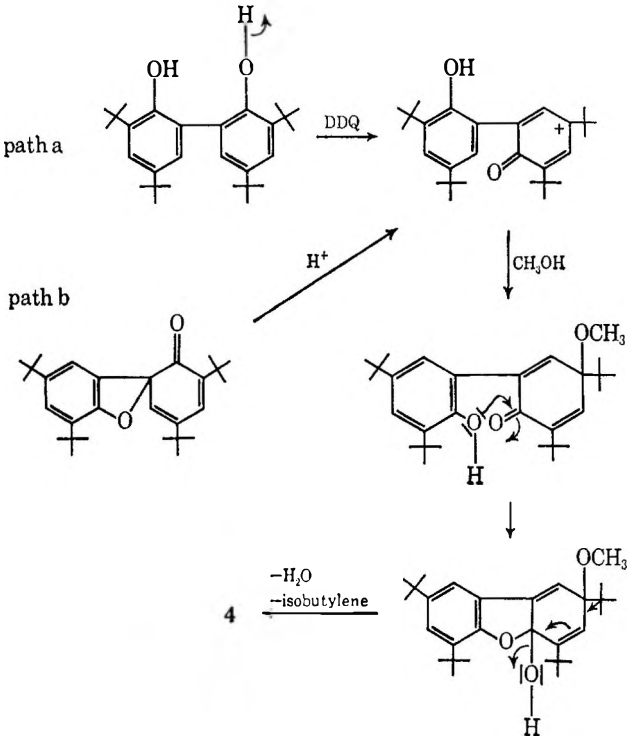
The oxidation of 2,4-di-*t*-butylphenol with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in methanol leads to 2-methoxy-4,6,8-tri-*t*-butyldibenzofuran and a tetra-*t*-butyl-substituted benzofuranoxepinone. A sequence of one-electron and two-electron transfers to DDQ is proposed for this unusual dehydrogenation reaction. The preparation and isolation of a stable benzofuranoxepinoxy radical is described.

The oxidation of 2,4-di-*t*-butylphenol **1** with common one-electron oxidizing agents results in the formation of 2,2′-dihydroxy-3,3′,5,5′-tetra-*t*-butyldiphenyl (**2**) which is rapidly further oxidized to the spiroquinol ether **3**.[2,3] Similar spiroquinol ethers are known to be formed by intramolecular oxidative coupling of other bisphenols.[4]



We have now investigated the dehydrogenation of 2,4-di-*t*-butylphenol with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) since it appeared desirable to substantiate the recently[5] proposed one-electron mechanism of phenol–DDQ interaction by further examples of oxidative coupling.

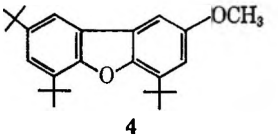
SCHEME I



Results and Discussion

The oxidation of 2,4-di-*t*-butylphenol with DDQ in methanol solution proceeds smoothly at room temperature, giving 2,3-dichloro-5,6-dicyanohydroquinone ($DDQH_2$) and approximately equal amounts of two products which precipitate from the reaction mixture and which can be separated by fractional crystallization. The same product mixture is obtained by oxidation of 2,2′-dihydroxy-3,3′,5,5′-tetra-*t*-butyldiphenyl[6] (**2**) with DDQ in methanol, indicating that the first step of an apparent sequence of reactions probably is that of the expected C–C coupling of phenol **1**.

The structure of one component of the product mixture, a colorless crystalline compound, was readily determined as that of 2-methoxy-4,6,8-tri-*t*-butyldibenzofuran (**4**) on the basis of its C and H analysis, molecular weight, and ir, nmr, and uv spectrum. The latter is strikingly similar to that of 2,4,6,8-tetra-*t*-butyldibenzofuran (Figure 1). The assignment of the methoxy group into the 2 position is based on literature data on the chemical shift of *t*-butyl groups in the nmr spectra of dibenzofurans.[7]



The methoxytri-*t*-butyldibenzofuran **4** became the major product when the oxidation of **1** or **2** with DDQ (molar ratio 1:2 or 1:1, respectively) was carried out in acidified methanol. It appeared conceivable that the introduction of the methoxy group into the reaction product was the result of a heterolytic oxidation of **2** (path a, Scheme I). However, the methoxytri-*t*-butyldibenzofuran **4** is also formed in the absence of DDQ in an acid-catalyzed reaction of the spiroquinol ether **3** with methanol (path b, Scheme I). Thus, the

(1) For part II of this series, see H.-D. Becker, *J. Org. Chem.*, **30**, 989 (1965).
(2) E. Müller, R. Mayer, B. Narr, A. Rieker, and K. Scheffler, *Ann.*, **645**, 25 (1961).
(3) E. C. Horswill and K. U. Ingold, *Can. J. Chem.*, **44**, 269 (1966).
(4) For a recent review, see H. Musso, in "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, Inc., New York, N. Y., 1967, p 1.
(5) H.-D. Becker, *J. Org. Chem.*, **30**, 982 (1965).
(6) We found in the course of this study that 2,2′-dihydroxy-3,3′,5,5′-tetra-*t*-butyldiphenyl is easily prepared in excellent yield by oxidation of 2,4-di-*t*-butylphenol with chloranil at 200° (see Experimental Section).
(7) F. R. Hewgill and D. G. Hewitt, *J. Chem. Soc., C*, 726 (1967).

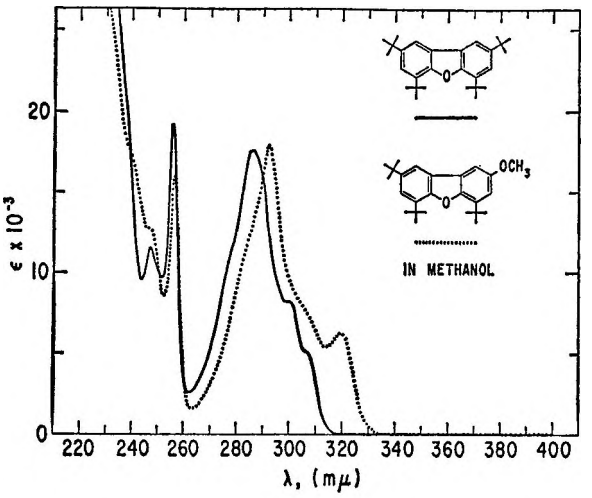
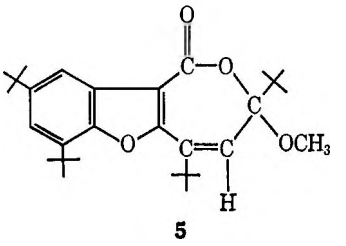


Figure 1.

around 260 mμ attributed to the aromatic system and one broad maximum around 355 mμ attributed to the α,β,γ,δ-unsaturated carbonyl system. The ir spectrum of **5** (in KBr) shows a carbonyl absorption at 1760 cm^{-1}



5

typical of esters or lactones. (Two recently synthesized β,γ,δ,ε-unsaturated ε-lactones show a carbonyl absorption at 1770 and 1772 cm^{-1}, respectively.)[9] The pseudoester structure—and thus the position of the

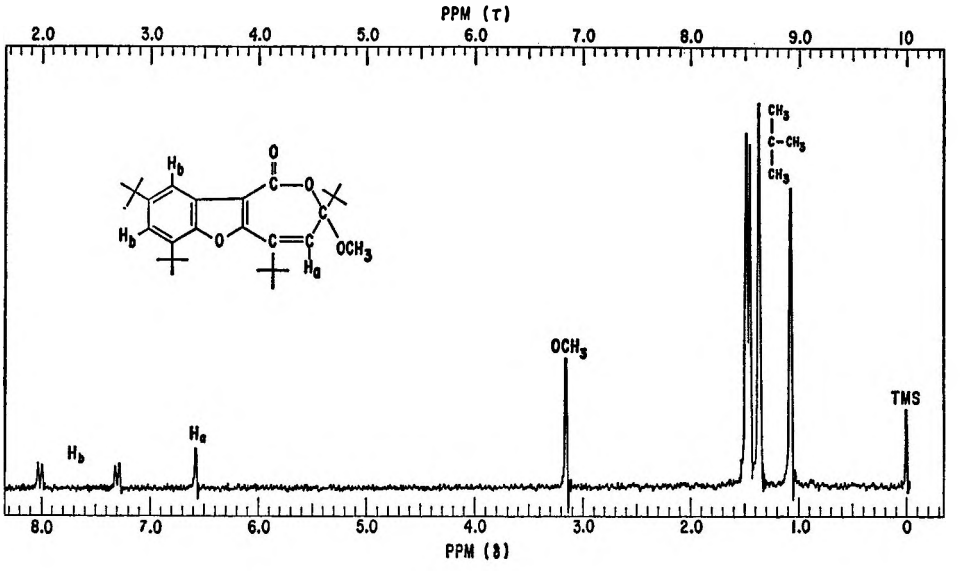


Figure 2.

formation of **4** does not necessarily involve a two-electron oxidation. Most likely, it is the result of a nucleophilic attack[8] of solvent onto the charge-transfer complex of DDQ with spiroquinol ether **3**, which in turn is formed by intramolecular homolytic oxidative coupling of bisphenol **2**.

The second product from the oxidation of 2,4-di-*t*-butylphenol, a yellow crystalline substance, analyzed for $C_{29}H_{42}O_4$. It was also formed as the major product (isolated in 85–88% yield) of the reaction of 2 mol of DDQ with 1 mol of spiroquinol ether **3** in 96% methanol. No reaction, however, was observed in absolute methanol. Based on the following evidence, we propose the benzofuranoxepinone structure **5** for this reaction product.

The nmr spectrum of **5** (Figure 2) reveals four different *t*-butyl groups, one methoxy group, one olefinic proton (3.4 ppm), and two aromatic (*meta*) protons coupling with each other (J_{ab} = 3 cps). The uv spectrum of **5** (Figure 3) shows two narrow maxima

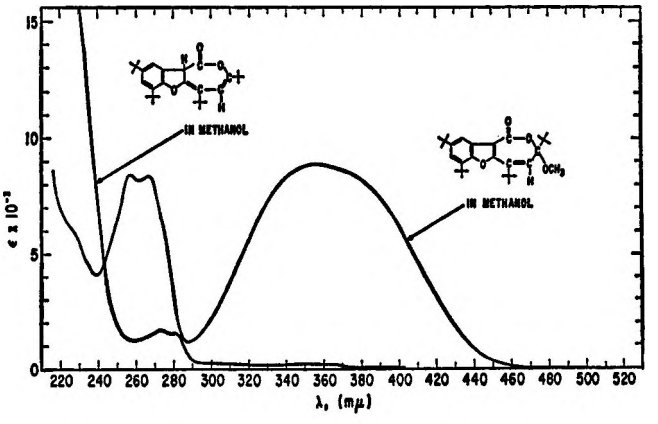


Figure 3.

methoxy group—is confirmed by the transesterification experiment with ethanol which gives the ethoxy compound **6**.

(8) Nucleophilic displacement reactions in spiroquinol ethers have been observed earlier; see F. R. Hewgill and B. R. Kennedy, *ibid.*, 362 (1966).

(9) M. Foá, L. Cassar, and M. Tacchi Venturi, *Tetrahedron Lett.*, 1357 (1968).

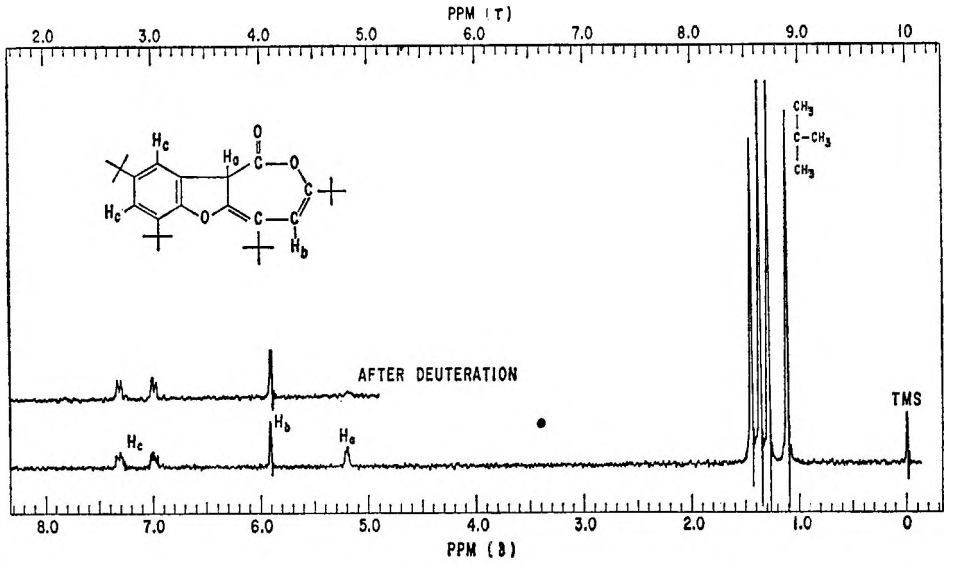
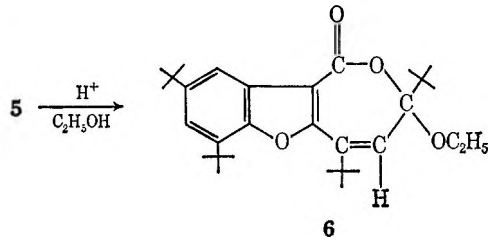
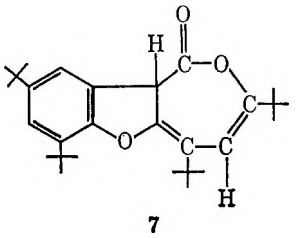


Figure 4.



6

Though compound **5** resists catalytic hydrogenation (Pd–C), it liberates 1 mol of iodine upon treatment with sodium iodide in acetic acid and gives a colorless product which is also obtained by reaction of **5** with zinc and hydrochloric acid. The colorless "reduction" product is also formed by reaction of 1 mol of DDQ with spiroquinol ether **3** in 96% methanol. Structure **7** is assigned to this new compound on the basis of elemental analysis, molecular weight, and the following evidence.



7

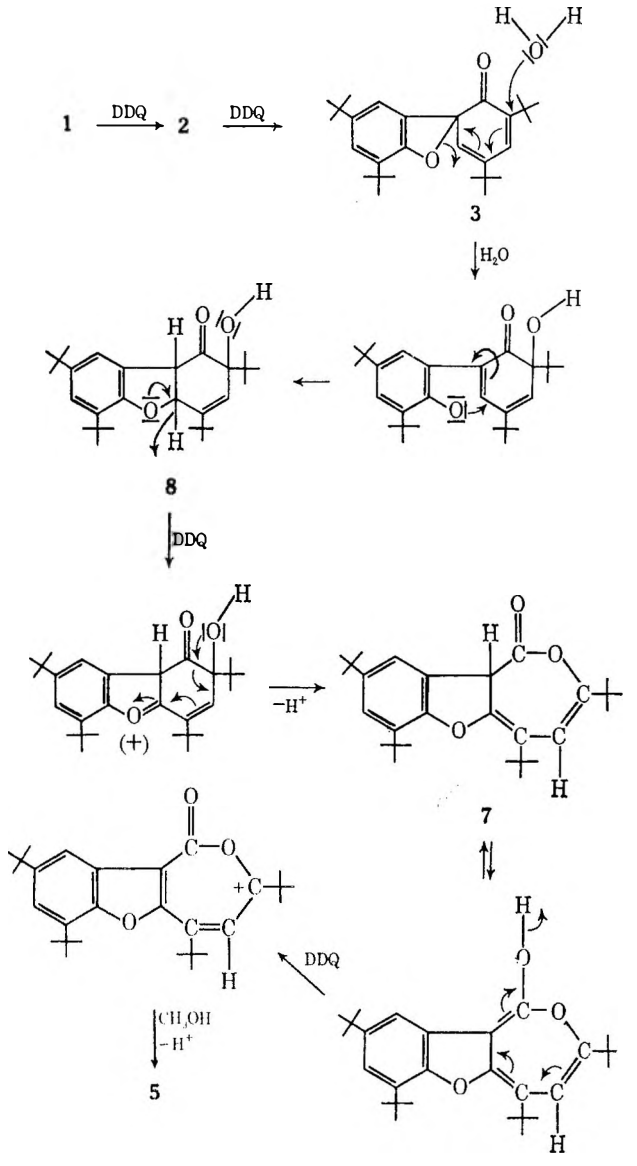
The nmr spectrum of **7** (Figure 4) reveals the reductive removal of the methoxy group from compound **5** and shows the presence of four different *t*-butyl groups, one olefinic proton (H_b, 4.08 ppm), and one proton (H_a) at 4.8 ppm which couples with the two aromatic *meta* protons. The proton with the chemical shift of 4.8 ppm can be exchanged for deuterium by deuteration with D_2O, preferably in the presence of pyridine. Deuteration restores normal *meta* coupling of the aromatic protons and thus confirms the position of H_a in compound **7**. The uv spectrum of **7** (see Figure 3) indicates the presence of the aromatic system and the disappearance of the α,β-unsaturation of the carbonyl group. No absorption is observed above 300 mμ when the uv spectrum of **7** is measured in ether solution. This finding suggests that the low absorption between 300 and 400 mμ observed in the more polar solvent may be due to the presence of small amounts of enolized **7**. However, the ir spectrum of **7** (in KBr) does not show any absorption in the hydroxyl region but exhibits a split carbonyl absorption at 1789–1815 cm^{-1}. Oxidation of the "reduction" product **7** with DDQ (1 mol) in methanol smoothly regenerates the original methoxy compound **5**.

The reaction of DDQ with 2,4-di-*t*-butylphenol leading to compound **5** apparently involves many steps. Based on the experiments described above, we would like to propose the following mechanism for the formation of **5** (see Scheme II).

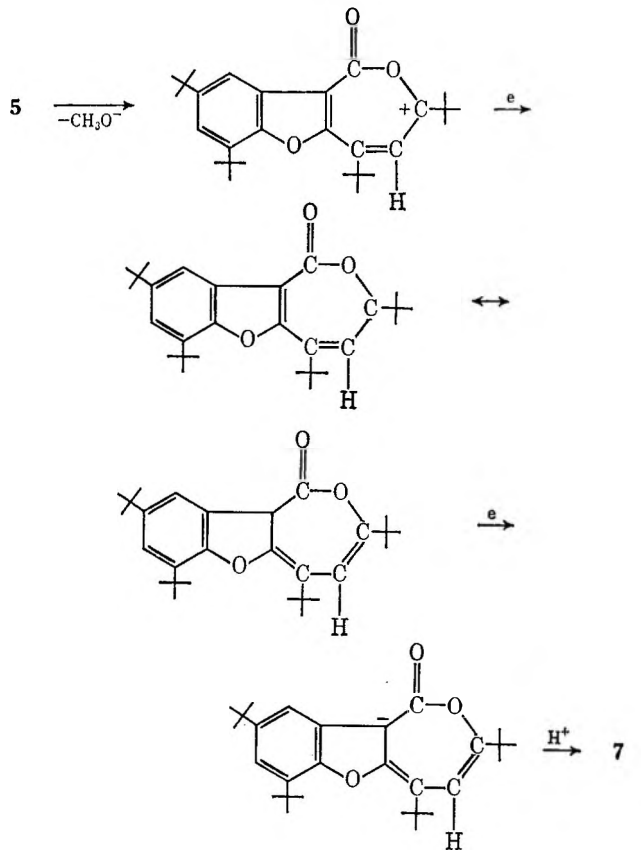
DDQ reacts with 2,4-di-*t*-butylphenol to give $DDQH_2$ and the C–C coupled dehydro dimer **2**. Oxidation of **2** by DDQ then leads to the spiroquinol ether **3** and $DDQH_2$. Both reactions are typical one-electron oxidations. The next step apparently involves nucleophilic attack of water onto the spiroquinol ether *via* its charge-transfer complex with DDQ to give the α-hydroxy ketone **8**. Over-all two-electron oxidation, depicted as hydride-ion abstraction by DDQ from the α-ether carbon atom of **8** results in the lactonization to give the "reduction" product **7**. Also the final step of the reaction sequence involves an over-all two-electron oxidation formulated as hydride-ion abstraction reaction by DDQ from enolizable **7** to give a resonance-stabilized carbonium ion which reacts with the solvent to give the benzofuranoxepinone **5**.

Evidence for the existence of the proposed carbonium ion is found in the formation of deep purple solutions of **5** in strong acids. Furthermore, the double-bond migration which accompanies the reductive removal of the methoxy group in benzofuranoxepinone **5** is well explained by two successive one-electron reductions of the carbonium ion (Scheme III). During the reaction of **5** with zinc and hydrochloric acid the radical stage formulated in Scheme III actually is indicated by the appearance of a transient deep green color. Also, we have been able to produce the radical by carrying out a one-electron oxidation of the "reduction" product **7**. Thus, oxidation of **7** with active manganese dioxide

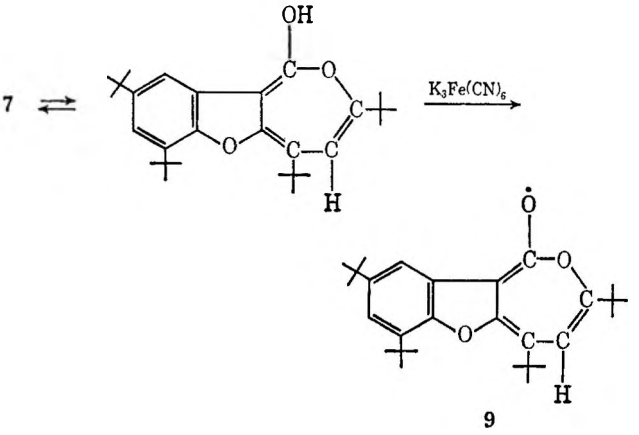
Scheme II



Scheme III



and/or 2,4,6-tri-*t*-butylpenoxy radical in benzene gives the deep blue [λ_{max} 700 mμ ($\epsilon \approx 10000$)] stable free radical **9** which we have isolated in the form of its



crystalline dimer. The first derivative esr spectrum of the benzofuranoxepinoxy radical **9** (Figure 5A) appears as an overlapping pair of doublets, as confirmed by the second derivative spectrum shown in Figure 5B.

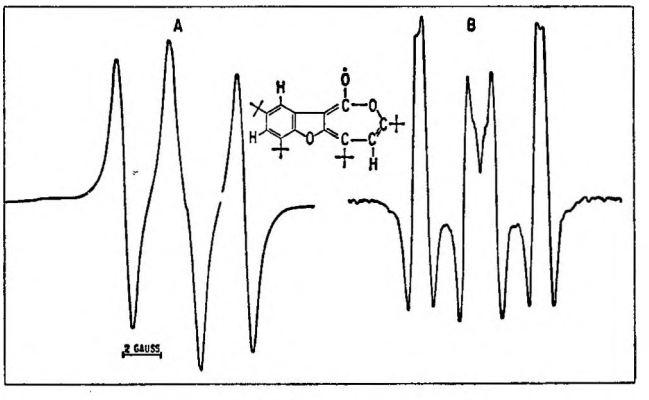
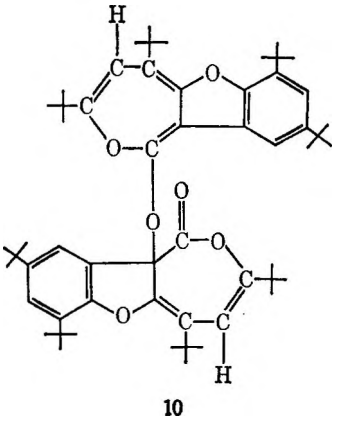


Figure 5.

The structure of the radical dimer probably is that of a carbon–oxygen coupled product **10** since the ir spectrum exhibits the carbonyl absorption at 1812



10

cm^{-1}, similar in position to that of the "reduction" product **7**.

The results presented in this paper are in agreement with the earlier[5] proposed homolytic mechanism for the oxidation of phenols by DDQ. The only oxidation reactions requiring a heterolytic mechanism are those of the nonphenolic intermediates **7** and **8**. Since we have demonstrated the existence of the benzofuranoxepinoxy radical, however, even these reactions may occur in a sequence of two one-electron transfers to DDQ.

Experimental Section

DDQ was recrystallized from methylene chloride. Absolute methanol was commercial grade. It was generally used without further drying. All oxidation reactions were carried out in screw cap bottles under nitrogen. Melting points were taken on a hot-stage microscope and are not corrected. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Molecular weights were determined by thermoelectric measurements in solvents specified in each case.

Oxidation of 2,4-Di-*t*-Butylphenol with Chloranil (2).—Chloranil (1.23 g, 5 mmol) was dissolved in warm 2,4-di-*t*-butylphenol (4.12 g, 20 mmol) and the deep red solution was heated for 5 min to 200–230°. The solution by then had turned light orange. The reaction mixture was triturated with about 10 ml of methanol, diluted with a few drops of water and filtered, yielding 1.64 g (80%) of bisphenol **2**, mp 196–198° (lit.[2] mp 194.5–195.5°). Evaporation of the filtrate and treatment of the residue with chloroform (20 ml) gave 1.18 g (95%) of tetrachlorohydroquinone, mp 236°.

Oxidation of 2,4-Di-*t*-butylphenol with DDQ.—DDQ (3.41 g, 15 mmol) was added to a solution of 2,4-di-*t*-butylphenol (1.54 g, 7.5 mmol) in methanol (20 ml, Baker Grade Absolute). The deep green reaction mixture was shaken for 24 hr. Filtration gave 900 mg of a yellow crystalline material, which was analyzed by nmr and found to consist of a mixture of **4** and **5** in the ratio of about 1:1. The ratio, however, has been found to vary, probably depending on the amount of water present in the methanol used. The separation of the two products is described in the following experiment.

Oxidation of 2,2′-Dihydroxy-3,3′,5,5′-tetra-*t*-butyldiphenyl (2) with DDQ.—A suspension of bisphenol **2** (2.05 g, 5 mmol) and DDQ (2.50 g, 11 mmol) in methanol (15 ml) was shaken for 16 hr. Filtration gave 1.7 g of a yellow crystalline mixture of two products (nmr analysis) melting between 145 and 160°. The filtrate after evaporation of solvent and treatment of the residue with benzene gave 2.32 g (92%) of $DDQH_2$.

Separation of the two components of the product mixture was originally accomplished by fractional crystallization from much methanol in which the benzofuranoxepinone **5** is slightly less soluble than the dibenzofuran **4**. A more effective separation was achieved in the following way. The product mixture (1.25 g) was dissolved in boiling methanol (150 ml) and heated with zinc powder and few milliliters of concentrated hydrochloric acid. When the boiling solution turned colorless and part of the solvent had evaporated, it was filtered (hot). Upon cooling to room temperature, 350 mg of 2-methoxy-4,6,8-tri-*t*-butyldibenzofuran (**4**) crystallized from the filtrate and was removed by filtration. Addition of a little water to the filtrate gave 850 mg of a crystalline product (**7**), mp 125–130°, which was still contaminated with dibenzofuran **4**. It was suspended in methanol (25 ml) and oxidized by shaking for 16 hr with DDQ (425 mg). The yellow crystalline precipitate of **5** thus obtained was recrystallized from a mixture of chloroform and methanol: yield 750 mg, mp 193–195°.

2-Methoxy-4,6,8-tri-*t*-butyldibenzofuran (4). A. By Reaction of 2,2′-Dihydroxy-3,3′,5,5′-tetra-*t*-butyldiphenyl with DDQ in the Presence of HCl.—DDQ (681 mg, 3 mmol) was added to a suspension of bisphenol **2** (1.23 g, 3 mmol) in methanol (10 ml) containing concentrated hydrochloric acid (0.1 ml). The green reaction mixture was shaken for 12 hr. A very light yellow crystalline precipitate (840 mg, mp 150–160°) was then removed by filtration. Recrystallization from a hot mixture of chloroform and methanol gave 680 mg (62%) of colorless crystals: mp 162–163°; nmr data (ppm in τ), 8.56 (s, 9), 8.42 (s, 9), 8.38 (s, 9), 6.08 (s, 3), 3.0 (d, J_{ab} = 2.5 cps, 1), 2.7 (d, J_{ab} = 2.5 cps, 1), 2.55 (d, J_{ab} = 2 cps, 1), 2.2 (d, J_{ab} = 2 cps, 1).

Anal. Calcd for $C_{25}H_{34}O_2$ (366.52): C, 81.92; H, 9.35. Found: C, 82.06; H, 9.30; mol wt (in chloroform), 346.

B. By Reaction of Spiroquinol Ether 3 with Acidified Methanol.—A suspension of **3** (380 mg, 0.43 mmol) in methanol (4 ml) containing 1 drop of concentrated hydrochloric acid was shaken for 15 hr. The colorless precipitate in the reaction mixture was removed by filtration. The yield was 135 mg (40%), mp 158–161°. Recrystallization from hot methanol gave 110 mg (32%) of colorless crystals, melting between 162 and 163°. The mixture melting point with methoxytri-*t*-butyldibenzofuran (**4**) obtained under A was not depressed.

Benzofuranoxepinone 5. A. By Reaction of Spiroquinol Ether 3 with DDQ in Aqueous Methanol.—A suspension of spiroquinol ether **3** (2.05 g, 5 mmol) in a solution of DDQ (2.27 g, 10 mmol) in 96% aqueous methanol (24 ml) was shaken for 2 hr. The originally dark brown reaction mixture (exothermic reaction) turned orange and a yellow crystalline precipitate had formed within 20 min. It was removed by filtration and recrystallized by dissolving in little chloroform and adding methanol: yield 1.91 g (84%); mp 193–195°.

Anal. Calcd for $C_{29}H_{42}O_4$ (454.63): C, 76.61; H, 9.31. Found: C, 76.46; 76.80; H, 9.20; 9.26; mol wt, 429 (in chloroform), 432 (in benzene); mass$^+$, 454.

B. By Oxidation of 7 with DDQ.—DDQ (565 mg, 2.5 mmol) was added to a suspension of **7** (1.06 g, 2.5 mmol) in methanol (10 ml). The reaction mixture was shaken overnight and the yellow crystalline precipitate was then removed by filtration: yield 1.0 g (88%); mp 192–194°. A mixture melting point with **5** obtained under A was not depressed.

Reaction of 3 in Absolute Methanol.—Spiroquinol ether **3** (2.04 g, 5 mmol) was added to a solution of DDQ (2.27 g, 10 mmol) in *freshly dried and distilled absolute methanol* (20 ml) under nitrogen. After 2 hr the deep brown reaction mixture was still clear. Upon addition of 2 drops of water dissolved in 1 ml of methanol a yellow crystalline material precipitated after 1 min and the reaction mixture turned light orange. Filtration gave 1.87 g (82.5%) of **5**, mp 192–194°. A mixture melting point with **5** obtained under A was not depressed.

Transesterification of 5 with Ethanol (6).—A solution of **5** (454 mg, 1 mmol) in absolute ethanol (50 ml) containing concentrated sulfuric acid (0.3 ml) was refluxed for 5 hr. Evaporation of the solvent *in vacuo* left a yellow oily residue which was dissolved in ether (100 ml). The ether solution was washed with aqueous bicarbonate solution. Evaporation of the ether *in vacuo* gave a yellow oily residue which gave yellow crystals upon treatment with little methanol, melting between 138 and 140°. The yield was 350 mg (75%).

Anal. Calcd for $C_{30}H_{44}O_4$ (468.65): C, 76.88; H, 9.46. Found: C, 76.69; H, 9.34.

The ir spectra (in KBr) of the methoxy compound and the ethoxy compound are essentially identical. However, the nmr spectrum of the transesterified product showed the presence of the ethoxy group instead of the methoxy group.

Benzofuranoxepinone 7. A. By Reduction of 5 with Zinc–HCl.—A solution of **5** (1.14 g, 2.5 mmol) in a chloroform–methanol mixture (10:25 ml) containing zinc powder (1 g) and concentrated hydrochloric acid (3 ml) was boiled for 20 min. By then the originally yellow solution had turned transiently deep green and finally colorless. Filtration and partial evaporation of the solvent *in vacuo* gave colorless crystals which were recrystallized from hot aqueous methanol: yield 1.0 g (91%); mp 130–132°.

Anal. Calcd for $C_{28}H_{40}O_3$ (424.60): C, 79.20; H, 9.50. Found: C, 79.47; H, 9.47; mol wt, 407 (in chloroform).

B. By Reduction of 5 with Sodium Iodide.—A solution of **5** (454 mg, 1 mmol) and sodium iodide (500 mg) in acetic acid (100 ml) was boiled for 25 min. After the solution had cooled to room temperature the liberated iodine was titrated with 0.1 *N* sodium thiosulfate solution (20 ml). The colorless crystalline precipitate thus obtained was removed by filtration: yield 400 mg (94%); mp 130–131°. A mixture melting point with the reduction product obtained under A was not depressed.

C. By Reaction of Spiroquinol Ether 3 with 1 Mol of DDQ.—A suspension of **3** (510 mg, 1.25 mmol) in a solution of DDQ (285 mg, 1.25 mmol) in methanol (10 ml) was shaken for 13 hr. From the light yellow reaction mixture 12 mg of **5**, mp 192–193°, were removed by filtration. Evaporation of the filtrate left a light yellow crystalline residue which was washed with a little

cold methanol to give 200 mg (38%) of **7**, mp 130–132°. A mixture melting point with reduction product obtained under A was not depressed.

Benzofuranoxepinoxy Radical (9–10).—A solution of 2,4,6-tri-*t*-butylphenol (262 mg, 1 mmol) and benzofuranoxepinone **7** (424 mg, 1 mmol) in benzene (30 ml) was added under nitrogen to a stirred solution of potassium ferricyanide (3.3 g) and potassium hydrixide (0.6 g) in water (30 ml). Stirring was continued for 15 min. The deep blue benzene layer was then quickly separated, washed twice with water, shaken with sodium sulfate, and evaporated *in vacuo*. The green, partially crystalline residue was triturated with about 20 ml of methanol and stirred for few minutes. Filtration gave a light blue to green crystalline residue (150 mg, 35%), melting around 130° dec.

Anal. Calcd for $C_{56}H_{78}O_6$ (846.60): C, 79.40; H, 9.30. Found: C, 79.28, 79.46; H, 9.24, 9.43.

Compound **10** forms deep blue solutions in chloroform.

The oxidation was also carried and in the absence of 2,4,6-tri-*t*-butylphenol, giving the oxidation product in only 2.5% yield.

Anal. Found: C, 79.19; H, 9.17.

Esr Measurement.[10]—The benzofuranoxepinoxy radical **9** was generated by dissolving dimer **10** in benzene. It can also be generated by dissolving **7** (5 mg) in benzene (5 ml) containing 1 drop of pyridine, and adding activated MnO_2 (50 mg). Filtration under nitrogen through a sintered-glass funnel gave a deep blue filtrate which was used for the esr experiment.

Spectra.[11]—Infrared spectra were taken on a Perkin-Elmer grating ir spectrophotometer, Model 521. Ultraviolet spectra were recorded on a Cary spectrophotometer, Model 14. The uv spectrum of radical **9** was obtained by dissolving **10** (8.46 mg) in chloroform (100 ml) under nitrogen. Proton magnetic resonance spectra were taken in $CDCl_3$ on a Varian A-60 instrument.

Registry No.—**1**, 96-76-4; **4**, 19566-63-3; **5**, 19566-64-4; **6**, 19566-65-5; **7**, 19566-66-6; **10**, 19566-67-7.

Acknowledgment.—The author is very much indebted to Dr. A. S. Hay for providing the spiroquinol ether **3**. Part of this work was carried out during the author's stay, 1966–1967, at the Department of Chemistry, Chalmers University of Technology, Gothenburg, Sweden. The author is very much indebted to Professor Adler for his kind hospitality.

(10) The author is indebted to Mr. Kobayashi of JEOLCO, Inc., for recording the esr spectra during a demonstration of the JEOLCO JES-ME-1X esr spectrometer. Thanks are also due to Dr. A. Factor of this laboratory for discussions concerning the spectrum.

(11) Thanks are due to Miss Dorothy McClung for measuring all uv and ir spectra.

Quinone Dehydrogenation. IV.[1] One-Electron Oxidations with 2,3-Dichloro-5,6-dicyanobenzoquinone

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The dehydrogenation by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) of a variety of phenolic compounds is described. Substituted 4-hydroxytriphenylmethanes are found to be easily oxidized to give stable quinone methides in high yields. A new mechanism for the disproportionation of 4-alkyl-substituted phenoxy radicals is discussed. Dehydrogenation of substituted 4,4′-dihydroxytetraphenylmethanes results in an intramolecular coupling reaction leading to bispirodienones in excellent yields. Several addition reactions of DDQ are described. A quinone ketal capable of undergoing homolytic dissociation is obtained by addition of 3,4,5-trimethoxyphenol to DDQ. 2,6-Dichlorophenol and DDQ react to give 2,3-dicyano-4,4′-dihydroxy-5,5′,6-trichlorodiphenyl ether. DDQ was found to add, together with methanol, to 1,1-diphenylethylene. 2,3-Dichloro-5,6-dicyanohydroquinone bisdiphenyl methyl ether is formed in high yield from DDQ and diphenylmethane. The reaction of methanol with DDQ results in the displacement of one cyano group to give 2-cyano-5,6-dichloro-3-methoxybenzoquinone. Diazomethane reacts with DDQ to give a spiroepoxydienone. A one-electron mechanism for the oxidation and addition reactions involving dissociation of a substrate–quinone charge-transfer complex into radical ions is discussed.

2,3-Dichloro-5,6-dicyanobenzoquinone (henceforth abbreviated DDQ) in methanol solution was recently found to be a powerful oxidant for phenols[1-3] and enols.[4] However, contrary to the common concept of quinone dehydrogenation involving a hydride-ion transfer reaction,[5,6] all products observed in these oxidations could have been formed in one-electron processes.

In view of the general interest in reactions of DDQ[6] it appeared desirable to extend the quinone dehydrogenation to phenolic compounds of structural types not previously investigated. We have now applied DDQ for the oxidation of substituted α,α-diphenyl-*p*-cresols (4-hydroxytriphenylmethanes), substituted 4,4′-dihydroxytetraphenylmethanes, and phenols having either a free *ortho* or *para* position. To gain a better understanding of the dehydrogenation mechanism, the reaction of DDQ with some hydrocarbons was included in this investigation.

Results and Discussion

A. Quinone Methide Formation.—Several substituted *p*-cresols **1** have previously[2] been found to react with DDQ in methanol solution, giving the corresponding carbonyl compounds **6**. The unstable

(1) For part III of this series, see H.-D. Becker, *J. Org. Chem.*, **34**, 1198 (1969).

(2) H.-D. Becker, *ibid.*, **30**, 982 (1965).

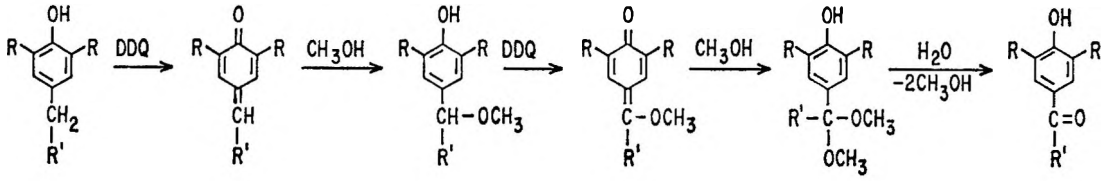
(3) The oxidation of phenols by DDQ has also been under investigation by E. Adler and R. Wettstrom (unpublished work, private communication by Professor Adler); see R. Wettstrom, *Svensk Kem. Tidskr.*, **75**, 429 (1963) (abstract of talk).

(4) H.-D. Becker, *J. Org. Chem.*, **30**, 989 (1965).

(5) L. M. Jackman in "Advances in Organic Chemistry: Methods and Results," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1960, p 329. *Cf.* B. M. Trost, *J. Amer. Chem. Soc.*, **89**, 1847 (1967).

(6) For a comprehensive review of DDQ and its reactions, see D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1967).

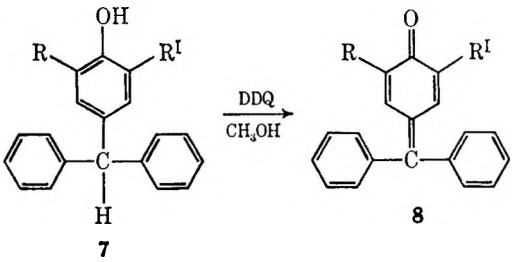
SCHEME I



a. R = CH_3; R' = H
b. R = t-BUTYL; R' = H
c. R = t-BUTYL; R' = OCH_3
d. R = H; R' = PHENYL

quinone methides **2** and **4** were postulated as intermediates[2,7] (Scheme I).

We have now found that quinone methides are the stable end products in the reaction of DDQ with 4-hydroxytriphenylmethanes.[8] Addition of DDQ (1 mol) to a methanol solution of 4-hydroxytriphenylmethanes **7a–7f** (1 mol) leads to quinone methides **8a–8f** in yields of 73–95% (see Table I). The reaction

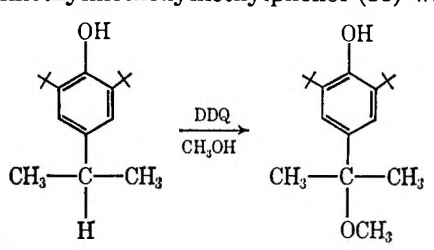


proceeds smoothly at room temperature. As the quinone dissolves, the quinone methides precipitate and are isolated in a high state of purity simply by filtration.

TABLE I
THE OXIDATION OF 4-HYDROXYTRIPHENYLMETHANES

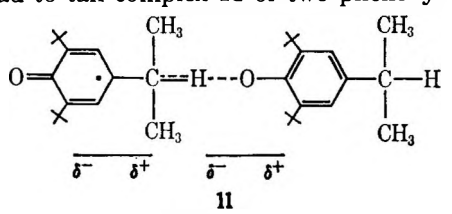
Compd	R	R^I	Yield, %
8a	*t*-Butyl	*t*-Butyl	95
8b	*t*-Butyl	Phenyl	90
8c	Cyclohexyl	Cyclohexyl	95
8d	Isopropyl	Isopropyl	73
8e	Methyl	Phenyl	86
8f	Phenyl	Phenyl	88

The α,α-diphenyl substitution was found to be essential for the formation of stable quinone methides by oxidation of *p*-cresols with DDQ. In accordance with Scheme I, the reaction of DDQ with 2,6-di-*t*-butyl-4-isopropylphenol (**9**) in methanol leads to 2,6-di-*t*-butyl-4-dimethylmethoxymethylphenol (**10**) which was

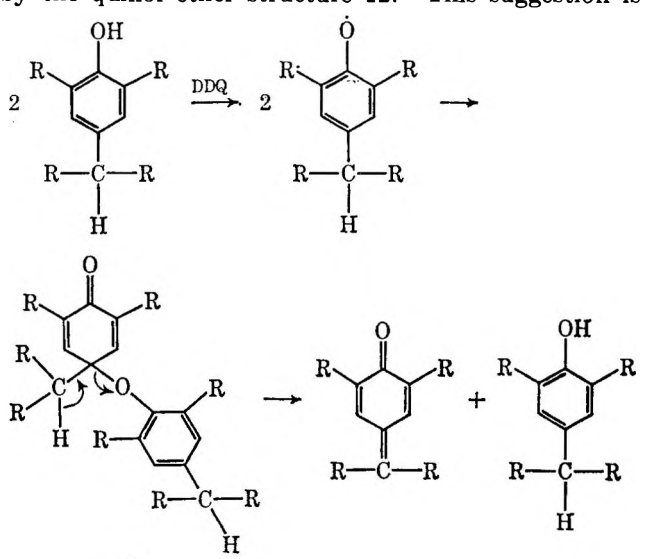


isolated in 71% yield. The slowly fading blue color observed when small quantities of DDQ are added to excess **9** in methanol under nitrogen may be due to 2,6-di-*t*-butyl-4-isopropylphenoxy radicals which undergo spontaneous disproportionation into **9** and the corresponding quinone methide susceptive to nucleophilic attack by methanol.

The disproportionation of *p*-alkyl-substituted phenoxy radicals[9] into parent phenol and quinone methide has frequently been observed in phenol dehydrogenation. However, little seems to be known about the mechanism of this oxidation–reduction reaction. In a comprehensive study, Cook and Norcross showed that the disproportionation of 2,6-di-*t*-butyl-4-isopropylphenoxy radicals follows second-order kinetics.[10] They suggested that the reaction proceeds *via* a head-to-tail complex **11** of two phenoxy radicals.



We believe, however, that the precursor of the parent phenol and the quinone methide is better represented by the quinol ether structure **12**. This suggestion is



(7) W. Brown, J. W. A. Findlay, and A. B. Turner, *Chem. Comm.*, 10 (1968); see also A. B. Turner and H. J. Ringold, *J. Chem. Soc., C*, 1720 (1968).

(8) H.-D. Becker, *J. Org. Chem.*, **32**, 2943 (1967).

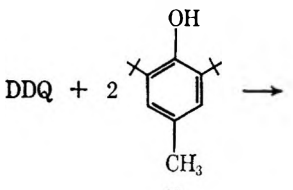
(9) The subject of phenoxy radicals has been treated in a recent comprehensive review article; see E. R. Altwicker, *Chem. Rev.*, **67**, 475 (1967).

(10) C. D. Cook and B. E. Norcross, *J. Amer. Chem. Soc.*, **81**, 1176 (1959).

TABLE II
THE OXIDATION OF 4,4'-DIHYDROXYTETRAPHENYLMETHANES

Compd	R	R^I	R^{II}	R^{III}	R^{IV}	18 Mp, °C	18 Yield, %	18 Formula (mol wt)	Anal, % Calcd C	Calcd H	Found C	Found H
17a	t-Butyl	t-Butyl	H	t-Butyl	t-Butyl	257–258	98	$C_{61}H_{50}O_2$ (574.86)	85.67	8.77	85.62	8.64
17b	t-Butyl	t-Butyl	Br	t-Butyl	t-Butyl	245–246	96	$C_{41}H_{49}BrO_2$ (653.77)	75.40	7.55	75.22	7.58
17c	t-Butyl	t-Butyl	Cl	t-Butyl	t-Butyl	252–254	95	$C_{41}H_{49}ClO_2$ (609.31)	80.82	8.11	80.52	8.24
17d	t-Butyl	t-Butyl	$COOCH_3$	t-Butyl	t-Butyl	244–245	95	$C_{43}H_{52}O_4$ (632.85)	81.60	8.28	81.62	8.33
17e	t-Butyl	t-Butyl	H	t-Butyl	Phenyl	208–209	84	$C_{43}H_{46}O_2$ (594.80)	86.82	7.80	86.87	7.88
17f	t-Butyl	t-Butyl	H	Phenyl	Phenyl	185–190	91	$C_{45}H_{42}O_2$ (614.79)	87.91	6.89	87.72	6.94

supported by our finding that oxidation of 2,6-di-*t*-butyl-4-methylphenol (**13**) with DDQ gives 2,6-di-*t*-butyl-4-methylphenoxy radicals which dimerize to give the quinol ether **14** high yield.[2,11] In solution as



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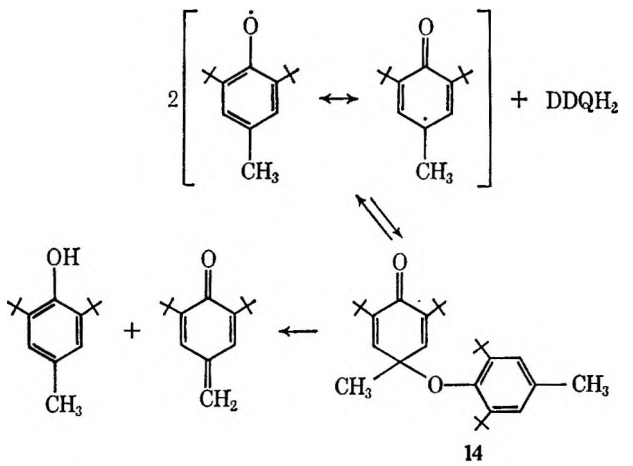

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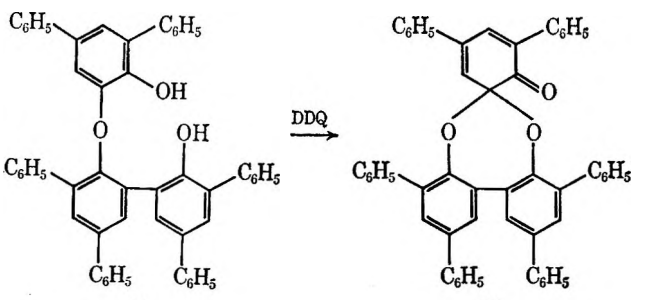
well as the solid state, **14** spontaneously disproportionates at room temperature, giving equimolar amounts of 2,6-di-*t*-butyl-4-methylphenol and the corresponding quinone methide. After much controversy, other workers indeed have shown that the diappearance of 2,6-di-*t*-butyl-4-methylphenoxy radicals also follows second-order kinetics.[12] Thus, it seems likely that the intermolecular oxidation–reduction reaction of phenoxy radicals deriving from *p*-cresols proceeds according to the quinol ether mechanism[13] rather than *via* a radical complex. There is no ultraviolet (uv) spectroscopic evidence[2] for a significant concentration of phenoxy radicals (λ_{max} at 320 mμ[12]) during the disproportionation of **14** (λ_{max} at 280 mμ) in solution, suggesting that the reaction may be described in terms of a heterolytic process as indicated in structure **12**.

B. Intramolecular Coupling Reactions.—Suitable bisphenols give spirodienones by heterogeneous oxidation with alkaline potassium ferricyanide or metal oxides.[14–16] We have now found that such bisphenols also undergo intramolecular coupling by oxidation with DDQ.

Upon treatment with an equimolar amount of DDQ in methanol solution, bisphenol **15** is converted into the dioxepin **16**[17] in high yield.



15 16

DDQ was also found to be a powerful oxidant for bisphenols deriving from tetraphenylmethane which have only recently[18,19] become available. The oxidation of 4,4'-dihydroxytetraphenylmethanes **17a–17f** (see Table II) proceeds rapidly at room temperature in methanol solution to give bispirodienones **18a–18f** in excellent yield and a high state of purity. The yellow to brown bispirodienones precipitate from the reaction mixture as the quinone dissolves. The infrared (ir) and uv spectra of **18** (see Figure 1) are in full agreement with the bispirodienone structure assigned to the oxidation products. As reported previously[16] for **18a**, no evidence was found that the tetra-*t*-butyl-substituted bispirodienones **18b–18d** are in equilibrium with their corresponding diradicals. Solutions of bispirodienones **18e** and **18f** in chloroform containing 2,4,6-tri-*t*-butylphenol, however, turn blue-green upon

(11) It is worth noting that the oxidation of 2,6-bistrimethylsilyl-4-methylphenol has recently been reported to give the corresponding quinol ether; see G. A. Razuvaev, I. L. Khrzhanovskaia, N. S. Vasileiskaia, and D. V. Muslim, *Dokl. Akad. Nauk SSSR*, **177**, 600 (1967).

(12) E. J. Land and G. Porter, *Trans. Faraday Soc.*, **57**, 1885 (1961).

(13) *Cf.* H.-D. Becker, *J. Org. Chem.*, **29**, 3068 (1964); see also L. R. Mahoney and M. A. DaRooge, *J. Amer. Chem. Soc.*, **89**, 5619 (1967).

(14) (a) E. A. Chandross and R. Kreilick, *ibid.*, **85**, 2530 (1963); (b) E. A. Chandross and R. Kreilick, *ibid.*, **86**, 117 (1964).

(15) A. Rieker, H. Kaufmann, R. Mayer, and E. Muller, *Z. Naturforsch.*, **19b**, 558 (1964).

(16) H.-D. Becker, *J. Org. Chem.*, **32**, 2115 (1967).

(17) H.-D. Becker, *ibid.*, in press.

(18) H.-D. Becker, *ibid.*, **32**, 2124 (1967).

(19) H.-D. Becker, *ibid.*, **32**, 2131 (1967).

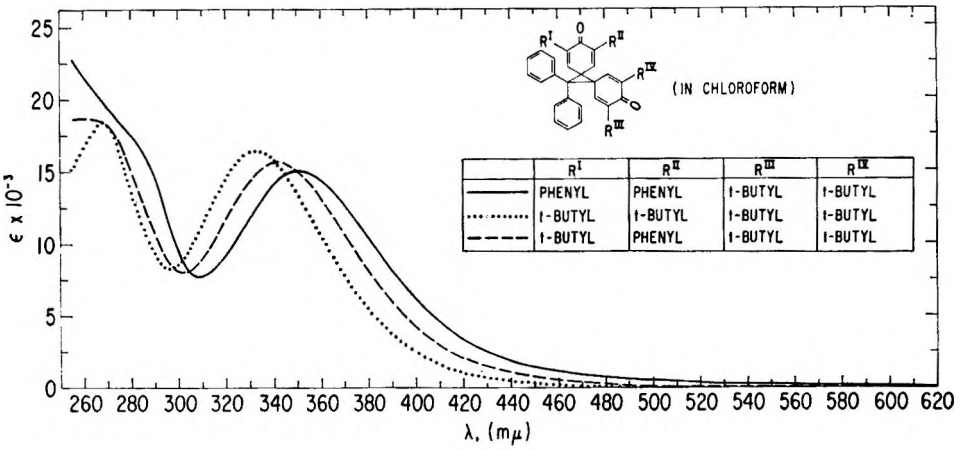
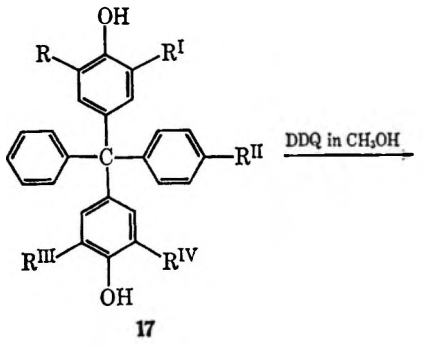


Figure 1.

heating, indicating that diradicals may be formed from **18** at elevated temperature.



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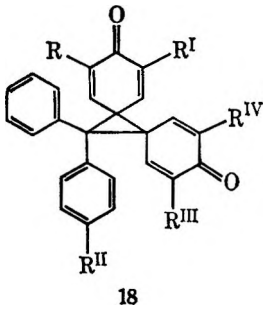
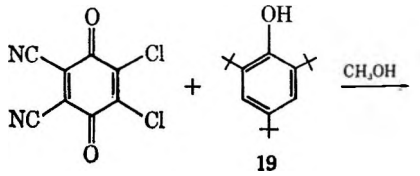


18

C. Addition Reactions of DDQ.—DDQ reacts with 2,4,6-tri-*t*-butylphenol **19** to give the quinol ether **20**.[2]



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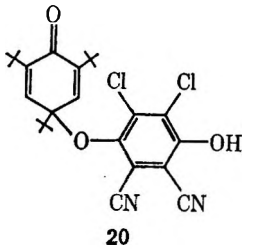
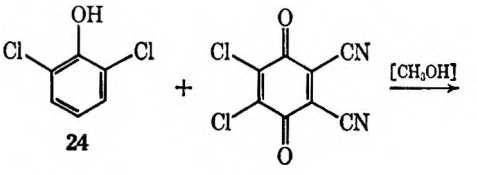


20

The result of mixed coupling does not seem surprising since 2,4,6-tri-*t*-butylphenoxy radicals do not dimerize because of steric hindrance. We have now found, however, that DDQ can undergo a similar coupling reaction even with such phenols for which oxidative dimerization by either C–C or C–O coupling is structurally possible.

Addition of DDQ to a methanol solution of 3,4,5-trimethoxyphenol **21** (see Scheme II) gives (*via* a deep colored transient assumed to be a charge-transfer complex) a colorless crystalline product which precipitates from the reaction mixture in excellent yield. The quinone ketal structure **22** for the 1:1 adduct is supported by its ir spectrum which shows a broad hydroxyl absorption (in KBr) around 3000 and a carbonyl band at 1665 cm^{-1}. The compound readily dissociates into free radicals at room temperature, forming deep purple paramagnetic solutions in chloroform and acetone. Chemical evidence for the quinone ketal structure is found in the acid-catalyzed hydrolysis of **22** which gives $DDQH_2$ (97%) and 2,6-dimethoxy-*p*-benzoquinone (**23**, 98%).

Another example of adduct formation was found in the reaction of DDQ with 2,6-dichlorophenol (**24**). In this case, however, the primary addition product **25** cannot be isolated but it tautomerizes to give the 4,4′-dihydroxydiphenyl ether (**26**). Since the final



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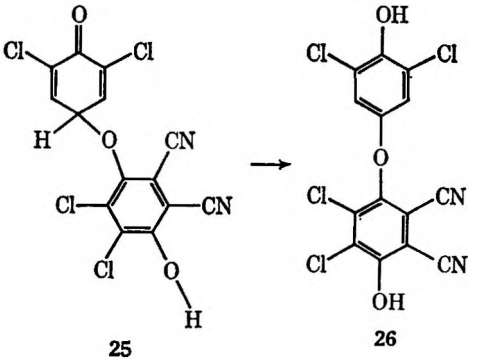


25 **26**

product itself is a phenol and thus subject to further dehydrogenation, the yield of **26** increases significantly when the DDQ/2,6-dichlorophenol ratio is decreased (see Table III).

Scheme II

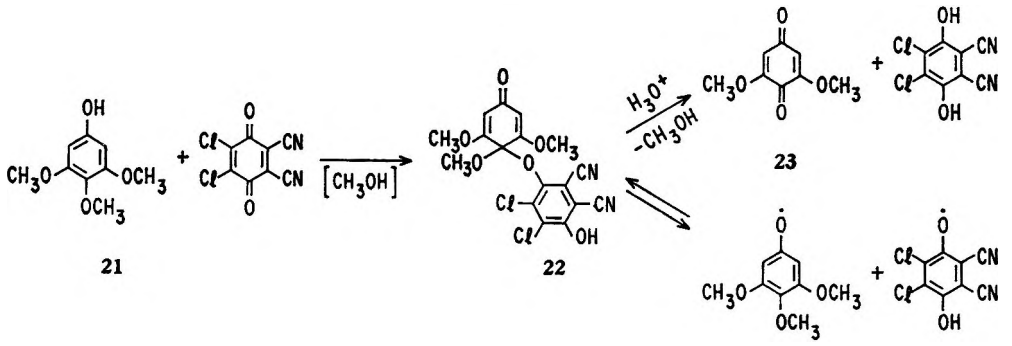


Table III

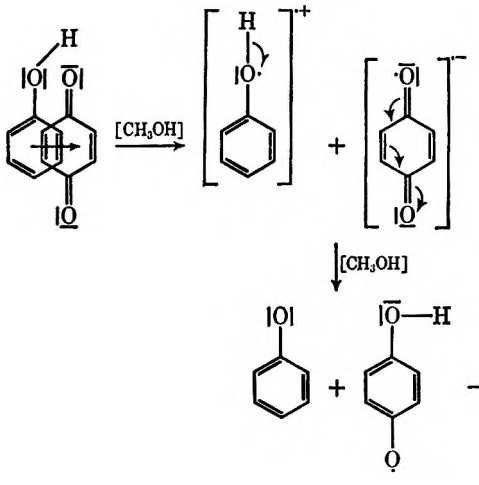
The Effect of DDQ/Phenol Ratio on the Product Yield

DDQ, mmol	2,6-Dichloro-phenol, mmol	CH_3OH, ml	Time, hr	Yield, %
2	2	4	72	32
20	40	40	48	64
20	80	40	48	76

The DDQ-phenol adducts **20**, **22**, and **26** are of particular interest since their formation according to the common concept of quinone dehydrogenation could be described in terms of a hydride-ion transfer reaction followed by collapse of the resulting ion pair. We have previously suggested, however, that the primary step in the reaction of DDQ with phenols consists in the formation of a charge-transfer complex which can undergo homolytic dissociation. It is worth noting that since we made this proposal the formation of radical ions by dissociation of charge-transfer complexes of high-potential quinones and suitable electron donors has indeed been established for polar solvents such as methanol.[20] It has been suggested subsequently that the formation of radical ions results from a chemical reaction between the neutral donor–acceptor complex and the polar solvent.[21]

Applying this concept to the reaction of phenols with DDQ, dissociation of the phenol–quinone charge-transfer complex followed by transfer of a proton from the radical cation to the radical anion would give the phenoxy radical and the DDQH· radical (see Scheme III). These two radicals may then combine to give "DDQ-phenol adducts" or they may undergo further independent reactions giving rise to typical phenol oxidation products and $DDQH_2$.

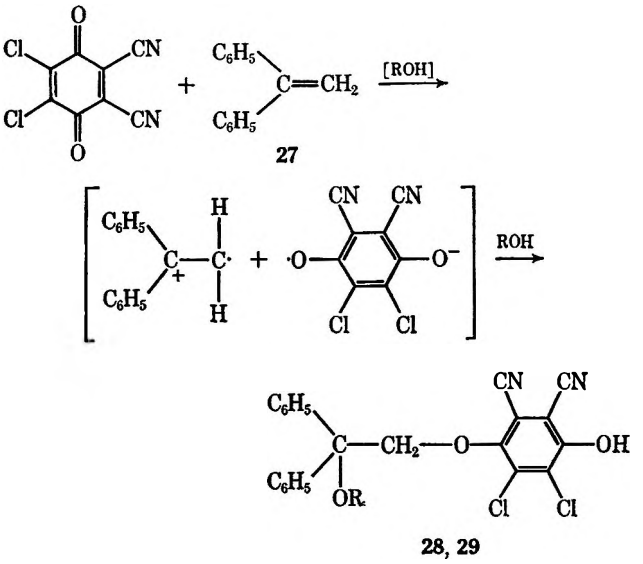
Scheme III



(20) P. H. Emslie, R. Foster, and T. J. Thomson, *Rec. Trav. Chim.*, **83**, 1311 (1964).

(21) K. M. C. Davis and M. C. R. Symons, *J. Chem. Soc.*, 2079 (1965).

In order to obtain more evidence for the proposed one-electron oxidation by DDQ we have investigated its reaction with 1,1-diphenylethylene (**27**) under conditions similar to those applied in the oxidation of phenols. Addition of DDQ to 1,1-diphenylethylene (molar ratio 1:1) in methanol under nitrogen at room temperature gives a deep brown solution from which a colorless crystalline material precipitates. The main product, isolated in 82% yield, was found to be the DDQ-olefin-methanol adduct **28** (R = CH_3).

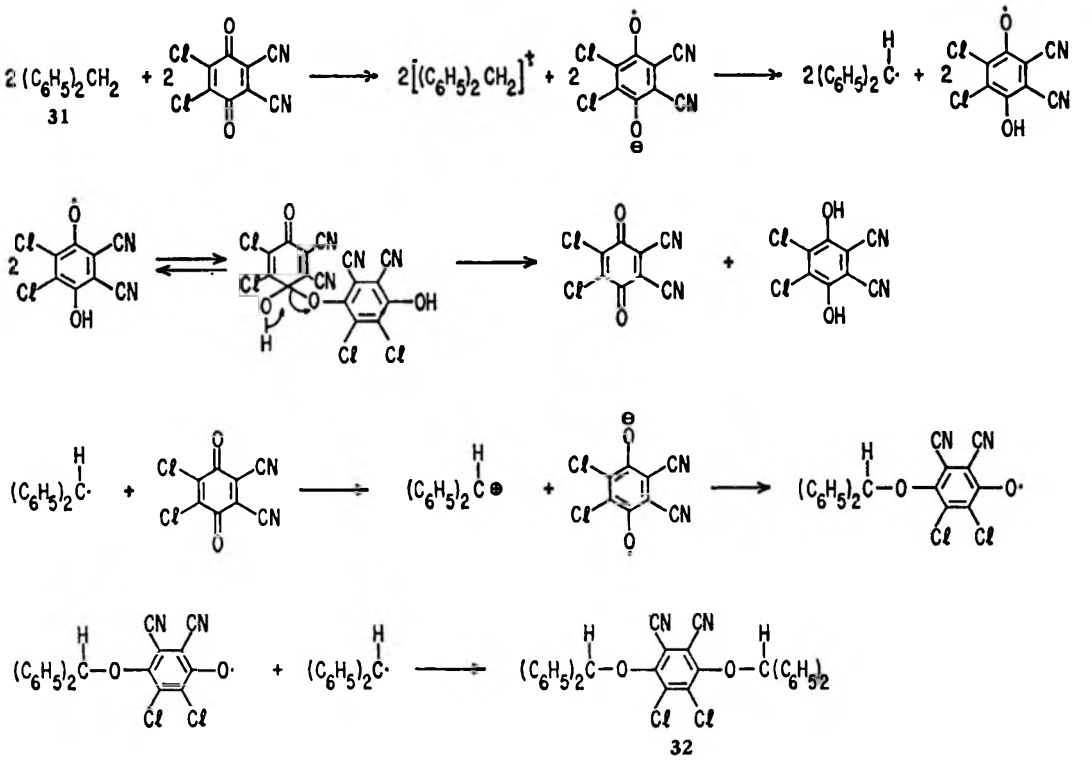


Its structure is based on elemental analysis, molecular weight, and spectroscopic data (ir and nmr). A second product was isolated in only 2.8% yield. Its elemental analysis and molecular weight are in agreement with an adduct consisting of 1 mol of DDQ, 2 mol of 1,1-diphenylethylene, and 2 mol of methanol. The structure of the adduct was not determined. The ir spectrum shows a strong band at 1720 cm^{-1}, but neither an OH nor a CN absorption.

The reaction of DDQ with 1,1-diphenylethylene in ethanol smoothly leads to a DDQ-olefin-ethanol adduct for which elemental analysis, molecular weight, and spectroscopic data (ir and nmr) are in agreement with structure **29** (R = C_2H_5).

We consider the formation of **28** and **29** as interesting and significant with regard to the one-electron *vs.* two-electron mechanism. Obviously, hydride-ion abstraction from 1,1-diphenylethylene appears improbable

SCHEME IV



while charge-transfer complex formation and one-electron transfer is conceivable.[22] The transient deep color observed during the reaction is indicative of a charge-transfer complex which, according to the mechanism outlined above, dissociates in alcohol solution to give the diphenylethylene radical cation and the semiquinone radical anion. Their combination followed by reaction with the alcohol would lead to the observed products **28** and **29**, respectively. The combination of the radical-ion pair presumably is favored by a solvent cage.

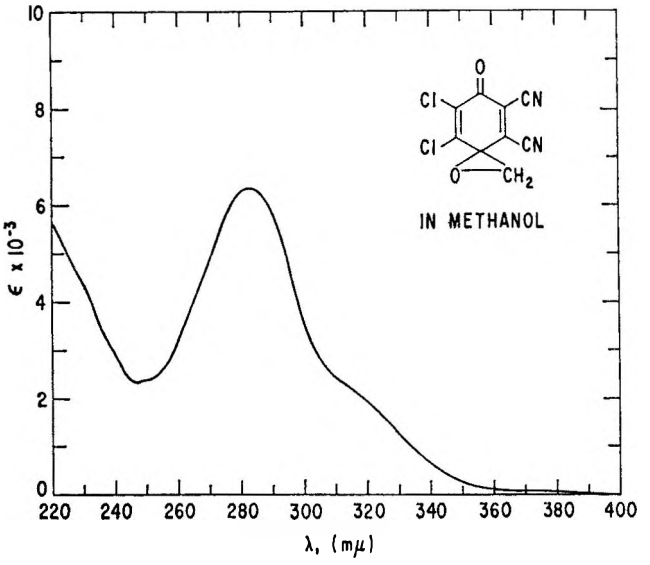
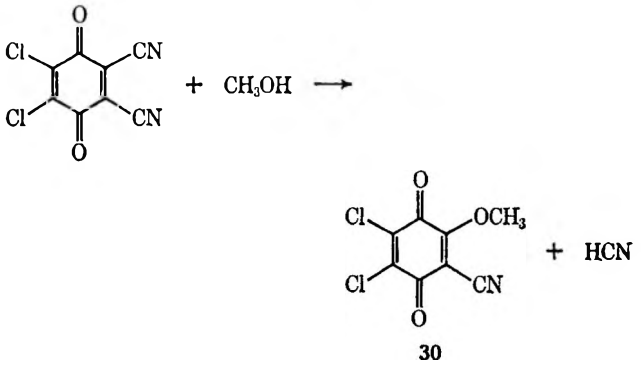


Figure 2.

The results obtained with 1,1-diphenylethylene prompted us to extend the dehydrogenation by DDQ to diphenylmethane. Oxidation of diphenylmethane with tetra-*t*-butyldiphenoquinone at 260° had previously been reported to result in the formation of 1,1,2,2-tetraphenylethane.[23]

An attempt to bring about the dehydrogenation of diphenylmethane by DDQ at room temperature in methanol solution was not successful. Interestingly, however, the product isolated from this reaction mixture derived from the nucleophilic displacement of a cyano group in DDQ by methanol. The resulting 2-cyano-5,6-dichloro-3-methoxybenzoquinone (**30**) also forms when solutions of DDQ in methanol are kept overnight at room temperature.



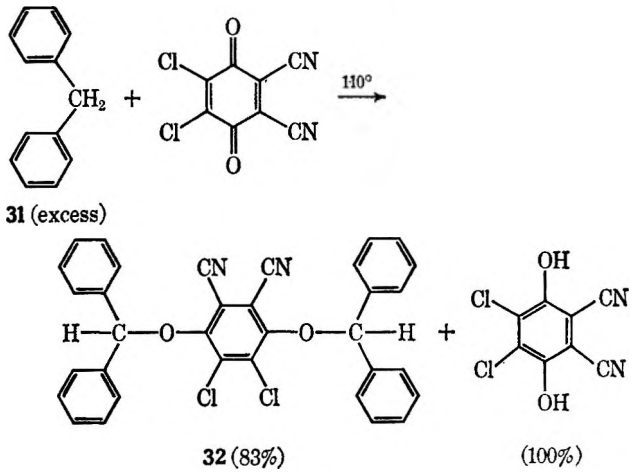
30

In the absence of any solvent, diphenylmethane (**31**) was found to react smoothly with DDQ at elevated

(22) An example of one-electron transfer from a substituted 1,1-diphenylethylene by a radical cation has recently been reported by C. E. H. Bawn, F. A. Bell, and A. Ledwith, *Chem. Comm.*, 599 (1968).

(23) A. S. Hay, *Tetrahedron Lett.*, 4241 (1965). The oxidative coupling of phenols by diphenoquinones has been reported recently by R. G. R. Bacon and O. J. Stewart, *Chem. Comm.*, 977 (1967).

temperature, yielding $DDQH_2$ (100%) and its bis-diphenylmethyl ether (**32**, which was isolated in 83% yield).



Similar hydroquinone ethers have been obtained previously by reaction of alkyl-substituted benzenes with DDQ.[24] However, their formation has always been described in terms of a hydride-ion mechanism, although it is well known that alkyl radicals do undergo addition reactions to quinones.[25] Thus, triphenylmethyl radicals add to the oxygen of benzoquinone to give the bistriphenylmethyl ether of hydroquinone.[26a] Therefore, the formation of any 2,3-dichloro-5,6-dicyanohydroquinone bisalkyl ether probably can also be described in terms of a one-electron mechanism, as exemplified in Scheme IV for the formation of **32**. This mechanism does not imply that DDQ reacts as a diradical, but we suggest that bond formation between DDQ and the diphenylmethyl radical is preceded by electron transfer.[26b] A disproportionation mechanism is proposed for the formation of $DDQH_2$.

The typical quinone rather than diradical behavior of DDQ also is evident in its reaction with diazomethane[27] which leads to the spiroepoxydienone **33**. The structure of **33** is supported by its ir spectrum showing a carbonyl band at 1710–1720 cm^{-1} (in KBr), by its uv spectrum (Figure 2), and by its catalytic reduction to 2,3-dichloro-5,6-dicyano-4-hydroxybenzyl alcohol (**34**). The reduction product was characterized by its diacetate **35** and its dimethyl ether **36**.

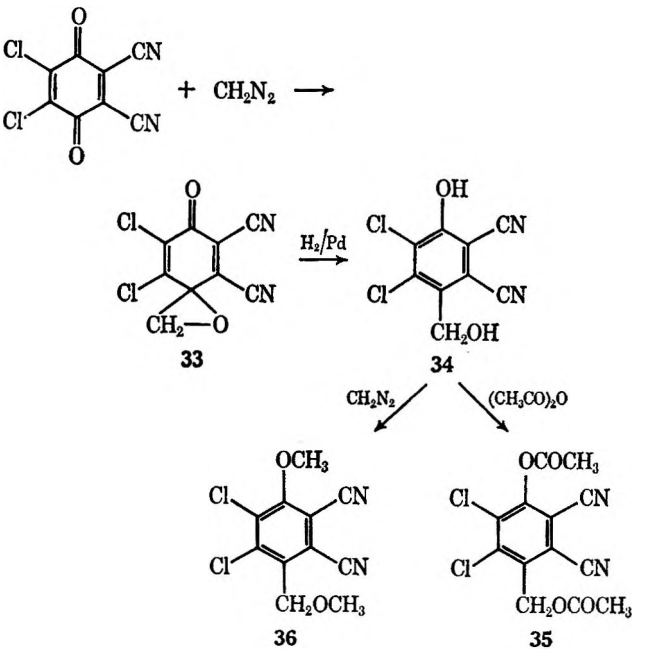
We conclude from the results obtained in the course of this investigation that reactions of DDQ with phenols are well explained by one-electron oxidation processes. Furthermore, addition reactions of DDQ to hydrocarbons to give hydroquinone ethers do not necessarily involve hydride-ion abstraction but may be the result of a one-electron transfer.

(24) R. Foster and I. Horman, *J. Chem. Soc., B*, 1049 (1966). For other examples of ether formation, see ref 6.

(25) A. F. Bickel and W. A. Waters, *J. Chem. Soc.*, 1764 (1950).

(26) (a) J. Schmidlin, J. Wohl, and H. Thommen, *Ber.*, **43**, 1293 (1910); (b) *Cf.* K. A. Bilevitch, N. N. Bubnov, and O. Yu. Okhlobystin, *Tetrahedron Lett.*, 3465 (1968).

(27) *Cf.* B. Eistert and L. Klein, *Chem. Ber.*, **101**, 391 (1968), and earlier papers of that series, especially B. Eistert and G. Bock, *ibid.*, **92**, 1247 (1959).



Experimental Section

2,3-Dichloro-5,6-dicyanobenzoquinone was purchased from Arapahoe Chemicals, Boulder, Colo. All DDQ used was recrystallized from methylene chloride. Absolute methanol was commercial grade. Oxidations were carried out in screw-cap bottles under nitrogen. All melting points were taken on a hot-stage microscope. Molecular weights were determined by thermoelectric measurement in solvents as indicated in each case. Analyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Quinone Methides 8 (Standard Procedure).—DDQ (1 mmol) was added to a solution of 4-hydroxytriphenylmethane **7** (1 mmol) in methanol. The reaction mixture was shaken for time periods as indicated in Table IV. In all cases the mixture melting point with authentic[16,28] samples was not depressed.

TABLE IV

THE DEHYDROGENATION OF 3,5-DISUBSTITUTED 4-HYDROXYTRIPHENYLMETHANES

Compd	R	R^1	CH_3OH, ml	Time, hr	Yield of **8**, %
7a	*t*-Butyl	*t*-Butyl	10	0.2	95
7b	*t*-Butyl	Phenyl	5	8	90
7c	Cyclohexyl	Cyclohexyl	10	0.5	95
7d	Isopropyl	Isopropyl	5	0.5	73
7e	Methyl	Phenyl	5	8	86
7f	Phenyl	Phenyl	10	20	88

Oxidation of 2,6-Di-*t*-butyl-4-isopropylphenol with DDQ to Give 10.—2,6-Di-*t*-butyl-4-isopropylphenol (1.24 g, 5 mmol) was added to a solution of DDQ (1.135 g, 5 mmol) in methanol (5 ml) under nitrogen. After 24 hr the partly crystalline reaction mixture was evaporated *in vacuo* and the essentially colorless residue was triturated with benzene. Filtration gave 1.06 g (93%) of $DDQH_2$. The benzene filtrate was evaporated to dryness and the residue thus obtained was treated with a little aqueous methanol. Filtration gave 1.13 g (81%) of crude 2,6-*t*-butyl-4-dimethylmethoxymethylphenol. Recrystallization from pentane gave 990 mg (71%) of colorless crystals, mp 106–108° (lit.[29] 106.5–108.5°).

Dioxepin 16.—DDQ (113 mg, 0.5 mmol) was added to a stirred suspension of **15** (367 mg, 0.5 mmol) in methanol (10 ml). Filtration after 10 hr gave 320 mg of crude precipitated oxidation product, mp 245–250°. Recrystallization from a boiling acetone–chloroform mixture gave 285 mg (78%) of

(28) H.-D. Becker, *J. Org. Chem.*, **32**, 2943 (1967).

(29) C. D. Cook and B. E. Norcross, *J. Amer. Chem. Soc.*, **78**, 3797 (1956).

dioxepin 16, mp 250–252°. The mixture melting point with authentic[17] 16 was not depressed.

Oxidation of 4,4'-Dihydroxy-3,3',5,5'-tetra-*t*-butyltetraphenylmethane with DDQ to Give 18a.—DDQ (277 mg, 1 mmol) was added to a suspension of 4,4'-dihydroxy-3,3',5,5'-tetra-*t*-butyltetraphenylmethane (576 mg, 1 mmol) in methanol (10 ml). After 6 hr of shaking, the precipitated bispirodienone was removed by filtration. The yield was 560 mg (98%), mp 257–258°. The mixture melting point with authentic[16] material was not depressed.

Spirodienones 18b–18f were prepared in the same manner as that described for **18a**. Their uv data are summarized in Table V.

TABLE V
THE ULTRAVIOLET SPECTRA OF BISPIRODIENONES 18 (IN METHANOL)

	Max₁		Max₂	
Compd	λ, mμ	ε × 10⁻³	λ, mμ	ε × 10⁻³
18a	333	16.5	268	18.5
18b	332	16.2	268	20.2
18c	332	16.5	268	19.7
18d	330	16.2	258	26
18e	341	15.7	260	18.7
18f	350	15.0	255	16.3

Addition of DDQ to 3,4,5-Trimethoxyphenol (22).—DDQ (908 mg, 4 mmol) was added to a solution of 3,4,5-trimethoxyphenol (736 mg, 4 mmol) in methanol (15 ml) agitated with a stream of nitrogen. As the DDQ dissolved, a colorless to light yellow crystalline precipitate formed. Filtration yielded a very light yellow material which was washed with little cold acetone to give 1.3–1.4 g (79–85%) of colorless addition product. The compound decomposes without melting above 100°.

Anal. Calcd for $C_{17}H_{12}Cl_2N_2O_6$: C, 49.66; H, 2.94; Cl, 17.24; N, 6.81; mol wt, 411.20. Found: C, 49.39; H, 3.12; Cl, 17.30; N, 6.80.

Acid-Catalyzed Hydrolysis of Quinone Ketal 22.—A suspension of the quinone ketal **22** (1.23 g, 3 mmol) in a mixture of methanol (20 ml) and concentrated hydrochloric acid (3 ml) was stirred for 5 min. Vacuum evaporation of the solvents and treatment of the solid residue with boiling chloroform left 650 mg of $DDQH_2$ (97%) undissolved. The filtrate was evaporated to dryness and the solid residue was washed with methanol to give 495 mg (98%) of 2,6-dimethoxybenzoquinone, mp 258–259°.

Anal. Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80; mol wt, 168.14. Found: C, 56.85; H, 4.79.

Addition of DDQ to 2,6-Dichlorophenol (26).—DDQ (4.54 g, 20 mmol) was added to a solution of 2,6-dichlorophenol (13.04 g, 80 mmol) in methanol (40 ml), agitated with a stream of nitrogen. The dark brown solution was kept in a closed flask for 24 hr. The colorless precipitate was then removed from the light yellow solution by filtration. The yield was 5.14 g. An additional 0.8 g of **26** was isolated from the partly evaporated filtrate. The total yield was 5.94 g (76%), mp 260° dec. Recrystallization from hot methanol or vacuum sublimation [220° (1 mm)] raised the melting point to 262° dec.

Anal. Calcd for $C_{14}H_4Cl_4N_2O_4$: C, 43.12; H, 1.03; Cl, 36.36; N, 7.18; mol wt, 390.01. Found: C, 43.14; H, 1.02; Cl, 36.10; N, 7.30; mol wt, 409 (in dioxane).

Reaction of DDQ with 1,1-Diphenylethylene in Methanol to Give 28.—A solution of DDQ (2.27 g, 10 mmol) and 1,1-diphenylethylene (1.8 g, 10 mmol) in absolute methanol (10 ml) placed in a screw-cap bottle was shaken for 24 hr. The colorless crystalline precipitate that had formed was removed by filtration (3.8 g) and boiled in 50 ml of methanol, leaving 180 mg (2.8%) of a crystalline substance, mp 298–300°, undissolved.

Anal. Calcd for $C_{38}H_{20}Cl_2N_2O_4$: C, 70.25; H, 4.66; Cl, 10.92; N, 4.31; mol wt, 649.14. Found: C, 70.04; H, 4.60; Cl, 11.07; N, 4.46; mol wt, 652 (in chloroform).

From the hot filtrate 3.4 g of colorless **28** separated at room temperature. The substance was vacuum dried [50° (1 mm)] for 3 hr, mp 187–188° dec, yield 77%.

Anal. Calcd for $C_{28}H_{16}Cl_2N_2O_2$: C, 62.89; H, 3.67; Cl, 16.14; N, 6.38; mol wt, 439.30. Found: C, 62.91; H, 3.82.

From the original methanol filtrate 114 mg of $DDQH_2$ was isolated.

Reaction of DDQ with 1,1-Diphenylethylene in Ethanol to Give 29.—The reaction was carried out in the same manner as that described above. Filtration yielded 2.85 g (63%) of colorless crystals, mp 180° dec.

Anal. Calcd for $C_{34}H_{18}Cl_2N_2O_2$: C, 63.59; H, 4.00; Cl, 15.64; N, 6.18; mol wt, 453.33. Found: C, 63.60; H, 4.02; Cl, 15.53; N, 6.20; mol wt, 451 (in chloroform).

2-Cyano-5,6-dichloro-3-methoxy-1,4-benzoquinone (30).—A solution of 2,3-dichloro-5,6-dicyanobenzoquinone (2.27 g, 10 mmol) in absolute methanol (10 ml) was kept standing in a dark closed flask for 48 hr. The yellow crystalline precipitate was removed by filtration. The yield was 350 mg (15%), mp >220° dec. Recrystallization from boiling methanol raised the melting point to 225–226° dec.

Anal. Calcd for $C_9H_3Cl_2NO_3$: C, 41.41; H, 1.30; Cl, 30.56; N, 6.04; mol wt, 232.03. Found: C, 41.44; H, 1.55; Cl, 30.56; N, 6.21; mol wt, 237 (in benzene).

Reaction of DDQ with Diphenylmethane (32).—A deep red solution of DDQ (5.68 g, 25 mmol) in diphenylmethane (50 ml, 300 mmol) was kept at 110° under nitrogen agitation for 15 min. As the red color disappeared, a colorless precipitate $DDQH_2$ formed. The reaction mixture was cooled to room temperature and filtered through a sintered-glass funnel, leaving 2.75 g (100%) of $DDQH_2$ undissolved.

The light orange filtrate was subjected to vacuum distillation at about 1-mm pressure and a bath temperature of 120°, thus removing the excess diphenylmethane. The light pink residue was washed with little methanol and recrystallized by dissolving in little warm benzene and adding ether. The yield was 5.8 g (83%) of colorless needle-shaped crystals, mp 189–190° dec.

Anal. Calcd for $C_{34}H_{22}Cl_2N_2O_2$: C, 72.72; H, 3.95; N, 4.99; mol wt, 561.48. Found: C, 72.86; H, 4.12; N, 4.93; mol wt, 561 (in chloroform).

Reaction of DDQ with Diazomethane (33).—An ether solution of diazomethane was added dropwise to a solution of DDQ (1.135 g) in benzene (75 ml) until the yellow color due to the quinone disappeared. At that point a colorless crystalline precipitate formed. It was removed by filtration and recrystallized from boiling methanol under addition of little water. The yield was 1.12 g (93%), mp ~250° dec.

Anal. Calcd for $C_9H_2Cl_2N_2O_2$: C, 44.85; H, 0.84; mol wt, 241.03. Found: C, 44.96; H, 0.96; mol wt, 239 (in acetone).

Catalytic Reduction of DDQ–CH_2 Adduct 33 (35 and 36).—Spiroepoxydienone **33** (482 mg, 2 mmol) was hydrogenated with Adams catalyst (15 mg) in acetone (6 ml). After 2 hr, when 55 ml of hydrogen (120% of theory) had been absorbed, the reaction mixture was filtered. The crystalline product obtained after evaporation of the solvent had mp 160–175° dec. Since it was difficult to recrystallize, it was methylated with diazomethane in ether solution to give 300 mg (55%) of the dimethyl ether of 2,3-dichloro-5,6-dicyano-4-hydroxybenzyl alcohol, mp 122–124°.

Anal. Calcd for $C_{11}H_8Cl_2N_2O_2$: C, 48.74; H, 2.97; mol wt, 271.10. Found: C, 49.05; H, 3.18; mol wt, 250 (in acetone).

The diacetate of 2,3-dichloro-5,6-dicyano-4-hydroxybenzyl alcohol was prepared by dissolving the reduction product of **33** in acetic anhydride containing a few drops of concentrated sulfuric acid. The yield was 300 mg (46%), mp 163–164°.

Anal. Calcd for $C_{13}H_8Cl_2N_2O_4$: C, 47.73; H, 2.47; mol wt, 327.13. Found: C, 47.61; H, 2.60; mol wt, 312 (in acetone).

Registry No.—DDQ, 84-58-2; **18a**, 13145-52-3; **18b**, 19566-50-8; **18c**, 19566-51-9; **18d**, 19566-52-0; **18e**, 19566-53-1; **18f**, 19566-54-2; **22**, 19566-55-3; **23**, 530-55-2; **26**, 19566-56-4; **28**, 19566-57-5; **29**, 19566-58-6; **30**, 19566-59-7; **32**, 19566-60-0; **33**, 19566-61-1; **35**, 19566-62-2; **36**, 19556-79-7.

New Stable Phenoxy Radicals. The Oxidation of Hydroxystilbenes

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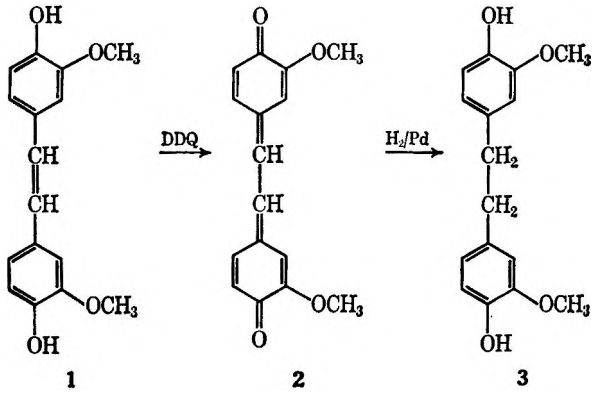
Dehydrogenation of 3,5-disubstituted 4-hydroxystilbenes with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or alkaline potassium ferricyanide leads to new bisquinone methides which in solution spontaneously dissociate into their monomeric phenoxy radical precursors. Methoxy substitution is found to enhance the homolytic cleavage reaction. The 2,6-disubstituted 4-β-styrylphenoxy radicals are characterized by ultraviolet and electron spin resonance spectroscopy. Oxidation of 2-hydroxy-3-methoxystilbene results in the formation of dimethoxydi-β-styryldiphenoquinone.

Although the field of phenol oxidation has received continuous attention during the past 50 years, little seems to be known about the dehydrogenation of hydroxystilbenes.[1] The oxidation of 4,4′-dihydroxystilbenes has been reported to give the corresponding stilbene quinones.[2] Thus, for instance, dehydrogenation of 4,4′-dihydroxy-3,3′-dimethoxystilbene **1** with either lead tetraacetate[3] or 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[4] at room temperature gives 3,3′-dimethoxystilbene quinone **2** whose structure is confirmed by its catalytic reduction to 4,4′-dihydroxy-3,3′-dimethoxybibenzyl **3**.



1 **2** **3**

The oxidation of monohydroxystilbenes apparently has not been reported previously. We found in a preliminary experiment that the known[5] 2-hydroxy-3-methoxystilbene **4** is readily oxidized with chromic acid[6] to give the crystalline dimethoxydi-β-styryldiphenoquinone **5** (probably as a mixture of *cis–trans* isomers), which forms intensely purple solutions. The structure of **5** is based on its ultraviolet and visible spectrum which is similar to that of known diphenoquinones (see Figure 1). Reduction of **5** with hydrazine hydrate gives colorless bisphenol **6** which is easily reoxidized and whose structure is supported by elemental analysis and molecular weight.

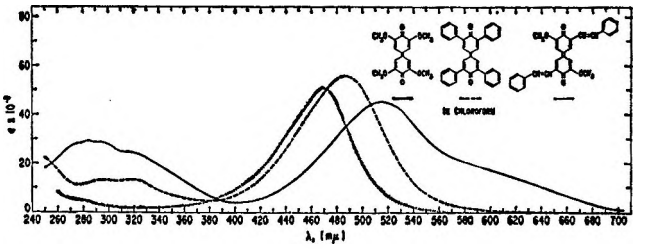
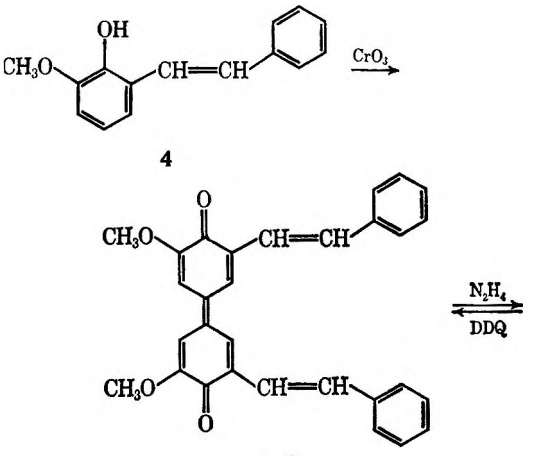
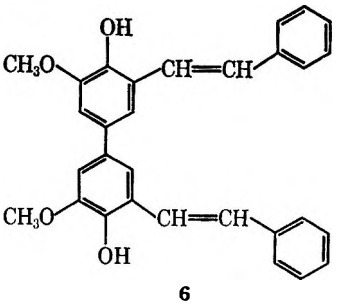


Figure 1.





6

It appeared interesting to study the oxidation of 3,5-disubstituted 4-hydroxystilbenes **7** since their corresponding phenoxy radicals **8** conceivably could be more stable than other 2,4,6-trisubstituted phenoxy radicals[7] because of the resonance effect of the β-styryl group.

The preparation of the 3,5-disubstituted 4-hydroxystilbenes[8] involved the reaction of benzylmagnesium

(1) For a recent review on the oxidation of phenols, see H. Musso in "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, Inc., New York, N. Y., 1967, p 1.

(2) H. v. Euler and E. Adler in "The Svedberg, 1884–1944" (Memorial Volume), Uppsala, Sweden, 1944, p 246.

(3) E. Adler and S. Häggroth, *Svensk Papperstidn.*, **52**, 321 (1950).

(4) *Cf.* H.-D. Becker, *J. Org. Chem.*, **30**, 982 (1965).

(5) E. Adler and K. Lundquist, *Acta. Chem. Scand.*, **17**, 13 (1963).

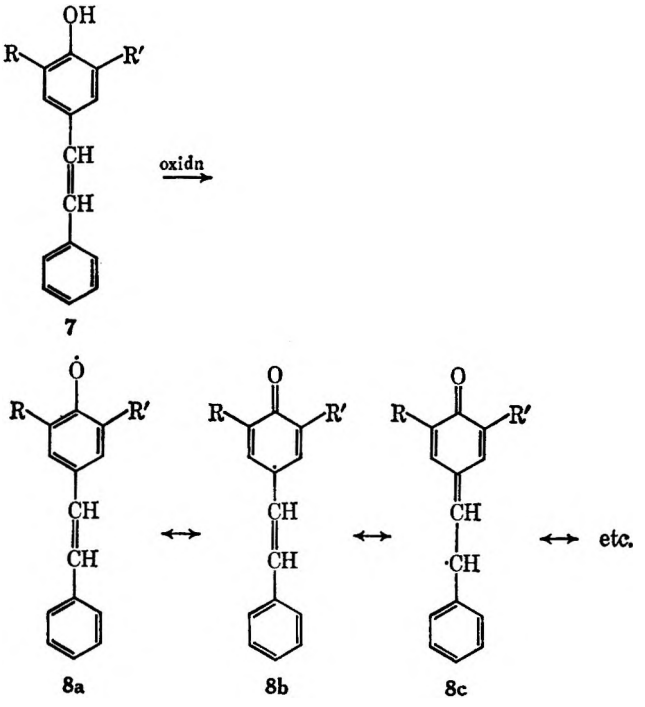
(6) Other oxidants such as DDQ or active MnO_2 seemed to give a mixture of products.

(7) For a recent review of phenoxy radicals, see E. Altwicker, *Chem. Rev.* **67**, 475 (1967).

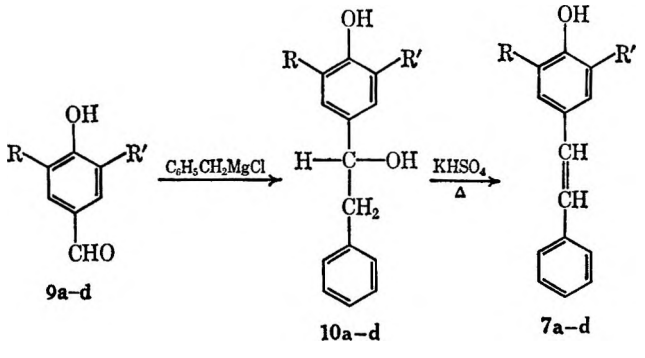
(8) *Cf.* H. P. Kaufmann, *Ann.*, **433**, 237 (1923).

TABLE I
THE PREPARATION OF
3,5-DISUBSTITUTED 4-HYDROXYSTILBENES

	R	R′	Yield of 10, %	Yield of 7, %
a	*t*-Butyl	*t*-Butyl	79	81
b	Methyl	Methyl	78	86
c	Allyl	Methoxy	40	74
d	Methoxy	Methoxy	51	78

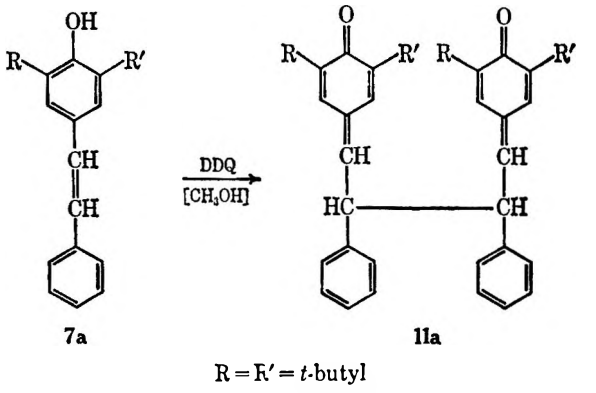


chloride with known 3,5-disubstituted 4-hydroxybenzaldehydes **9** to give the secondary alcohols **10** which were then dehydrated in the presence of potassium hydrogen sulfate. The results on the synthesis of the 3,5-disubstituted 4-hydroxystilbenes **7** are summarized in Table I.



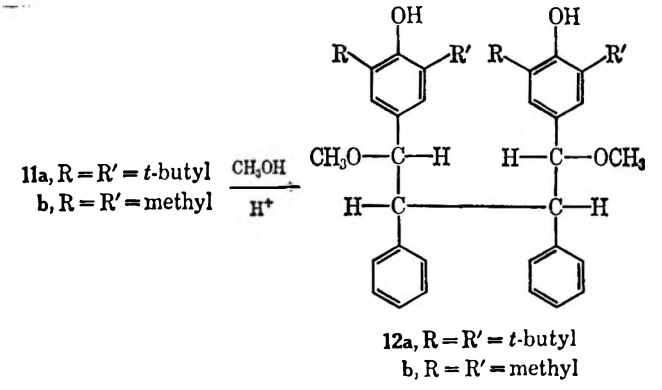
Results and Discussion

The oxidation of 3,5-di-*t*-butyl-4-hydroxystilbene **7a** with 2,3-dichloro-5,6-dicyanobenzoquinone in methanol at room temperature proceeds rapidly to give a yellow crystalline product (71% yield) for which spectroscopic data (ir, nmr), elemental analysis, and molecular weight are in agreement with dehydro dimer **11a**. The bisquinone methide structure of **11a** is supported by the acid-catalyzed reaction with methanol leading



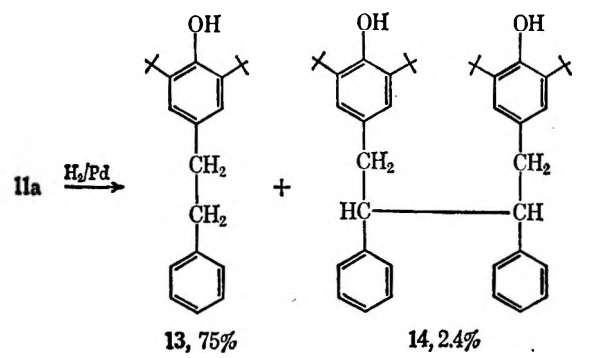
R = R′ = *t*-butyl

to a bisphenol for which elemental analysis, molecular weight, and spectroscopic data (ir, nmr) are in excellent agreement with structure **12a**.



12a, R = R′ = *t*-butyl
b, R = R′ = methyl

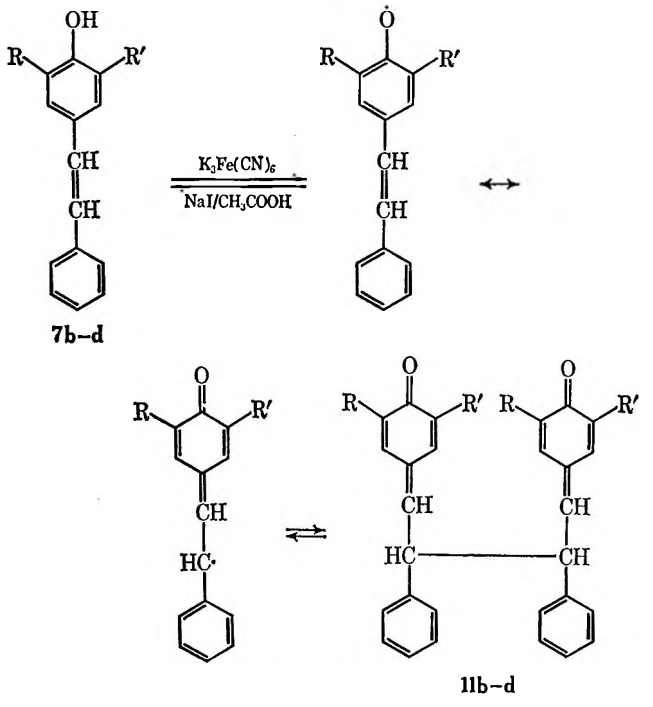
Crystalline bisquinone methide **11a** appears to be quite stable since no changes have been observed in samples which have been stored at room temperature for more than 18 months. However, evidence for an unprecedented equilibrium in solution between a dimeric bisquinone methide[9] and its monomeric radical precursors was found in the behavior of **11a** toward reducing agents. Thus, upon treatment with sodium iodide in a chloroform–acetic acid mixture, bisquinone methide **11a** liberates 1 molar equiv of iodine and regenerates 3,5-di-*t*-butyl-4-hydroxystilbene **7a**. Catalytic reduction of **11a**, using Pd/C catalyst in ethyl acetate, gives 3,5-di-*t*-butyl-4-hydroxybibenzyl **13** in 75% yield, and in only 2.4% yield the dimeric reduction product **14**. Obviously, the rate of reduction of phenoxy radical **8** is much greater than that of bisquinone methide **11a**.



(9) The oxidation of 3,5-di-*t*-butyl-4-hydroxycinnamates had been reported to give bisquinone methides which do not dissociate into free radicals. *Cf.* E. Müller, R. Mayer, H.-D. Spanagel, and K. Scheffler, *Ann.*, **645**, 53 (1961).

In agreement with the chemical indications for a spontaneous homolytic cleavage reaction, solutions of **11a** in chloroform indeed are found to be paramagnetic, giving rise to an esr spectrum (see Figure 2) consistent[10] with the assigned structure of 2,6-di-*t*-butyl-4-β-styrylphenoxy radical (**8**, R = R′ = *t*-butyl). By comparison with diphenylpicrylhydrazyl (DPPH), a 2.5 × 10^{-4} *M* solution of **11a** was found to be approximately 5 × 10^{-6} *M* in free radical.

The oxidation of 3,5-dimethyl-4-hydroxystilbene **7b**, 3-allyl-4-hydroxy-5-methoxystilbene **7c**, and 3,5-dimethoxy-4-hydroxystilbene **7d** with alkaline potassium ferricyanide gives the crystalline bisquinone methides **11b–d** (see Table II) with similar chemical properties as those described for *t*-butyl compound **11a**. For example, bisquinone methide **11b** undergoes



acid-catalyzed addition of methanol to give bisphenol **12b**. Spontaneous homolytic dissociation of **11b–d** at room temperature is indicated by the generation of 2,4,6-tri-*t*-butylphenoxy radical upon addition of 2,4,6-tri-*t*-butylphenol. Treatment of **11d** with sodium iodide at room temperature results in the rapid formation of 1 molar equiv of iodine and regeneration of 3,5-dimethoxy-4-hydroxystilbene **7d**.

TABLE II
THE OXIDATION OF 4-HYDROXYSTILBENES

7, 11	R	R′	Yield of 11, %
b	Methyl	Methyl	94
c	Allyl	Methoxy	84
d	Methoxy	Methoxy	69

Solutions of bisquinone methides **11b–d** are found to be paramagnetic at room temperature. Surprisingly, however, dimethoxy compound **11d** which is pale green is paramagnetic even in its crystalline state, indicating partial dissociation into free radicals. In solution, **11d** gives rise to an esr spectrum which is similar to that of the *t*-butyl analog. Quantitative determination of spin by comparison with DPPH revealed that a 2.5 × 10^{-4} *M* solution of **11d** in chloroform was 5 × 10^{-5} *M* in 2,6-dimethoxy-4-β-styrylphenoxy radical. This corresponds to a tenfold increase of free radicals as compared with the amount of free 2,6-di-*t*-butyl-4-β-styrylphenoxy radicals measured under identical conditions.

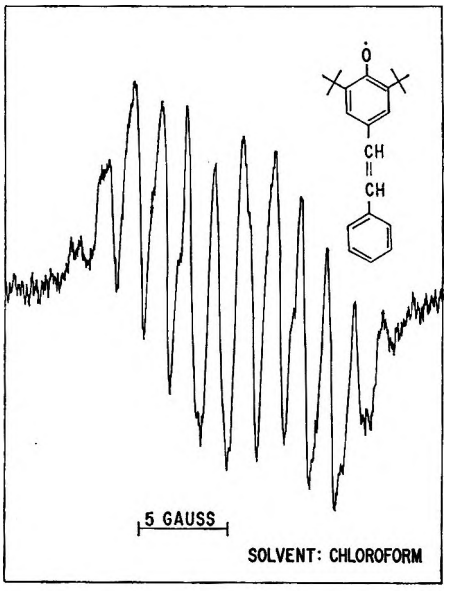


Figure 2.

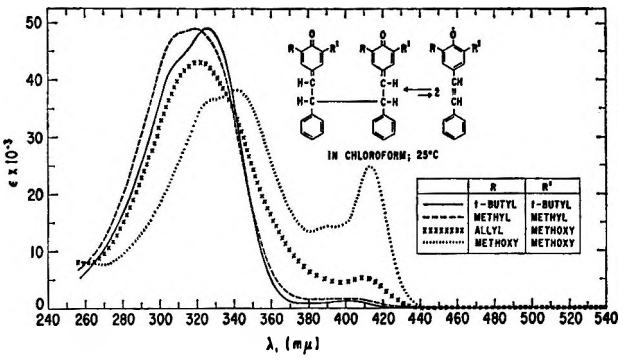


Figure 3.

The results of the ultraviolet spectroscopic investigation of bisquinone methides **11** are in excellent agreement with the esr spectroscopic findings. Phenoxy radicals are known to exhibit a characteristic ultraviolet absorption spectrum with generally three maxima around 320, 380, and 400 mμ, respectively.[11] On the other hand, alkyl-substituted quinone methides have been found to show one symmetric absorption maximum between 289 and 322 mμ.[12] The main absorption maximum in the spectrum of **11a** due to the quinone methide chromophore is found at 326 mμ (see Figure 3). An additional absorption maximum which we attribute to the 2,6-di-*t*-butyl-4-β-styrylphenoxy radical is found at 400 mμ. The reported short wavelength maximum typical of phenoxy radicals is apparent as a pronounced shoulder around 315 mμ. The generally weakest absorption maximum of phenoxy

(10) The twelve-line spectrum is explained by coupling of the unpaired electron with the benzylic hydrogen atom and the *ortho and para* hydrogen atoms of the phenyl substituent.

(11) E. J. Land and G. Porter, *Trans. Faraday Soc.*, **59**, 2016 (1963).

(12) L. J. Filar and S. Winstein, *Tetrahedron Lett.*, No. 25, 9 (1960).

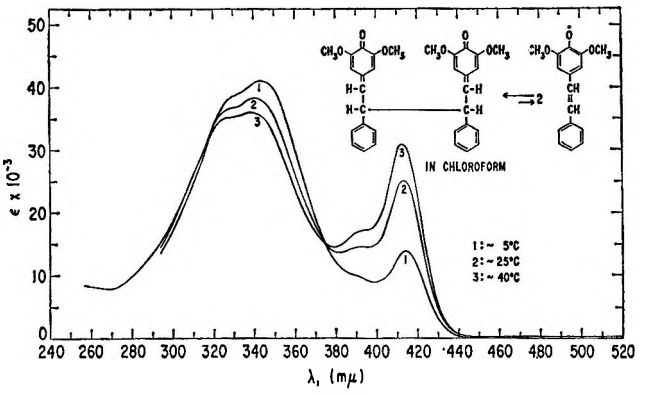


Figure 4.

radicals around 380 mμ may be indicated by the broadness of the long wavelength maximum.

The increased concentration of free 2,6-dimethoxy-4-β-styrylphenoxy radicals in solutions of bisquinone methide **11d** is obviously reflected by the increased absorbance of the long wavelength maximum at 420 mμ and the pronounced shoulders at 330 and 390 mμ, while the absorption due the quinone methide chromophore at 340 mμ is found decreased (see Figure 3). Upon heating, the phenoxy radical absorption increases at the expense of the bisquinone methide absorption. Cooling the solution of **11d** has the reverse effect. The appearance of two isosbestic points (see Figure 4) suggests that these spectral changes indeed are due to changes in the equilibrium between the bisquinone methide and 2,6-dimethoxy-4-β-styrylphenoxy radical.

Based on the ultraviolet spectrum of bisquinone methide **11b**, the concentration of 2,6-dimethyl-4-β-styrylphenoxy radicals is about the same as that of 2,6-di-*t*-butyl-4-β-styrylphenoxy radicals. Compared with bisquinone methides **11a** and **11b**, an approximately threefold increase of radical concentration is indicated by the absorbance of the long wavelength maximum in the spectrum of bisquinone methide **11c**. These findings suggest that the degree of dissociation of bisquinone methides **11** into the phenoxy radicals depends on the electronic nature of the substituents rather than on their steric influence. A similar enhancing effect of the methoxy substituent on the generation of phenoxy radicals from quinol ethers[13] and quinone ketals[14] has only recently been reported. It is worth noting, however, that a spontaneous dissociation of dimeric bisquinone methides into their monomeric phenoxy radical precursors has not been observed previously.

Experimental Section

Melting points were determined on a hot-stage microscope and are not corrected. Analyses were carried out by A. Bernhardt, Mülheim (Germany), and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Molecular weights were determined by thermoelectric measurement.

3,3'-Dimethoxystilbenequinone (2).—DDQ (227 mg, 1 mmol) was added to a stirred suspension of 4,4'-dihydroxy-3,3'-dimethoxystilbene[15] (272 mg, 1 mmol) in absolute ethanol (5 ml). After 30 min of stirring the deep red reaction product was removed by filtration and washed with absolute ethanol: yield, 150 mg (55%); mp 195–205° (depending on the rate of heating). When the reaction was repeated on a 2-mmol scale, the yield of **2** was 72%, mp 202–206° (lit.[3] mp 210°, unsharp). The ir spectrum of **2** did not show any absorption in the OH region but showed a strong band at 1610 cm^{-1} (in KBr). *Anal.* Calcd for $C_{16}H_{14}O_4$ (270.27): C, 71.10; H, 5.22. Found: C, 70.93; H, 5.26.

Catalytic Reduction of 3,3'-Dimethoxystilbenequinone (3).—3,3'-Dimethoxystilbenequinone (135 mg, 0.5 mmol) was suspended in ethyl acetate (5 ml) and hydrogenated in the presence of Pd/C (10%) catalyst (100 mg). The hydrogen uptake after 50 min was 225 ml. Filtration and evaporation of the solvent gave 118 mg (91%) of 3,3'-dimethoxy-4,4'-dihydroxybibenzyl, mp 158° (lit.[16] mp 158°). The melting point was unsharp (as reported), probably because the compound is autoxidized at elevated temperature to give the stilbene. The structure of **3** is fully supported by its nmr spectrum.

3,3'-Dimethoxy-5,5'-di-β-styryldiphenoquinone (5).—A solution of chromic acid (1.8 g) in acetic acid (15 ml) and pyridine (15 ml) was added dropwise to a stirred solution of 2-hydroxy-3-methoxystilbene[5] (2.26 g) in acetic acid (25 ml). The reaction mixture was then diluted with acetic acid (40 ml) and water (40 ml). Since the crystalline precipitate was difficult to remove by filtration, the suspension was subjected to centrifugation. The precipitate thus obtained was washed four times with ethanol and separated each time by centrifugation: yield, 980 mg (43%) of deep green shiny crystals; mp 210–213° dec. The ir spectrum of **5** shows a strong split absorption of 1605/1625 cm^{-1}. Diphenoquinone **5** is essentially insoluble in ethanol or methanol, but dissolves with a deep purple color in chloroform. *Anal.* Calcd for $C_{30}H_{24}O_4$ (448.49): C, 80.33; H, 5.39. Found: C, 80.21; H, 5.31.

4,4'-Dihydroxy-3,3'-dimethoxy-5,5'-di-β-styrylbiphenyl (6).—Hydrazine hydrate (2 ml) was added dropwise to a stirred solution of 3,3'-dimethoxy-5,5'-di-β-styryldiphenoquinone (350 mg) in chloroform (80 ml) and methanol (40 ml). The reaction mixture rapidly turned light yellow and a colorless crystalline precipitate formed. Filtration and recrystallization by dissolving in boiling chloroform and adding methanol gave 330 mg (94%) of colorless crystals, mp 241–242°. The ir spectrum of the compound shows an OH absorption at 3420 cm^{-1} (in KBr). *Anal.* Calcd for $C_{30}H_{26}O_4$: C, 79.98; H, 5.82; mol wt, 450.51. Found: C, 79.79; H, 5.85; mol wt (in acetone), 494.

Oxidation of 4,4'-Dihydroxy-3,3'-dimethoxy-5,5'-di-β-styrylbiphenyl.—DDQ (56 mg, 0.25 mmol) was added to a stirred suspension of **6** (113 mg, 0.25 mmol) in methanol (5 ml). As the DDQ dissolved, a dark green crystalline precipitate formed. Stirring was continued for 15 min. Filtration and recrystallization of the residue by dissolving in boiling chloroform and adding methanol gave 100 mg (88%) of green crystals, mp 210–213°. The ir spectrum of the product was completely identical with that of diphenoquinone **5** obtained by oxidation of 2-hydroxy-3-methoxystilbene with chromic acid.

3,5-Di-*t*-butyl-4-hydroxystilbene (7a).—A mixture of 1-[3,5-di-*t*-butyl-4-hydroxyphenyl]-2-phenylethanol **10a** (3.26 g, 10 mmol) and potassium hydrogen sulfate (410 mg) was kept for 10 min at 185–190°. The reaction mixture was then dissolved in a little ethanol and filtered in order to remove the inorganic material. Dilution of the filtrate with little water gave colorless crystals: yield, 2.5 g (81%); mp 91–93°. *Anal.* Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15; mol wt, 308.44. Found: C, 85.48; H, 9.03; mol wt (in benzene), 310.

Stilbenes 7b–d were prepared in the same manner as described for **7a**: dehydration temperature 150–155°; yields are shown in Table I.

3,5-Dimethyl-4-hydroxystilbene (7b) had mp 140–143°. *Anal.* Calcd for $C_{16}H_{16}O$ (224.29): C, 85.68; H, 7.19. Found: C, 86.09; H, 7.45.

3-Allyl-4-hydroxy-5-methoxystilbene (7c) had mp 103–104°. *Anal.* Calcd for $C_{18}H_{18}O_2$ (266.32): C, 81.17; H, 6.81. Found: C, 80.91; H, 6.70.

(13) L. R. Mahoney and M. A. DaRooge, *J. Amer. Chem. Soc.*, **89**, 5619 (1967); M. A. DaRooge and L. R. Mahoney, *J. Org. Chem.*, **32**, 1 (1967); J. Petranek, J. Pilar, and D. Doskocilova, *Tetrahedron Lett.*, 1979 (1967).

(14) J. D. Fitzpatrick, C. Steelink, and R. E. Hansen, *J. Org. Chem.*, **32**, 625 (1967). *Cf.* also C. Steelink and R. E. Hansen, *Tetrahedron Lett.*, 105 (1966).

(15) H. Richtzenhain and C. V. Hofe, *Ber.*, **72**, 1890 (1939).

(16) W. Manchot and C. Zahn, *Ann.*, **345**, 315 (1906).

3,5-Dimethoxy-4-hydroxystilbene (7d) had mp 123–124°. *Anal.* Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29; mol wt, 256.29. Found: C, 74.92; H, 6.49; mol wt (in benzene), 256.

1-[3,5-Di-*t*-butyl-4-hydroxyphenyl]-2-phenylethanol (10a).—3,5-Di-*t*-butyl-4-hydroxybenzaldehyde (9.36 g, 40 mmol) dissolved in ether (1500 ml) was allowed to react with benzylmagnesium chloride prepared from benzyl chloride (35 g) and magnesium (7 g) in ether (200 ml). After 5 hr of refluxing the reaction mixture was acidified with aqueous acetic acid. The ether layer was separated and dried over sodium sulfate. After evaporation of the solvent the residue was subjected to vacuum distillation at about 0.2-mm pressure and a bath temperature of 100° in order to remove the by-product bibenzyl. The oily residue was treated with pentane to give colorless crystals which were recrystallized from boiling pentane: yield 10.5 g (79%); mp 77–79°. *Anal.* Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26; mol wt, 326.42. Found: C, 80.75; H, 9.23; mol wt (in benzene), 323.

Compounds **10b–d** were prepared in the same manner as described for **10a**. Yields are shown in Table I.

1-[3,5-Dimethyl-4-hydroxyphenyl]-2-phenylethanol (10b) had mp 122–130°. *Anal.* Calcd for $C_{16}H_{18}O_2$ (242.30): C, 79.31; H, 7.49. Found: C, 79.18; H, 7.41.

1-[3-Allyl-4-hydroxy-5-methoxyphenyl]-2-phenylethanol (10c) had mp 101°. *Anal.* Calcd for $C_{18}H_{20}O_3$ (284.34): C, 76.03; H, 7.09. Found: C, 76.22; H, 7.29.

1-[3,5-Dimethoxy-4-hydroxyphenyl]-2-phenylethanol (10d) had mp 117–118°. *Anal.* Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61; mol wt, 274.30. Found: C, 69.83; H, 6.66; mol wt (in chloroform), 280.

Oxidation of 3,5-Di-*t*-butyl-4-hydroxystilbene (11a).—DDQ (568 mg, 2.5 mmol) was added to a stirred suspension of 3,5-di-*t*-butyl-4-hydroxystilbene (1.54 g, 5 mmol) in methanol (10 ml). As the DDQ dissolved a yellow crystalline precipitate formed. Filtration after 5 min gave 1.10 g (71%) of yellow crystals, mp 202–204°. Recrystallization by dissolving in a little chloroform and adding methanol raised the melting point to 207–209°. *Anal.* Calcd for $C_{44}H_{54}O_2$: C, 85.94; H, 8.85; mol wt, 614.87. Found: C, 85.75; H, 8.87; mol wt (in benzene), 610.

Oxidation of 3,5-Dimethyl-4-hydroxystilbene (11b).—A solution of 3,5-dimethyl-4-hydroxystilbene (2.24 g, 10 mmol) in benzene (200 ml) was added dropwise under nitrogen to a stirred solution of potassium ferricyanide (16.5 g) and potassium hydroxide (3 g) in water (150 ml). After 10 min of stirring, the benzene layer was separated, washed with water, shaken with sodium sulfate, filtered, and evaporated to give a pale yellow crystalline residue. It was washed with methanol and removed by filtration to give 2.1 g (94%) of yellow crystals, mp 134–135°. Recrystallization by dissolving in warm benzene, adding methanol, and evaporating part of the solvent did not raise the melting point. *Anal.* Calcd for $C_{32}H_{30}O_2$ (466.56): C, 86.06; H, 6.77. Found: C, 86.12; H, 6.84.

Oxidation of 3-Allyl-4-hydroxy-5-methoxystilbene (11c).—A solution of 3-allyl-4-hydroxy-5-methoxystilbene (1.07 g, 4 mmol) in benzene (125 ml) was added under nitrogen to a stirred solution of potassium ferricyanide (6.6 g) and potassium hydroxide (1.2 g) in water (60 ml). After 5 min, additional benzene was added and the benzene layer was separated, washed with water, shaken with sodium sulfate, and filtered. Evaporation of the solvent *in vacuo* gave an oily residue which crystallized upon treatment with methanol. The yield of yellow crystalline product was 0.9 g (84%), melting between 126 and 129° dec. *Anal.* Calcd for $C_{36}H_{34}O_4$: C, 81.48; H, 6.46; mol wt, 530.63. Found: C, 81.76; H, 6.41; mol wt (in benzene), 521.

Oxidation of 3,5-Dimethoxy-4-hydroxystilbene (11d).—A solution of 3,5-dimethoxy-4-hydroxystilbene (512 mg, 2 mmol) in benzene (15 ml) was added dropwise under nitrogen to a stirred solution of potassium ferricyanide (3.3 g) and potassium hydroxide (0.6 g) in water (30 ml). A colorless crystalline precipitate formed immediately, and stirring was continued for 15 min. The reaction product was then removed by filtration, dried, and recrystallized by dissolving in little chloroform and adding methanol, and passing a stream of nitrogen through the green solution: yield 350 mg (69%) of light green to yellow crystals; mp 180–185° dec (the substance turns deep red upon heating). The ir spectrum (in KBr) shows a strong absorption band at 1645 cm^{-1} (shoulder at 1625 cm^{-1}). *Anal.* Calcd for $C_{32}H_{30}O_6$: C, 75.25; H, 5.92; mol wt, 510.56. Found: C, 75.15; H, 5.99; mol wt (in chloroform), 446.

Acid-Catalyzed Addition of Methanol to 11a (12a).—Bisquinone methide **11a** (154 mg, 0.25 mmol) was dissolved in a mixture of ether (10 ml) and methanol (10 ml) acidified with a trace of HCl vapor. As the yellow color of the solution faded, a colorless crystalline precipitate formed. Filtration gave 110 mg (65%) addition product **12a**, mp 257–259°. *Anal.* Calcd for $C_{46}H_{62}O_4$: C, 81.37; H, 9.20; mol wt, 678.96. Found: C, 81.20; H, 9.36; mol wt (in benzene), 680.

Acid-Catalyzed Addition of Methanol to 11b (12b).—Bisquinone methide **11b** (446 mg, 1 mmol) was added to methanol (10 ml) which was acidified with a trace of HCl vapor. As the bisquinone methide dissolved, a colorless precipitate formed. After 2 hr of stirring the reaction mixture was filtered to give 400 mg (78%) of colorless crystalline product, mp 294–295°. Recrystallization from boiling methanol raised the melting point to 296–300°. *Anal.* Calcd for $C_{34}H_{38}O_4$ (510.64): C, 79.97; H, 7.50. Found: C, 80.21; H, 7.36.

Reduction of 11a with Sodium Iodide.—A solution of sodium iodide (100 mg) in acetic acid (10 ml) was added to a solution of bisquinone methide **11a** (154 mg, 0.25 mmol) in chloroform (10 ml). The reaction mixture was kept at 50° for 30 min and the liberated iodine was titrated with 0.1 *N* sodium thiosulfate solution (5 ml, corrected). The slightly reddish chloroform layer was separated and the aqueous layer was extracted once more with little chloroform. Evaporation of the combined chloroform solutions gave 90 mg (60%) of colorless crystalline residue, mp 89–92°. The mixture melting point with 3,5-di-*t*-butyl-4-hydroxystilbene was not depressed.

Reduction of 11d with Sodium Iodide.—Bisquinone methide **11d** (255 mg, 0.5 mmol) was added to a solution of sodium iodide (300 mg, 2 mmol) in acetic acid (10 ml). The reaction mixture was shaken for 10 min. The liberated iodine was titrated with 0.1 *N* sodium thiosulfate solution (10 ml, corrected) and the colorless precipitate which formed during the titration was removed by filtration: yield 176 mg (69%) of 3,5-dimethoxy-4-hydroxystilbene, mp 120–122°. The mixture melting point with authentic material was not depressed.

Catalytic Reduction of Bisquinone Methide 11a (13, 14).—Bisquinone methide **11a** (500 mg, 0.815 mmol), dissolved in ethyl acetate (20 ml), was reduced in the presence of Pd/C (10%) catalyst (300 mg). The hydrogen uptake (60 ml, 2.67 mmol) stopped after 80 min. Filtration and evaporation of the filtrate *in vacuo* gave an oily residue which crystallized upon treatment with a little aqueous methanol. The crystalline product was removed by filtration and subjected to vacuum sublimation at about 0.1 mm pressure and a bath temperature of 65°: yield of colorless crystalline **13**, 380 mg (75%); mp 56°. *Anal.* Calcd for $C_{22}H_{30}O$: C, 85.11; H, 9.74; mol wt, 310.49. Found: C, 85.21; H, 9.85; mol wt (acetone), 291.

The sublimation left a small amount of a colorless crystalline residue which was recrystallized from boiling methanol: yield 12 mg (2.4%); mp 218–221°. *Anal.* Calcd for $C_{44}H_{58}O_2$ (618.94): C, 85.39; H, 9.45. Found: C, 85.29; H, 9.53.

Registry No.—**5**, 19566-69-9; **6**, 19566-70-2; **7a**, 19566-71-3; **7b**, 19566-72-4; **7c**, 19566-73-5; **7d**, 19566-74-6; **10a**, 19566-75-7; **10b**, 19566-76-8; **10c**, 19566-77-9; **10d**, 19566-78-0; **11a**, 19594-77-5; **11b**, 19566-82-6; **11c**, 19566-83-7; **11d**, 19566-84-8; **12a**, 19566-79-1; **12b**, 19566-80-4; **13**, 15017-98-8; **14**, 19566-68-8.

Acknowledgment.—This work was started during the author's stay 1966–1967 at the Department of Organic Chemistry, Chalmers University of Technology, Gothenburg, Sweden. The author is very much indebted to Professor E. Adler for his kind hospitality. Thanks are also due to Dr. T. Vänngård, Department of Biochemistry, University of Gothenburg, for recording the esr spectra, and to tekn. lic. K. Lundquist, Chalmers University of Technology, for an authentic sample of 2-hydroxy-3-methoxystilbene.

Nonoxidative Routes to Quinones[1,2]

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On heating 1,4-dimethallyloxy-2,3,5,6-tetramethylbenzene (1) to 200° duroquinone (2) and 5,6-dimethallyl-2,3,5,6-tetramethyl-2-cyclohexene-1,4-dione (3) were obtained in 21 and 42% yields, respectively. On heating 4-methallyloxy-2,3,5,6-tetramethylphenol (5) and 1-benzyloxy-4-methallyl-2,3,5,6-tetramethylbenzene (6) to 200° about 68 and 84% yields, respectively, of 2 were obtained in addition to isobutene and 2-methyl-4-phenyl-1-butene. Thus a new nonoxidative method of preparation of certain quinones is at hand. The last step in the proposed mechanism involves the formation of an intermediate which breaks down *via* a cyclic mechanism to give the second carbonyl group of the quinone and an unsaturated hydrocarbon. Similarly allyldimethylcarbinol and 1-allylcyclohexanol yield acetone and cyclohexanone, respectively (together with propene), on heating to 290°.

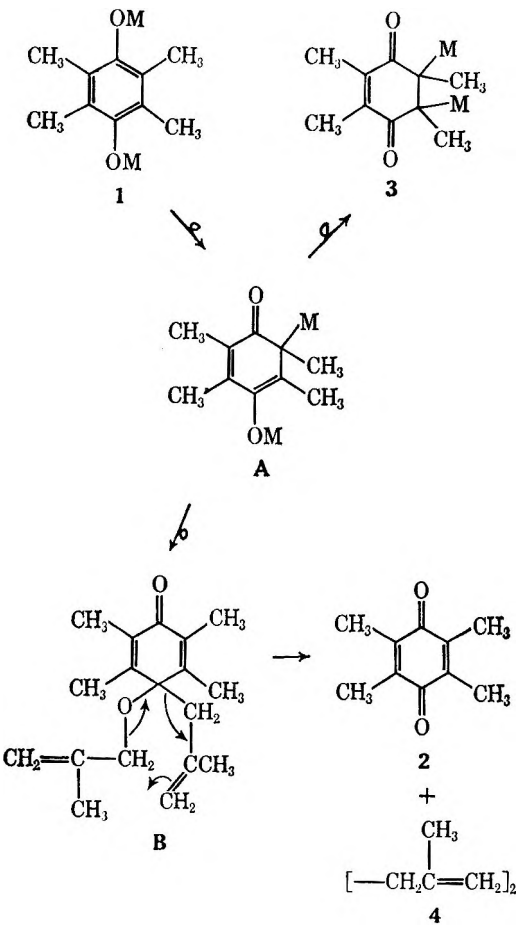
As pointed out previously[3] only four of the fifteen possible phenanthrenequinones are known. Also only three (the 1,2, 1,4, and 2,6 isomers) of the six possible naphthalenequinones are known. Since many hydroquinones corresponding to the unknown quinones are known, oxidative attempts to prepare the corresponding quinones have probably been made but not reported because of failure. Accordingly we initiated a program to develop what might be termed "nonoxidative" methods to prepare quinones. By nonoxidative methods we mean methods which do not require the use of conventional oxidants.

Our first successful result was obtained when 1,4-dimethallyloxy-2,3,5,6-tetramethylbenzene (1) yielded 21% duroquinone (2) on heating to 200°. In addition, a 42% yield of 5,6-dimethallyl-2,3,5,6-tetramethyl-2-cyclohexene-1,4-dione (3) was obtained. These results are explained as shown in Scheme I.[4]

The rearrangement of 1 to A represents the first step in a Claisen rearrangement.[5] Further shift of the methallyl group to the *para* position affords B which then undergoes pyrolysis into duroquinone (2) and dimethallyl (4). The last step represents another cyclic no-mechanism reaction and will be discussed further below. To show that the methallyl group can migrate to the *para* position in durene derivatives, 1-methallyloxy-2,3,5,6-tetramethylbenzene was shown to rearrange to 4-methallyl-2,3,5,6-tetramethylphenol in high yield on heating.

The poor yield of quinone 2 may be explained by assuming that the hypothetical intermediate A is readily converted irreversibly into 3. Pure 3 is recovered essentially unchanged when heated under similar conditions. This new nonoxidative route[6] to duroquinone

SCHEME I



suffers from the fact that methallylation of durohydroquinone affords the bismethallyl ether 1 in 39% yield at best as larger amounts (59%) of 3 are obtained (see Experimental Section).

To see if higher yields of duroquinone (2) could be obtained by a variation of the above route, the monomethallyl ethers 5, 6, and 7 were prepared (see Experimental Section) and heated. High yields of 2 were obtained in the cases of 5 and 6 but only tars were obtained with 7 (Scheme II). The successful results are explained by a path similar to that shown above for pyrolysis of 1 with one main difference. Because there is only one methallyl group in 5 and 6, no compound such as 3 can be formed irreversibly.

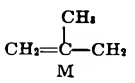
The preparation of 5 by alkylation of durohydroquinone with methallyl chloride proved complicated. Only about 18% pure 5 could be obtained. In addi-

(1) This work was taken from the Ph.D. thesis presented by F. W. H., June 1968, to The Ohio State University.

(2) This work was supported by Grant 5552 from the National Science Foundation. A nonoxidative route means that no external oxidant is used and hence the quinone produced is not subject to further oxidation.

(3) M. S. Newman and R. L. Childers, *J. Org. Chem.*, **32**, 62 (1967)

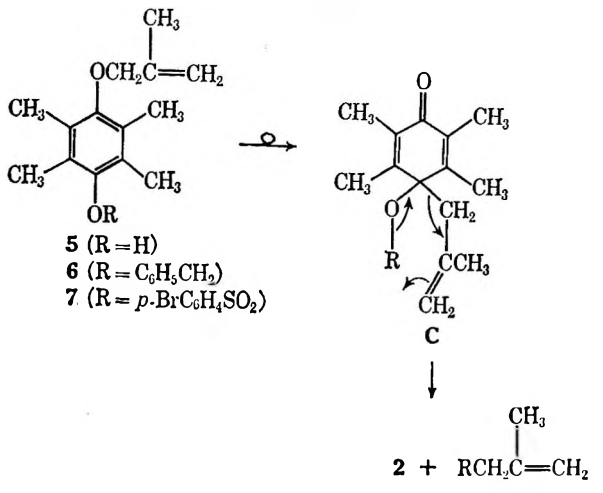
(4) In all formulas M represents methallyl, while letters A. etc., represent nonisolated hypothetical intermediates.



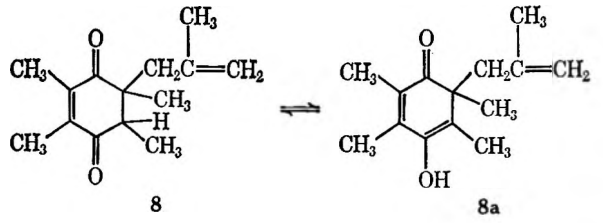
(5) For a recent review of the Claisen rearrangement, consult S. J. Rhoads in "Molecular Rearrangements," P. de Mayo, Ed., John Wiley & Sons, Inc., New York, N. Y., 1959, p 655.

(6) This route is really an intramolecular oxidation–reduction process in which the quinone represents the oxidized product and the diolefin (4) the reduced product. It is called a nonoxidative route because no external oxidant is used and hence the quinone produced is not subject to further oxidation.

SCHEME II



tion, about the same amount of **1** and larger amounts (*ca.* 45%) of a compound we believe to be 6-methallyl-2,3,5,6-tetramethyl-2-cyclohexene-1,4-dione (**8**) were obtained. The latter compound was isolated from the Claisen's alkali-insoluble fraction of the reaction products. The infrared (ir) spectrum of **8** (run neat between salt plates) showed a very weak OH band at about 3 μ, but on heating the intensity of this band increases. We believe the OH band is due to the enolic modification, **8a**. The nmr spectrum in carbon tetrachloride shows one CH_3 group as a doublet [δ 1.08 (J = 6 cps)] which fits structure **8**. On pyrolysis at 180°, **8** yielded duroquinone in high yield.



When the R group in **5** and **6** was methyl or ethyl, no pyrolysis to **2** took place as the ethers were recovered unchanged. In the pyrolysis of **6** to **2** and 2-methyl-4-phenyl-1-butene, the last step (*e.g.*, C when R = benzyl) represents a new variant of the cyclic process described[7] in that a carbon–oxygen, rather than a hydrogen–oxygen, bond is broken and a carbon–carbon bond (rather than a carbon–hydrogen) bond is formed.

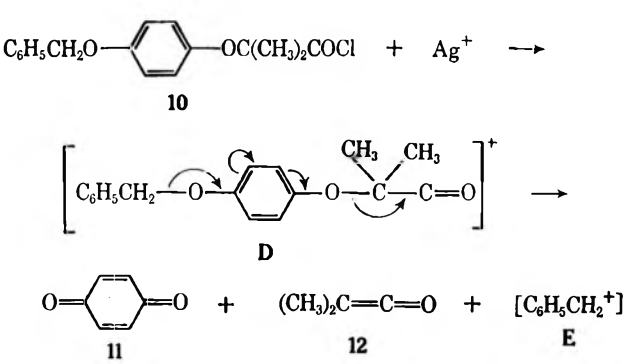
The last step in the pyrolysis of **5** to **2** and olefin is comparable with the formation of heptaldehyde and undecylenic acid by pyrolysis of ricinoleic acid.[8a] A complete discussion of this type of reaction (when R = H in C) and examples of its scope have been provided.[8a] The main difference is that in our work the intermediate C is hypothetical, whereas in the cases mentioned[7,8] definite compounds were used as starting materials. Two additional examples are provided herein by the pyrolysis of allyldimethylcarbinol and 1-allylcyclohexanol to acetone and cyclohexanone (plus propene).

In the pyrolysis of the monomethylallyl ether **5** a 27% yield of durohydroquinone (**9**) was obtained in addition to a 68% yield of quinone **2**. The formation of **9** may have been due to homolytic cleavage of the methallyl oxygen bond. Such fragmentations have been observed before in studies of the Claisen rearrangement.[9] However, the formation of quinone **2** from **1** was not affected by the presence of free-radical trapping agents, such as an aryl mercaptan, and hence the mechanism outlined for **1** seems likely to be correct.

Thus, one method for preparing quinones without the use of an external oxidant is at hand. However, this route is only applicable to molecules in which the Claisen rearrangement to allylphenol types is prohibited because of appropriate substitution.[5] Therefore, we have attempted to find another route which would be more generally useful. Although our efforts in this area are not complete, a preliminary report of such a route seems in order because of success, even though the yields were low.

On treatment of a solution of α-p-benzyloxyphenoxyisobutyryl chloride (**10**) in acetronitrile with a solution of silver tetrafluoroborate in acetonitrile, a 10% yield of p-benzoquinone (**11**) was obtained. This result may be explained by postulating that silver ion first removes the chlorine by forming silver chloride and the oxocarbonium ion (D). The latter decomposes to yield a phenylcarbonium ion (E), dimethylketene (**12**), and **11** as shown in Scheme III.

SCHEME III



The formation of **12** was confirmed by passing a stream of nitrogen through the reaction mixture into cooled methanol. A 60% yield of methyl isobutyrate was obtained. The fate of E is not known at present. Considerable amounts of tarry materials are formed and may possibly arise from reaction of E with **10**, **11**, and **12**. We hope to improve this nonoxidative route by structural modifications of **10** so that a carbonium ion more stable than E be produced. Alternately, the inclusion of a substance in the reaction medium which would react effectively with the carbonium ion formed (E or another ion) might allow greater yields of quinones to be obtained.

The preparation of **10** was accomplished by routine methods as described in the Experimental Section.

(7) R. T. Arnold and G. Smolinsky, *J. Org. Chem.*, **25**, 129 (1960).

(8) (a) C. D. Hurd, "The Pyrolysis of Carbon Compounds," the Chemical Catalog Co., Inc., (Reinhold Publishing Corp.), New York, N. Y., 1929, p 164. (b) R. T. Arnold and G. Smolinsky, *J. Amer. Chem. Soc.*, **81**, 6443 (1959); **82**, 4918 (1960). (o) R. T. Arnold and G. Metzger, *J. Org. Chem.*, **26**, 5185 (1961).

(9) Pyrolysis of allyl-2,6-dimethyl-4-phenyl phenyl ether yielded 75% parent phenol instead of the expected out-of-the-ring Claisen product: A. Nickon and B. R. Aaronoff, *ibid.*, **29**, 3014 (1964).

Experimental Section[10]

1,4-Dimethallyloxy-2,3,5,6-tetramethylbenzene (1).—To 400 ml of a stirred, cooled solution of 41 g of durohydroquinone (1,4-dihydroxy-2,3,5,6-tetramethylbenzene)[11] in dimethylformamide (DMF) under nitrogen was added 12 g of sodium hydride. After the deep red reaction mixture was stirred for 3 hr, 50 g of freshly distilled methallyl chloride was added and the mixture heated on a steam bath for 8 hr. The solution was poured into 2 l. of 10% HCl; the product was taken into $CHCl_3$ and worked up as usual. The crystalline residue was recrystallized from methanol to yield 27 g (39%) of 1, mp 83–84°.

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.8; H, 9.5. Found: C, 78.9; H, 9.5.

Several attempts at methallylation in ethanol, benzene, and ethanol–DMF at temperatures ranging from 25° to reflux did not increase the yield of 1.

5,6-Dimethallyl-2,3,5,6-tetramethyl-2-cyclohexene-1,4-dione (3).—The mother liquors from the above 1 were removed and the yellow residue was chromatographed over silica gel, using 9:1 hexane–benzene as eluent. Distillation of the main fraction yielded 40 g (59%) of 3 as a yellow oil, bp 108–110° (0.1 mm).

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.8; H, 9.5. Found: C, 78.9; H, 9.7.

Spectral data (ir and nmr) were consistent with 3 but do not distinguish between *meso* and racemic forms.

4-Methallyloxy-2,3,5,6-tetramethylphenol (5).—To a stirred cooled solution of 82 g of 1,4-dihydroxy-2,3,5,6-tetramethylbenzene in 400 ml of DMF was added 2.4 g of NaH under nitrogen. After stirring for 3 hr, 27 g of methallyl chloride was added in one portion. Stirring at reflux was continued for 8 hr. After pouring on 1 l. of 10% HCl, the product was extracted with benzene. The combined benzene extracts were washed with Claisen's alkali. The alkaline extract afforded 4.0 g (18% calculated on 0.1 mol as 100%) of 5, mp 121–122° after recrystallization from Skellysolve C (petroleum ether, bp 90–97°). This product proved identical with the 5 prepared by the alternate route described below.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.4; H, 9.1. Found: C, 76.1; H, 9.1.

Durenequinone (2).—This quinone, mp 109–110°, was prepared from durene[12] as described.[13] Reduction to durohydroquinone, mp 230–233°, was carried out quantitatively as described.[11]

4-(Methallyloxy)-2,3,5,6-tetramethylphenol (5).—As poor yields of 5 were obtained in attempts to monoalkylate durohydroquinone, a synthetic route from 2,2′,3,3′,5,5′,6,6′-octamethylbenzophenone was studied.

To a stirred suspension of 268 g of $AlCl_3$ in 1 l. of CS_2 was added a solution of 120 g of phosgene in 500 ml of cold CS_2 while the temperature was held at 0–10° (1 hr). After being stirred at 5° for 4 hr and at 25° for 14 hr the mixture was poured into 2 l. of 10% HCl. After a conventional work-up the neutral fraction was recrystallized three times from methanol to yield 83 g (35%) of octamethylbenzophenone,[14] mp 161.0–161.5°.

To a cooled solution prepared from 65 g of acetic anhydride, 30 g of concentrated H_2SO_4 and 25 g of 30% H_2O_2 was added 22.9 g of the above ketone. The mixture was held at 5° for 2 hr and then diluted with water. The crude solid ester thus obtained was heated at reflux for 8 hr with a solution of 10 g of KOH in 60 ml of alcohol and 15 ml of water. After acidification with HCl, the products were taken into ether–benzene. Extraction with 10% $NaHCO_3$ solution removed the carboxylic acid. After removal of solvent, 10.4 g (57% from ester) of durenol was obtained as a solid, mp 121–122°.[15,16] Durenol was converted into 4-aminodurenol, mp 176–178°, in 94% yield as described.[17]

To a rapidly stirred solution of 15.6 g of 4-aminodurenol in 100 ml of DMF at 5–10° under nitrogen was added 2.4 g of sodium hydride in portions during 15 min. After stirring at 20–25° for 30 min, 12 g of methallyl chloride was added. After 4 hr at reflux, the mixture was poured into 400 ml of 10% NaOH and the products were isolated in the usual way after extraction with $CHCl_3$. Chromatography over silica gel (benzene) provided 5.0 g (25%) of product least strongly absorbed (probably an N,O-dimethallylated product not further studied except to show that a secondary amino hydrogen was present) and 14.5 g (68%) of a primary amine. Since the latter was sensitive to air, an ethereal solution was treated with hydrogen chloride to yield colorless crystals, mp 222–223°, of the hydrochloride of 4-amino-1-methallyloxy-2,3,5,6-tetramethylbenzene.

Anal. Calcd for $C_{14}H_{22}ClNO$: C, 65.7; H, 8.5; N, 5.7. Found: C, 65.6; H, 8.6; N, 5.5.

A cold solution (*ca.* 5°) of 19 g of the above salt and 15 ml of isoamyl nitrite in 200 ml of 50% acetic acid was slowly added to a boiling solution of 50 g of K_2SO_4 and 25 g of H_2SO_4 in 200 ml of water in a flask equipped with a large-bore condenser as much gas was evolved. The cooled mixture was worked up as usual (benzene–ether) to yield 10.5 g (55%) of 5, mp 116–118°.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.4; H, 9.1. Found: C, 76.6; H, 9.1.

4-Ethoxy-1-methallyloxy-2,3,5,6-tetramethylbenzene.—Methallylation in DMF of 4.0 g of 4-ethoxy-2,3,5,6-tetramethylphenol[18] yielded 2.2 g (44%) of pure 4-ethoxy-1-methallyloxy-2,3,5,6-tetramethylbenzene, mp 53.5–55.0° (recrystallized from methanol).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.4; H, 9.7. Found: C, 77.6; H, 9.7.

Essentially the same procedure[18] was used to prepare 4-methoxy-2,3,5,6-tetramethylphenol, mp 111–112°, in high yield from trimethyl phosphite and durenequinone.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.4; H, 8.9. Found: C, 73.2; H, 8.8.

Methallylation of the methoxy compound afforded of pure 4-methoxy-1-methallyloxy-2,3,5,6-tetramethylbenzene, mp 40–41° after crystallization from methanol. The analytical sample was sublimed.

Anal. Calcd for $C_{15}H_{22}O_2$: C, 77.0; H, 9.4. Found: C, 77.2; H, 9.4.

1-Benzyloxy-4-methallyloxy-2,3,5,6-tetramethylbenzene (6).—A solution of 4.4 g of 5 in 50 ml of DMF was stirred with 0.5 g of sodium hydride for 4 hr after which 2.5 g of benzyl chloride was added. The mixture was kept at room temperature for 8 hr and then at 100° for 4 hr. After pouring into 250 ml of 10% KOH solution, the mixture was extracted with benzene. After the usual work-up, recrystallization of the residue from methanol afforded 5.1 g (82%) of 6, mp 82–83° (analytical sample sublimed).

Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.3; H, 8.3. Found: C, 81.3; H, 8.1.

1-*p*-Bromophenylsulfonyloxy-4-methallyloxy-2,3,5,6-tetramethylbenzene (7).—The preparation of 7 from 5 was effected essentially as described[19] in 95% yield to yield 7 as a colorless solid, mp 114–115° after crystallization from ethanol.

Anal. Calcd for $C_{20}H_{23}BrO_4S$: C, 54.8; H, 5.2; Br, 18.2. Found: C, 55.0; H, 5.3; Br, 17.9.

Methallylation of Durenol.—To a stirred refluxing suspension of 60 g of durenol and 28 g of KOH in 100 ml of benzene and 200 ml of ethanol was added 68 g of methallyl chloride. After the mixture was heated for 8 hr, 300 ml of Claisen's alkali was added and the mixture was cooled. The alkaline layer was separated from the benzene layer and twice extracted with 100-ml portions of benzene. After the usual work-up, distillation of the product in the benzene layer yielded 14.0 g (17.5%) of 1-methallyloxy-2,3,5,6-tetramethylbenzene, bp 92–94° (0.4 mm), and 27.1 g

(10) All melting points were taken on a Fisher-Johns apparatus. Microanalyses were by the Galbraith Laboratories, Knoxville, Tenn. Nmr spectra for all new compounds were obtained on a Varian A-60 spectrometer and are reported in the thesis of F. W. H. The phrase "worked up in the usual way" means that an organic layer (usually ether–benzene) of the reaction products was washed with portions of Claisen's alkali and/or dilute hydrochloric acid, followed by saturated salt solution The organic layer was then filtered through a cone of anhydrous $MgSO_4$ and concentrated on a rotary evaporator. The Claisen's alkali was prepared by dissolving 35 g of KOH in 25 ml of water, cooling, and diluting with 100 ml of methanol.

(11) L. I. Smith and A. Dobrovolny, *J. Amer. Chem. Soc.*, **48**, 1420 (1926).

(12) We thank the Esso Research and Engineering Co., Baytown, Texas, for a generous gift of durene which was purified by recrystallization from ethanol.

(13) L. I. Smith in "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 254.

(14) H. Galenkamp and A. C. Faher, *Rec. Trav. Chim.*, **77**, 850 (1958). See also R. R. Rekker and W. T. Nauta, *ibid.*, **77**, 714 (1958).

(15) G. Lejeune, M. Sy, and A. Cheutin, *Bull. Soc. Chim. Fr.*, 1073 (1957), report mp 117–120°.

(16) A. Barnsworth, U. S. Patent 2,864,871 (1958).

(17) L. I. Smith and W. M. Schubert, *J. Amer. Chem. Soc.*, **70**, 2656 (1948).

(18) F. Ramirez, E. H. Cohen, and S. Dershowitz, *ibid.*, **81**, 4338 (1959).

(19) S. E. Hazlet, *ibid.*, **60**, 399 (1938).

(24%) of 4-methallyl-1-methallyloxy-2,3,5,6-tetramethylbenzene, bp 114–116° (0.4 mm).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.3; H, 9.8. Found: C, 82.1; H, 10.0. Calcd for $C_{18}H_{26}O$: C, 83.7; H, 9.9. Found: C, 83.5; H, 10.0.

From the above alkaline extracts there was obtained by chromatography over silica gel (5% ethyl acetate in benzene elution) 5 g (12%) of durenol and 21 g (27%) of 4-methallyl-2,3,5,6-tetramethylphenol. The latter was identified by conversion into the brosylate and comparison with a known sample, mp 144.5–146.0°, since the phenol was low melting.

Anal. Calcd for $C_{20}H_{23}BrO_3S$: C, 56.8; H, 5.5. Found: C, 56.8; H, 5.5.

Ethyl 2-(4-Benzyloxyphenoxy)-2-methylpropanoate.—A stirred solution of 100 ml of ethanol, 10.0 g of 4-benzyloxyphenol,[20] 10.0 g of ethyl α-bromoisobutyrate, and 2.8 g of potassium hydroxide was heated at reflux for 36 hr. Distillation of the neutral fraction yielded 8.1 g (55%) of desired ester, bp 167–170° (0.3 mm).

Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.6; H, 7.0. Found: C, 72.3, H, 7.0.

Alkaline hydrolysis and recrystallization of the acid from 3:1 Skellysolve C–ethanol afforded **2-(4-benzyloxyphenoxy)-2-methylpropanoic acid**, mp 130.5–131.5°, in high yield.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.4; H, 6.3. Found: C, 71.4; H, 6.2.

2-(4-Benzyloxyphenoxy-2-methylpropanoyl Chloride (10).—A mixture of 2.9 g of the above acid and 2.20 g of PCl_5 was magnetically stirred under dry nitrogen. After 30 min, the mixture liquefied. After further stirring for 90 min, the mixture was warmed to 60° and held under vacuum until all $POCl_3$ had been removed (absence of band at 7.75 μ). This material was used in the following experiment. The analytical sample was held under a vacuum of 0.2 mm for 24 hr and sealed under nitrogen.

Anal. Calcd for $C_{17}H_{17}ClO_3$: C, 67.0; H, 5.6; Cl, 11.7. Found: C, 67.1; H, 5.6; Cl, 11.4.

Quinone 11 from 10.—A solution of 6.1 g of **10** and 4.0 g of silver tetrafluoroborate in 100 ml of dry acetonitrile was stirred at room temperature for 8 hr during which time the solution ranged from colorless at the start through red to black. After heating to reflux for 2 hr, the solution was poured into 300 ml of 10% hydrochloric acid. A benzene extract of the products was treated as usual and concentrated to dryness. Vacuum sublimation yielded 0.22 g (10%) of 1,4-benzoquinone, mp and mmp 115–117° with authentic sample. Essentially the same result was obtained when the reaction was run in 2:1 dimethyl resorcinol–acetonitrile.

Pyrolysis Experiments.—All pyrolyses were carried out under nitrogen in clean flasks which had been steamed and dried.

1,4-Dimethallyloxy-2,3,5,6-tetramethylbenzene (1).—In a typical experiment 50.0 g of **1** was heated at 190–200° for 2 hr with a slow stream of nitrogen leading into a cooled solution of bromine in carbon tetrachloride. Purification of the reaction mixture by chromatography over silica gel using benzene–petroleum ether afforded 5.1 g (21%) of **2**, mp and mmp 110–111° with an authentic sample.[13] The second fraction was 20.4 g (42%) of **3**, identical in every respect with that prepared by methallylation of durohydroquinone. Only resinous material was obtained on further elution. Removal of solvent from the bromine–carbon tetrachloride trap yielded 15.0 g (19%) of colorless crystals, mp 95–98°. Recrystallization from methanol raised the melting point to 100.5–102.0° with little loss. This product proved essentially identical with a similar product prepared by addition of bromine to dimethallyl.[21]

Anal. Calcd for $C_8H_{14}Br_4$: C, 22.3; H, 3.3; Br, 74.4. Found: C, 22.3; H, 3.3; Br, 74.2.

When the above pyrolysis was carried out in the presence of equimolar 2-naphthalenethiol, a mixture was obtained from which a 25% yield of durohydroquinone, mp 231–233°, and a 45% yield of 2-naphthyl disulfide were isolated. When equal moles of **2** and 2-naphthalenethiol were heated at 200° for 2.5 hr, good yields (>50%) of durohydroquinone and 2-naphthyl disulfide,[22] mp 134–135°, were obtained.

4-Methallyloxy-2,3,5,6-tetramethylphenol (5).—Similarly, 22.0 g of **5** was heated at 200° for 20 min. A benzene solution of the products yielded 4.5 g (27%) of durohydroquinone, mp 231–233°. By sublimation of the remainder of the products was obtained 11.2 (68%) of **2**, mp 110–111°. From the carbon tetrachloride trap was isolated 7.5 g (35%) of 1,2-dibromo-2-methylpropane, bp 147–150°.

Anal. Calcd for $C_4H_8Br_2$: C, 22.2; H, 3.7; Br, 74.1. Found: C, 22.0; H, 3.7; Br, 74.0.

When the above pyrolysis was carried out for 20 min in the presence of 2-naphthalenethiol, essentially the same yields of products were obtained.

Pyrolysis of methyl and ethyl ethers of **5** resulted in recovery of the starting materials. Pyrolysis of the *p*-bromobenzenesulfonyl derivative of **5** yielded only tars.

1-Methallyloxy-2,3,5,6-tetramethylbenzene.—On heating 1-methallyloxy-2,3,5,6-tetramethylphenol at 200° for 2 hr there was isolated an 89% yield of the above 4-methallyl-2,3,5,6-tetramethylphenol, characterized[19] as the brosyl derivative by mp and mmp 144–146° and by ir and nmr spectra.

Registry No.—**1**, 19613-65-1; **3**, 19587-88-3; **5**, 19587-89-4; **6**, 19587-90-7; **7**, 19587-91-8; 4-ethoxy-1-methallyloxy-2,3,5,6-tetramethylbenzene, 19587-92-9; 4-methoxyl-2,3,5,6-tetramethylphenol, 19587-93-0; 4-methoxy-1-methallyloxy-2,3,5,6-tetramethylbenzene, 19587-94-1; 4-methallyl-1-methallyloxy-2,3,5,6-tetramethylbenzene, 19587-95-2; ethyl 2-(4-benzyloxyphenoxy)-2-methylpropanoate, 19587-96-3; 2-(4-benzyloxyphenoxy)-2-methylpropanoic acid, 17413-75-1; 1,2-dibromo-2-methylpropane, 594-34-3.

(20) Crude 4-benzyloxyphenol (Aldrich Chemical Co.) was distilled [bp 155–159° (0.3 mm)] and the distillate was recrystallized from Skellysolve C to yield a solid, mp 123.0–124.5°.

(21) The authors thank Dr. K. Greenlee, Chemical Samples Co., Columbus, Ohio, for a generous gift of pure 2,5-dimethyl-1,5-hexadiene.

(22) H. R. Al-Kazimi, D. S. Tarbell, and D. Plant, *J. Amer. Chem. Soc.*, **77**, 2479 (1955).

The Formation of Unsaturated Carbenes by Alkaline Treatment of N-Nitrosooxazolidones[1,2]

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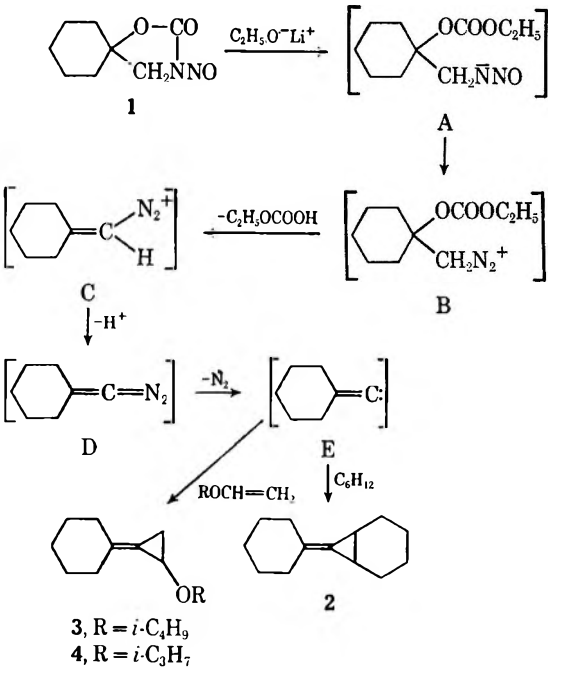
Treatment of 5,5-disubstituted N-nitrosooxazolidones with alkoxides initiates a series of reactions which are best explained by postulating the formation of unsaturated carbenes, $:C{=}CR_2$. The latter react with olefins, such as cyclohexene or alkyl vinyl ethers, to yield disubstituted methylenecyclopropanes, and with alcohols, ROH, by insertion into the O–H bond to yield vinyl ethers, $R_2C{=}CHOR'$ (see Table I). Treatment of 3-nitroso-1-oxa-3-azaspiro[4.5]decan-2-one (1) with sodium hydroxide in D_2O and with sodium methoxide in CH_3OD affords $(CH_2)_5CHCDO$ (after treatment with H_2O) and $(CH_2)_5C{=}CDOCH_3$, respectively. The mechanistic implications of these facts are discussed.

In previous work on the behavior of nitrosooxazolidones when treated with bases, all of the products isolated could be satisfactorily accounted for by posulating the intermediacy of unsaturated carbonium ions.[3-6] As a result of the development of carbene chemistry, Hine suggested that in certain cases an unsaturated carbene might be involved instead.[7] That this hypothesis is correct has recently been demonstrated.[8] In this paper a more detailed account of this work is given.

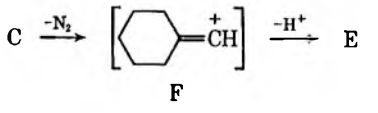
When 3-nitroso-1-oxa-3-azaspiro[4.5]decan-2-one (1) was suspended (partly dissolved) in cyclohexene and treated with lithium ethoxide[9] at room temperature an exothermic reaction took place rapidly to afford a good yield (isolated) of bicyclo[4.1.0]hept-7-ylidenecyclohexane (2).[10] In similar reactions of 1 with isobutyl vinyl ether and isopropyl vinyl ether, there were obtained 2-isobutoxycyclohexylidenecyclopropane (3) and 2-isopropoxycyclohexylidenecyclopropane (4) in good yields (isolated), respectively. Since the formation of cyclopropane rings by reaction of suitable precursors in the presence of olefins is generally accepted as evidence that a carbene is involved, the above reactions provide evidence that the unsaturated carbene (E) is an intermediate, as shown in Scheme I.

SCHEME I



The explanation (see Scheme I) for the paths by which the products are formed starts out as before[4] by assuming attack of ethoxide ion at the carbonyl function of 1 to yield intermediate A. As in previous cases[3,4] no attempt is made to time proton movements in the intermediate stages of conversion of the ring-opened intermediate, A, to the diazonium ion, B.[11] We believe that the diazonium character imparted to the nitrogens is responsible for increased acidity of the hydrogens on the adjacent carbon.[12] Thus the base-promoted elimination of ethyl bicarbonate to form C is facilitated. As Hine hypothesized[7] C can then lose a proton to yield D which loses nitrogen to form the unsaturated carbene (E), which reacts as expected with the olefins indicated to give 2, 3, and 4.

Alternately, C could first lose nitrogen to yield the unsaturated carbonium ion (F), which might lose a proton to yield E or react directly to give other products.[13]



(1) This research was supported by Research Grant GP-5552X from the National Science Foundation.

(2) Taken from the Ph.D. thesis presented by A. O. M. O. to The Ohio State University, 1968.

(3) M. S. Newman, *J. Amer. Chem. Soc.*, **71**, 378 (1949).

(4) M. S. Newman and A. Kutner, *ibid.*, **73**, 4199 (1951).

(5) M. S. Newman and W. M. Edwards, *ibid.*, **76**, 1840 (1954).

(6) M. S. Newman and A. E. Weinberg, *ibid.*, **78**, 4654 (1956).

(7) J. Hine, "Divalent Carbon," The Ronald Press Co., New York, N. Y., 1964, pp 89–90. Other references in which unsaturated carbenes are suggested are as follows: (a) A. A. Bothner-By, *J. Amer. Chem. Soc.*, **77**, 3293 (1955); (b) D. Y. Curtin, E. W. Flynn, and R. F. Nystrom, *ibid.*, **80**, 4599 (1958); (c) W. M. Jones, M. H. Grasley, and W. S. Brey, Jr., *ibid.*, **85**, 2754 (1963); (d) D. Y. Curtin, J. A. Kampmeier, and B. R. O'Connor, *ibid.*, **87**, 863 (1965); and (e) K. L. Erickson and J. Wolinsky, *ibid.*, **87**, 1142 (1965).

(8) M. S. Newman and A. O. M. Okorodudu, *ibid.*, **90**, 4189 (1968).

(9) Prepared as described in W. M. Jones, M. H. Grasley, and W. S. Brey, Jr., *ibid.*, **85**, 2754 (1963).

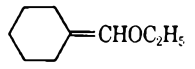
(10) M. Tanabe and R. A. Walsh, *ibid.*, **85**, 3522 (1963).

(11) See R. A. Moss and S. M. Lane [*ibid.*, **89**, 5655 (1967)] for a discussion of the mechanisms involved in the treatment of nitrosourethans with alkali. The cyclic nitrosourethans we are dealing with introduce additional complications concerning mechanism but much is common to the two systems. In the cyclic urethans, the elimination of a monoalkyl carbonate introduces unsaturation into the molecule, a feature absent in the other cases discussed by Moss and Lane.

(12) For discussions of similar problems in reactions of nitrosamides with bases, see E. H. White, *ibid.*, **77**, 6014 (1955), and J. H. Bayless, A. T. Jurewicz, and L. Friedman, *ibid.*, **90**, 4465 (1968).

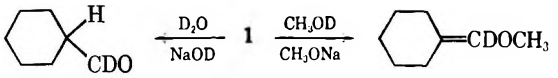
(13) In W. Kirmse ["Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 90], the hypothesis is made that diphenylcarbene adds a proton to form diphenylcarbonium ion prior to formation of benzhydryl methyl ether.

In order to try to distinguish between paths C → D → E and C → F → E the reaction of **1** with lithium ethoxide in the presence of a solvent composed of equimolar amounts of ethanol and cyclohexene was studied. The hypothesis was that E would react preferentially with cyclohexene to give **2** while F would react preferentially with ethanol to give the vinyl ether, ethoxymethylenecyclohexane (**5**). The ratio of **2** to **5** found would show the fate of C. These studies showed that larger amounts of **5** were formed (ratios of about 5–7 to 1) in the temperature ranges of about 25–65°, the higher ratios occurring at the higher temperature (see the Experimental Section).



5

After these results were obtained we realized that the formation of vinyl ethers did not prove that an unsaturated carbonium ion[6] is involved. The vinyl ether, **5**, might be formed by insertion of the unsaturated carbene, E, into the O–H bond of ethanol[14] and hence both **2** and **5** might be formed from E. Accordingly, a solution of **1** in CH_3OD was treated with dry sodium methoxide. The methylenic hydrogen in the **5a** formed was mainly deuterium. Treatment of **5** with sodium methoxide in CH_3OD did not result in incorporation of deuterium at the methylenic position. Similarly, when **1** was treated with alkali in D_2O the deuterated cyclohexylmethanal (**6**) was formed as during the work-up equilibration of the α hydrogen with water occurred.

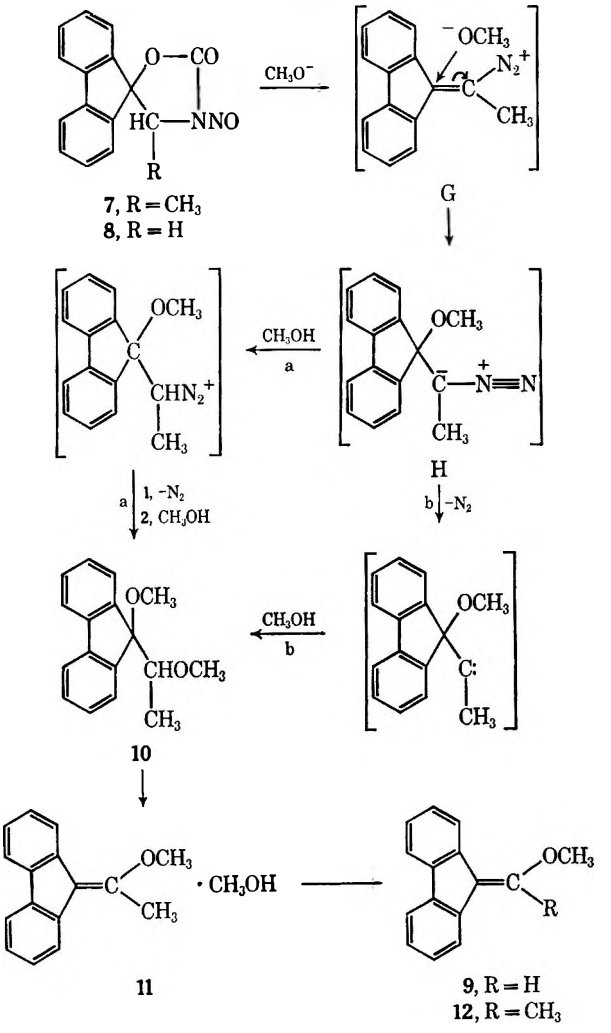


6 **5a**

These experiments indicate strongly that the unsaturated carbene (E) is the intermediate. If the unsaturated carbonium ion (F) were the precursor of **5a**, the methylenic hydrogen should be protium. A recent experiment performed by Dr. T. Patrick showed that when **1** was treated with insufficient sodium methoxide in CH_3OD, the **1** isolated after partial reaction contained no deuterium. This finding reinforces the argument that the path C → D → E is correct since deuterium exchange in **1** prior to reaction is ruled out. However, the possibility still remains that there may be deuterium exchange of some intermediate prior to the formation of E or F.

Since, in the work discussed above, the timing of the loss of a proton from the carbon to which the nitrogen was attached was involved, experiments were desired in which there was no hydrogen to be lost and hence the formation of an unsaturated carbene would be impossible. Accordingly, we prepared 3-nitroso-4-methylspiro[fluorene-9′,5-oxazolidin]-2-one (**7**) for study. This compound was chosen since a similar compound (**8**) without the 4-methyl group had already been shown[6] to yield 9-(methoxymethylene)fluorene (**9**) in 87% yield on treatment with methanolic potassium hydroxide. When a solution of **7** in methanol was treated with sodium methoxide at 5–10° there was formed in high yield a mixture composed of 9-methoxy-9-(1-methoxyethyl)-fluorene (**10**) and 9-(1-methoxyethylidene)fluorene methanolate (**11**) in a ratio of about 19:1 (see Experimental Section for details). On heating this mixture under vacuum the methanol was lost to yield 9-(1-methoxyethylidene)fluorene (**12**). The latter (**12**) could be partly reconverted into the alcoholate (**11**) on treatment with methanol but **11** could not be converted into **10** by treatment with neutral or alkaline methanol.[15] On gentle warming or on standing at room temperature **10** was easily converted into **11**. Thus **10** is shown to be the first product formed in the reaction of **7** with sodium methoxide in methanol and therefore an unsaturated carbonium is not the reactive intermediate, for, if it were, **11** and **12** would be expected to be formed but not **10**. Our explanation for the above results is shown in Scheme II.

SCHEME II



The conversion of **7** into G takes place as described for the conversion of **1** into A. Attack of methoxide ion at the 9 position of G leads to the hypothetical dipolar ion (H)[16] which could then yield the final product **10** by

(14) Tanabe and Walsh[10] reported the formation of a vinyl ether in a reaction involving an unsaturated carbene but did not attribute this to insertion of the carbene into the O–H bond of the alcohol. The formation of ethers by reaction of carbenes with alcohols has been reported. See R. M. G. Nair, E. Meyer, and G. W. Griffin, *Angew. Chem. Intern. Ed. Engl.*, **7**, 463 (1968), and references therein. In a private communication, Dr. J. Wolinsky of Purdue University has informed me that bromomethylenecyclohexane reacts with potassium *t*-butoxide to yield *t*-butoxymethylenecyclohexane.

(15) G. Wittig and M. Schlosser [*Ber.*, **94**, 1373 (1961)] showed that 9-(methoxymethylene)fluorene is converted into the 9-ethoxy compound on treatment with sodium ethoxide.

(16) For a discussion of reactions of a similar species, see ref 9.

paths a or b. Further work is in progress in an attempt to distinguish between these paths. In the earlier work[6] in which **8** was reported to yield **9** directly, no precautions regarding heating of the reaction product were taken so that if a compound comparable to **10** had been formed it would have been converted into **9**. Regardless of the details of mechanism regarding vinyl ether formation, further study of this method was undertaken and is described below.

Previous methods of forming vinyl ethers have involved acid-catalyzed reactions[17] or Wittig reagents.[18] The method starting from oxazolidones is unique in that basic reagents are used under very mild conditions.

The nitrosooxazolidones studied were **1**, **7**, **8**, **13**, and **14**. In general a solution of the nitrosooxazolidone in an alcohol at 0–5° was treated with a solution of 1 equiv of the corresponding sodium alkoxide. Nitrogen evolution was vigorous and controlled by the rate of addition of the alkali. The yields of vinyl ethers were generally very good and are reported in Table I. It may be seen

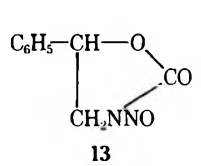
TABLE I

VINYL ETHER FORMATION FROM NITROSOOXAZOLIDONES

Nitroso-oxazolidone	Alcohol[a]	Product	Yield,[b] %
1	Methyl	Methyl ether[c]	85
1	Ethyl	Ethyl ether[c]	84
1	Propyl	1-Propyl ether[c]	80 (90)[d]
1	Isopropyl	2-Propyl ether[c]	71 (82)[d]
1	Butyl	1-Butyl ether[c]	85 (89)[d]
1	*t*-Butyl[e]	*t*-Butyl ether[c]	65 (72)[d]
1	Methallyl	Methallyl ether[c]	62[f]
14	Methyl	Methyl ether[c]	72
14	Butyl	1-Butyl ether[c]	64
13	Methyl	$C_6H_5C{\equiv}CH$[g]	65
13	Ethyl	$C_6H_5C{\equiv}CH$[g]	54
7	Methyl	Methyl ether[c]	85[h]
7	Ethyl	Ethyl ether[c]	81[h]
8	Methyl	Methyl ether[c]	90[h,i]
8	Ethyl	Ethyl ether	80[h,i]

[a] A solution of sodium alkoxide in the corresponding alcohol was used. [b] The yield represents distilled product homogenous by vpc. [c] All products were vinyl alkyl ethers, the vinyl group being that determined by the starting nitrosooxazolidone. [d] The yields in parentheses mean that additional vinyl ether was present in the forerun (see Experimental Section). [e] Potassium *t*-butoxide was used. [f] See Experimental Section for details. [g] The crude product contained some vinyl ether but no attempt was made to determine the yield accurately. [h] These products were isolated as solids by crystallization. [i] The initially found product was not the vinyl ether but the latter was formed on warming (see text).

that a general method for preparing vinyl ethers under alkaline conditions is at hand, except for the β-styryl vinyl ethers which would result from **13**. In the case of this phenyl derivative the formation of phenylacetylene takes precedence over vinyl ether formation.



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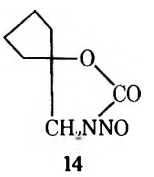
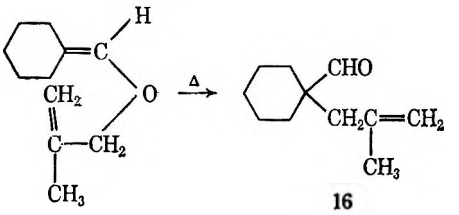


14

(17) D. B. Killian, G. F. Hennion, and J. A. Nieuwland, *J. Amer. Chem. Soc.*, **57**, 544 (1935); W. H. Watanabe and L. E. Conlon, *ibid.*, **79**, 2828 (1957).

(18) G. Wittig and M. Schlosser, *Ber.*, **94**, 1373 (1961); G. Wittig, W. Böll, and K. H. Krück, *ibid.*, **95**, 2514 (1962).

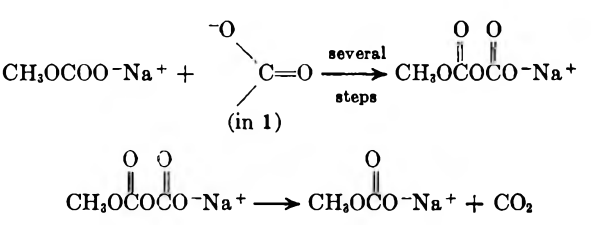
A synthetic use for the synthesis of tertiary aliphatic aldehydes is illustrated by the pyrolysis of methallyloxymethylenecyclohexane (**15**) to 1-methallylcyclohexanecarboxaldehyde (**16**). This Claisen-type rearrangement of allyl ethers has been reported.[19]



15 **16**

In general the reaction of **1** with alcohols took place rapidly as judged by the fact that the theoretical amount of nitrogen was evolved within minutes after the addition of 1 equiv of sodium alkoxide had been completed. However, if only catalytic amounts of sodium methoxide were used the rate of nitrogen evolution became quite slow (after the initial rapid evolution on addition of the methoxide) and about 1 day was required until gas evolution ceased. In these cases about 2 equiv of gas, one each of nitrogen and carbon dioxide, were evolved. We explain this fact by assuming that the base which attacks the carbonyl group in **1** (as in Scheme I) is sodium methylcarbonate (after the initially used sodium methoxide is converted into sodium methylcarbonate). By a series of steps similar to those in Scheme I there is generated a sodiomethyl derivative of carbonic acid anhydride, $NaOCOOCOOCH_3$, which decomposes into sodium methylcarbonate and CO_2 as shown in Scheme III.

SCHEME III



The fact that sodium methylcarbonate is a much weaker base than sodium methoxide accounts for the slower rate of reaction. The only alternate explanation for the facts involves a slow decomposition of $CH_3OCOO^-Na^+$ into CO_2 and $CH_3O^-Na^+$. We think the latter possibility is extremely unlikely.

Experimental Section[20]

Nitrosooxazolidones.—The known compounds, **1**,[3] **8**,[6] and **13**[4] were prepared essentially as described. The preparation of 3-nitroso-4-methylspiro[fluorene-9′,5-oxazolidin]-2-one (**7**) was started by a Reformatsky reaction of 36 g of fluorenone,[21] 51 g of ethyl α-brompropionate, and 22 g of activated zinc[22] in benzene to yield crude ethyl 2-(9-hydroxy-9-fluorenyl)propionate, which was not characterized but treated in 40 ml of methanol with 12.8

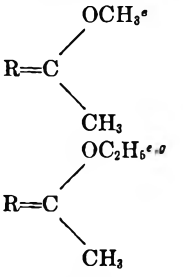
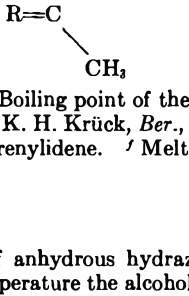
(19) C. D. Hurd and M. A. Pollack, *J. Amer. Chem. Soc.*, **60**, 1905 (1958).

(20) All melting points and boiling points are uncorrected. All microanalyses by the Galbraith Laboratories, Inc., Knoxville, Tenn. The term "worked up in the usual way" means that a solution of the products in an organic solvent, after washing with dilute alkali and/or acid, water, and saturated salt solution, was filtered through a cone of anhydrous magnesium sulfate. The solvent was then removed on a rotary evaporator.

(21) Prepared in 81% yield as described by E. H. Huntress, E. B. Hershberg, and I. S. Cliff, *ibid.*, **53**, 2720 (1931).

(22) L. F. Fieser and W. S. Johnson, *ibid.*, **62**, 576 (1940).

TABLE II
VINYL ETHERS

Vinyl ether	Registry no.	Bp (mm),[a] °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H
$(CH_2)_4C{=}CHOCH_3$	19684-48-1	58 (45)	74.9	10.8	75.1	10.9
$(CH_2)_4C{=}CHOC_4H_9$-*n*	19684-49-2	105–107 (48)	77.9	11.8	77.9	12.0
$(CH_2)_5C{=}CHOCH_3$[b]		85–89 (60)	76.1	11.2	76.3	11.4
$(CH_2)_5C{=}CHOC_2H_5$	19684-50-5	100 (100)	77.1	11.5	77.2	11.5
$(CH_2)_5C{=}CHOC_3H_7$-*n*	19684-51-6	112–114 (60)	77.9	11.8	77.8	11.8
$(CH_2)_5C{=}CHOC_3H_7$-*i*	19684-52-7	105–106 (65)	77.9	11.8	77.8	11.8
$(CH_2)_5C{=}CHOC_4H_9$-*n*[b]		105 (22)	78.5	12.0	78.4	12.1
$(CH_2)_5C{=}CHOC_4H_9$-*t*	19684-53-8	77–80 (10)	78.5	12.0	78.5	12.0
$(CH_2)_5C{=}CHOC_4H_7$[c]	19736-55-1	58–60 (1.5)	79.5	10.9	79.4	10.9
$R{=}CHOC_2H_5$[d,e]	19684-54-9	64–65[f]	86.3	6.3	86.6	6.6
		150 (0.4)	86.3	6.3	86.5	6.4
	19684-55-0	145–150 (0.4)	86.4	6.8	86.5	6.7

[a] Boiling point of the fraction on which analyses were obtained at the pressure listed. [b] Reported previously by G. Wittig, W. Böll, and K. H. Krück, *Ber.*, 95, 2514 (1962). [c] The methallyl group. [d] The corresponding methoxy compound has been reported.[6] [e] R = fluorenylidene. [f] Melting point. [g] Mp 70–71°.

g of anhydrous hydrazine. After standing for 15 hr at room temperature the alcohol was removed on a rotary evaporator and the excess hydrazine by keeping *in vacuo* over concentrated H_2SO_4. The crude solid was recrystallized from alcohol to give 48.5 g (90% from fluorenone) of 2-(9-hydroxy-9-fluorenyl)propionic acid hydrazide, mp 164–165°.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.6; H, 6.0; N, 10.4. Found: C, 71.6; H, 6.0; N, 10.3.

A solution of 13 g of $NaNO_2$ in 100 ml of water was added to a well-stirred solution of 46 g of the above hydrazide in 150 ml of 2 *N* HCl at 5–10°. Urea was added to destroy the excess HNO_2, then 100 ml of benzene and 200 ml of Skellysolve B (petroleum ether, bp 65–70°) were added. On warming to 70° gas evolution became vigorous (efficient provision for reflux important) and a solid began to precipitate. After all gas had been evolved and the mixture was cooled the solid was collected, dried, and recrystallized from benzene–alcohol to yield 34 g (80%) of 4-methylspiro[fluorene-9′,5-oxazolidin]-2-one, mp 234–235°. A sample was sublimed for analysis.

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.5; H, 5.2; N, 5.6. Found: C, 76.7; H, 5.4; N, 5.6.

A solution of 9.1 g of nitrosyl chloride in 30 ml of acetic anhydride was added slowly to a stirred suspension of 30.0 g of the above oxazolidone in 150 ml of dry pyridine at 0–5°. After stirring for a further 40 min the mixture was poured into ice water. The precipitate was collected, washed well with ice water, and dried *in vacuo*. Recrystallization from ethanol–Skellysolve B afforded 30.1 g (90%) of **7**, mp 156–157°.

Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.6; H, 4.3; N, 10.0. Found: C, 68.9; H, 4.5; N, 9.8.

The preparation of **14** is described below. Methyl 1-hydroxycyclopentylacetate, bp 90–92° (2 mm), was prepared in 64% yield by a Reformatsky reaction from cyclopentanone and methyl bromoacetate. To a stirred solution of 101 g of the hydroxy ester in 10 ml of dry methanol was added 42 g of anhydrous hydrazine. The mixture warmed spontaneously to 50° and solidified in 15 min. The solid was collected on a filter, washed with Skellysolve B, and dried *in vacuo* for 1 hr over concentrated H_2SO_4 to remove excess hydrazine. Recrystallization from methanol afforded 80 g (80%) of 1-hydroxycyclopentylacetic acid hydrazide, mp 142–144°. The analytical sample, mp 144.6–145.4°, was prepared by recrystallization from alcohol.

Anal. Calcd for $C_7H_{14}N_2O_2$: C, 53.1; H, 8.9; N, 17.7. Found:[23] C, 53.3; H, 8.7; N, 17.9.

(23) Analyses were by Mrs. E. H. Klotz in 1949.

A solution of 18 g of sodium nitrite in 30 ml of water was added dropwise to a stirred solution of 40 g of hydrazide in 150 ml of 2 *N* hydrochloric acid held at 8–12°. Then 150 ml of Skellysolve B was added and the mixture heated under reflux slowly to 65° when the evolution of nitrogen became vigorous. After standing overnight the solid was collected and added to more of the same obtained by further benzene–ether extraction of the aqueous layer. The combined solids were dried and recrystallized from benzene–Skellysolve B to yield 29.2 g (82%) of 1-oxa-3-azaspiro-[4,4]nonan-2-one, mp 100–102°. The analytical sample, mp 100.8–101.6° cor, was prepared by crystallization from benzene–Skellysolve B.

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.6; H, 7.9; N, 9.9. Found:[23] C, 59.9; H, 7.7; N, 10.1.

To a stirred mixture of 28.2 g of this oxazolidone in 55 ml of water, 55 ml of acetic acid, and 55 ml of concentrated HCl at 0–5° was added dropwise a solution of 14.5 g of sodium nitrite in 100 ml of water during 1 hr. The solid was collected, was washed with cold water, and dried *in vacuo*. Recrystallization from benzene–Skellysolve B gave 33.0 g (98%) of pale yellow **14**, mp 96.0–97.5°. The analytical sample, mp 97.6–98.2° with sintering at 94°, was prepared by crystallization from benzene–Skellysolve B.

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.4; H, 5.9. Found:[23] C, 49.2; H, 5.8.

Preparation of Vinyl Ethers (Table I).—The general procedure involved adding a solution of the sodium alkoxide in the alcohol in question to a cold (0–5°) suspension (part solution) of the nitrosooxazolidone in the same alcohol. Evolution of nitrogen was rapid and controlled by the rate of addition of alkoxide. After slightly more than 1 equiv of base had been added the theoretical amount of nitrogen was evolved. The mixture was then poured into water and the product extracted with ether–benzene as usual. Distillation was effected through a Nester–Faust spinning-band column. The yields of vinyl ethers having the boiling points listed in Table II are recorded in Table I. The infrared and nuclear magnetic resonance spectra are contained in the Ph.D. thesis[2] and were consistent with the structures assigned.

1-Methallylcyclohexanecarboxaldehyde (16).—A solution made by treating 10 g of sodium with 240 ml of methallyl alcohol was added slowly to a stirred ice-cold suspension of 18.4 g of **1** in 50 ml of methallyl alcohol until the theoretical amount of nitrogen had been collected. The mixture was worked up by diluting with water and worked up in the usual way. If distillation under reduced pressure were attempted mixtures of **15** and

16 were obtained. By chromatography over silica gel the first fraction eluted (2:1 hexane–benzene) was distilled to yield 8.5 g (51%) of pure **15**, bp 58–60° (1.5 mm).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.5; H, 10.9. Found: C, 79.4; H, 10.9.

The second fraction eluted (1:1 hexane–benzene) yielded 1.8 g (11%) of **16**, bp 68–70° (1.5 mm). This aldehyde was not analyzed but gave infrared and nmr spectra consistent with such a structure. The 2,4-dinitrophenylhydrazone, mp 141–142°, and semicarbazone, mp 195–196°, were prepared.

Anal. Calcd for $C_{17}H_{22}N_4O_4$: C, 58.9; H, 6.4; N, 16.2. Found: C, 58.8; H, 6.5; N, 16.1. Calcd for $C_{12}H_{21}N_3O$: C, 64.5; H, 9.5; N, 18.8. Found: C, 64.6; H, 9.7; N, 18.6.

On pyrolysis neat at 145–165° for 3 hr **15** was quantitatively converted into **16**.

9-Methoxy-9-(1-methoxyethyl)fluorene (10).—To a stirred suspension of 19 g of **7** in 125 ml of dry methanol at 5–10° was added a solution of sodium methoxide (prepared from 10 g of sodium and 115 g of methanol) until a slight excess had been added. The mixture was stirred for 30 min and poured into ice water. The product was isolated in high yield as usual using ether. Care was taken not to heat the product above room temperature. After drying *in vacuo* over $CaSO_4$, the product melted in the 110–115° range. This product had no ir absorption in the carbonyl region. The nmr spectrum showed a mixture of two compounds in a ratio of about 19:1. On crystallization from Skellysolve B using care not to overheat, a purer sample of the major component was obtained which gave an nmr spectrum consistent with the structure **10**, *e.g.*, a doublet at τ 9.08, (8 cps, 3 H, $CHCH_3$), two singlets at 7.23 and 6.58 (3 H, each $-OCH_3$), a quartet at 6.74 (8 cps, 1 H, $-CHCH_3$ partly obscured by the singlet at 6.58), in addition to aromatic H.

On warming in Skellysolve B for longer times or on heating **10** was converted mainly into **11** which was purified by crystallization to yield **11**, mp 136–137°, whose nmr spectrum had three singlets at τ 7.42 ($=CCH_3$), 6.68 (CH_3OH),[24] and 6.20 ($=COCH_3$) in addition to aromatic H.

Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1. Found: C, 80.3; H, 7.3.

In order to remove the last traces of methanol from **11** slow heating to 165° at atmospheric pressure followed by vacuum distillation was needed to obtain **12** as an oil, bp ~150° (0.4 mm). We were unable to obtain **12** in solid form. However, a picrate, mp 175–176.5°, was prepared.

Anal. Calcd for $C_{22}H_{17}N_3O_8$: C, 58.6; H, 3.8; N, 9.3. Found: C, 58.3; H, 3.9; N, 9.5.

The nmr spectrum of **12** had a singlet (3 H) at τ 7.46 ($=CCH_3$), a singlet (3 H) at 6.23 ($=COCH_3$), and a multiplet (8 H) of aromatic hydrogens centered at 2.2.

Bicyclo[4.1.0]hept-7-ylidenecyclohexane (2).—A suspension of 3.9 g of lithium ethoxide[9] in 15 ml of freshly distilled cyclohexene was added under nitrogen to a stirred suspension of **1** in 25 ml of cyclohexene at room temperature. The reaction was exothermic and was kept at about 45° by cooling. Nitrogen evolution was quantitative. After stirring for 2 hr the mixture was worked up as usual. Distillation on a spinning-band column yielded 4.6 g (65%) of **2**: bp 68–70° (0.3 mm); $n^{25}D$ 1.5065 (lit.[10] 1.5070); mol wt, 176 (mass spectrograph[25]); ir band at 5.5 μ (1818 cm^{-1}, strong) characteristic of a double bond exocyclic to a cyclopropane ring.[26] The analytical sample was obtained by preparative vpc using a 5-ft column of 20% silicon rubber SE30 on 60–80 mesh Chromosorb P 609 at 125°.

Anal. Calcd for $C_{13}H_{20}$: C, 88.6; H, 11.4. Found: C, 88.6; H, 11.4.

The nmr spectrum was not sufficiently characteristic to be used as proof of structure (three unresolved peaks between τ 7.5 and 9.0). In different runs the yields varied from 40 to 65%, yields being lower when potassium *t*-butoxide was used.

2-Isobutoxycyclohexylidenecyclopropane (3).—A suspension of 7.36 g of **1** in freshly distilled isobutyl vinyl ether[27] was treated as in the preparation of **2** with 2.4 g of lithium ethoxide.[9] After the usual work-up distillation on a spinning-band column afforded 5.8 g (74%)[28] of **3**: bp 58–60° (0.4 mm); $n^{25}D$ 1.4725; ir band at 5.6 μ. The analytical sample was obtained by preparative vpc (at 140°) as for **2**. The nmr spectrum was in good agreement with the postulated structure.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.4; H, 11.4. Found: C, 80.4; H, 11.4.

2-Isopropoxycyclohexylidenecyclopropane (4).—On treatment of **1** as in the case of **2**, except that isopropyl vinyl ether[27] was used, there was obtained 5.8 g (85%)[28] of **4**, bp 100° (8 mm), $n^{22}D$ 1.4765, on the analytical sample obtained by preparative vpc as above. The nmr spectra showed excellent agreement with the postulated structure.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.9; H, 11.2. Found: C, 79.7; H, 11.2.

Competition between Cyclohexene and Ethanol for Unsaturated Carbene.—Suspension of **1** in a mixture of equimolar amounts of cyclohexene and ethanol with lithium ethoxide at temperatures from 3 to 30° resulted in vigorous reaction which caused the final temperatures to be in the 30–65° range. The products were worked up as usual and distilled at atmospheric pressure. By vpc analyses using a 2-ft column of silicon rubber SE-30 on 60–80 W 609 which had been standardized with known mixtures of ethoxymethylenecyclohexene and **2**, the mixtures were found to consist of these compounds in ratios of 4.7:1 to 6.8:1, the higher ratios being found when the final temperatures were higher.

Deuterium Experiments.—To an ice-cooled mixture of 1.84 g of **1**, 6 ml of CH_3OD,[29] and 5 ml of glyme (1,2-dimethoxyethane) was added 0.6 g of alcohol-free sodium methoxide. The reaction mixture (cooling bath removed) was stirred for 1 hr during the first 15 min of which gas evolution was complete and quantitative. After dilution with water and the usual work-up there was obtained 0.83 g (65%) of **5a**, bp 84–85° (55 mm). A part of this material was purified by preparative vpc and submitted to nmr analysis. The presence of a very small peak at τ 4.4 showed that only a very small amount of vinylic hydrogen was present. When the corresponding nondeuterated vinyl ether was treated with sodium methoxide in CH_3OD, the ratio of the peaks at τ 4.4 and 6.6 (OCH_3) was 1:3 as in the case of the untreated vinyl ether.

When a suspension of **1** in D_2O and glyme was treated under N_2 with a small excess of aqueous NaOD in D_2O nitrogen was evolved rapidly. After the usual work-up, which included washing with dilute H_3O^+ (loss of α deuterium), the aldehyde **6** was obtained in 45–50% yield. The nmr showed the absence of the aldehyde hydrogen (τ 0.6). In addition the ir band at 3.68 μ, characteristic of the aldehydic hydrogen, was absent in the product obtained from the reaction of **1** in D_2O.

Registry No.—**2**, 19690-02-9; **3**, 19690-03-0; **4**, 19690-04-1; **7**, 19713-85-0; **10**, 19684-42-5; **11**, 19684-43-6; **12** (picrate), 19684-44-7; **14**, 19684-45-8; **16**, 19684-46-9; **16** (2,4-dinitrophenylhydrazone derivative), 19713-86-1; **16** (semicarbazone), 19684-47-0; 2-(9-hydroxy-9-fluorenyl)propionic acid hydrazide, 19684-56-1; 4-methylspiro[fluorene-9′,5-oxazolidin]-2-one, 19684-57-2; 1-hydroxycyclopentylacetic acid hydrazide, 19684-58-3; 1-oxa-3-azaspiro[4.4]nonan-2-one 19684-59-4.

(24) For pure CH_3OH, τ is 6.62: L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," The Macmillan Co., New York, 1959, p. 55.

(25) We thank Dr. Ralph Dougherty for this determination.

(26) H. E. Simmons, E. P. Blanchard, and H. D. Hartzler, *J. Org. Chem.*, **31**, 295 (1966).

(27) We thank the General Aniline and Film Corp. for a generous gift of this vinyl ether.

(28) Repetition of the preparations of **2** and **4** by Dr. T. Patrick gave somewhat lower yields (50–57% **2** and 41% **4**). These results may be due to unfamiliarity with the procedure used by D. Okorodudu or to unknown variations in procedure.

(29) CH_3OD (99+%) was obtained from Brinkmann Instruments Inc., Westbury, N. J.

The α,α′ Annelation of Cyclic Ketones. Synthesis of Bicyclo[3.2.1]octane Derivatives

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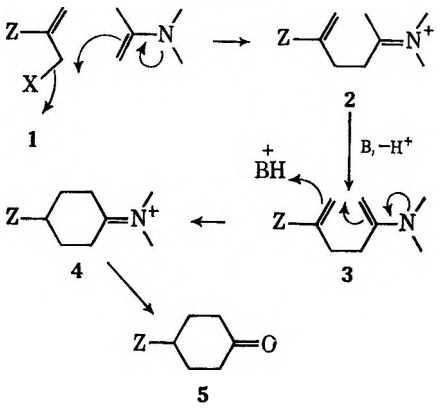
Reaction of cyclopentanone enamine with ethyl α-(1-bromomethyl)acrylate affords ethyl bicyclo[3.2.1]octan-8-one-3-*endo*-carboxylate. The reaction generally follows a pathway including alkylation and proton transfer to re-form an enamine, followed by Michael reaction. The preparation of *trans*-diaxial bicyclo[3.2.1]octanone diesters from γ-bromomesaconic ester and benzobicyclo[3.2.1]octanones from indanone is described. Proof of stereochemistry of these molecules reflects upon the mechanism of the reaction and provides interesting intermediates for further study.

Bridged bicyclic ring systems such as bicyclo[3.2.1]-octane or bicyclo[3.3.1]nonane continually serve as basic structural frames in investigations of conformational analysis[1] and carbonium-ion research.[2] Although there are numerous entries into these systems, the previously available methods often placed severe limitations upon the nature, quantity, distribution, and stereochemistry of their functionality.[3] The development of the α,α′-annelation procedure, described earlier[4] and elaborated here, provides a unique pathway for the construction of a wide variety of bicyclic systems having otherwise unobtainable functionality and stereochemistry. This paper discusses the development, mechanism, and some of the limitations of the synthesis involving the bicyclo[3.2.1]octane system.

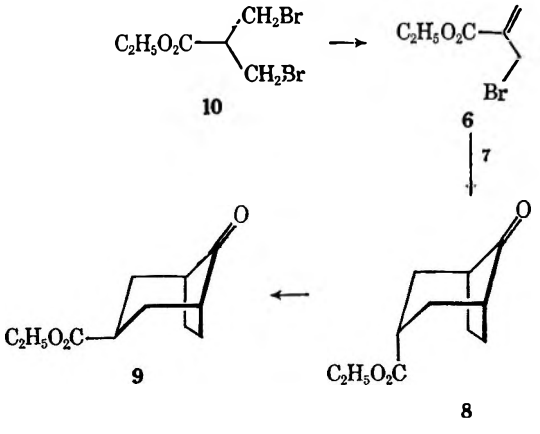
With the mildness and proven utility of the Stork enamine procedure in affecting both alkylation by allylic halides as well as by the Michael addition reaction,[5] speculation led to the possibility of causing the enamine of a ketone to react with a single reagent capable of serving sequentially as both an alkylation and Michael addition agent. In a structure having the appropriate distribution of functionality, a double bond could both serve to activate the leaving group as well as to provide conjugation with an electron-withdrawing function to provide the Michael acceptor moiety. The basic structure corresponding to this design is **1** where X is some leaving group and where Z is some electronegative function. Condensation of the annelation agent **1** with a ketone enamine would afford a substituted cyclohexanone by the process **1** → **5** (Scheme I). It is clear that one is allowed considerable latitude in the type and distribution of functionality in either enamine or annelating agent in this sequence.

SCHEME I



Ethyl α-bromomethylacrylate (**6**)[6] is one of the simplest substances capable of serving as an α,α′-annelation agent. Condensation of **6** with the pyrrolidine enamine of cyclopentanone (**7**)[5] in refluxing acetonitrile afforded an 80% yield of *endo*-3-carbethoxybicyclo[3.2.1]octan-8-one (**8**) (Scheme II). The axial or

SCHEME II



endo configuration of the ester function was established by the facile isomerization of keto ester **8** to a new *exo* ester **9** by sodium ethoxide in ethanol. This result indicated that, in the Michael stage of the reaction, the transition state assumed a chairlike conformation of the developing ring and that a concerted or kinetic protonation of the formed enolate occurred from the least

(1) (a) W. D. K. Macrosson, J. Martin, and W. Parker, *Tetrahedron Lett.*, 2589 (1965); (b) G. Eglington, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965); (c) W. A. C. Brown, G. Eglington, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, **57** (1964); (d) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 296; (e) H. O. House, P. P. Wickam, and H. C. Muller, *J. Amer. Chem. Soc.*, **84**, 3139 (1962); (f) H. O. House, H. C. Muller, C. G. Pitt, and P. P. Wickam, *J. Org. Chem.*, **28**, 2407 (1963); (g) A. A. Youssef, M. E. Baum, and H. M. Walborsky, *J. Amer. Chem. Soc.*, **81**, 4709 (1959).

(2) (a) C. S. Foote and R. B. Woodward, *Tetrahedron*, **20**, 687 (1964); (b) H. L. Goering and M. F. Sloan, *J. Amer. Chem. Soc.*, **83**, 1397 (1961).

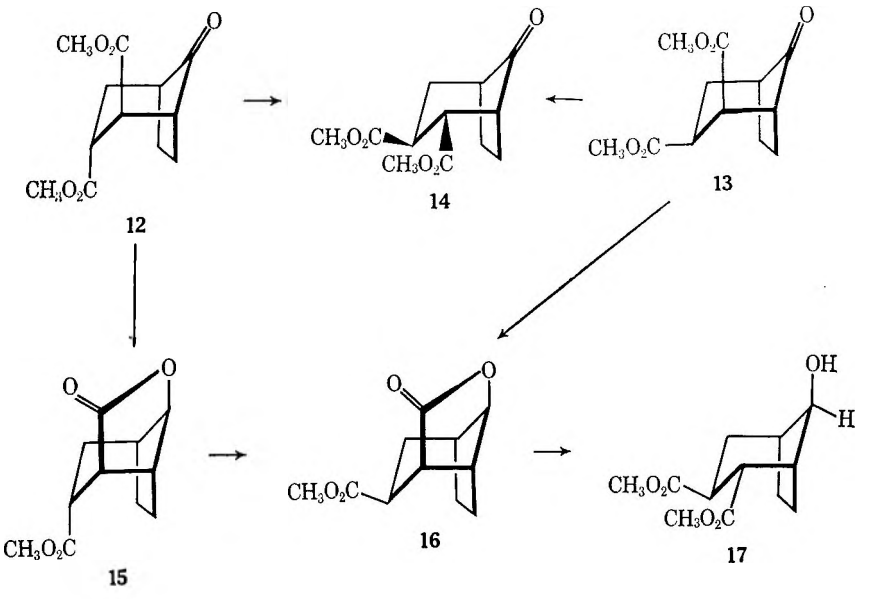
(3) (a) A. C. Cope, D. L. Nealy, P. Scheiner, and G. Wood, *J. Amer. Chem. Soc.*, **87**, 3130 (1965); (b) J. A. Marshall and D. J. Schaeffer, *J. Org. Chem.*, **30**, 3642 (1965); (c) A. C. Cope and M. E. Synerholm, *J. Amer. Chem. Soc.*, **72**, 5228 (1950); (d) J. Martin, W. Parker, and R. A. Raphael, *J. Chem. Soc.*, 289 (1964); (e) S. Julia, *Bull. Soc. Chim. Fr.*, 780 (1954); (f) G. Stork and H. K. Landesman, *J. Amer. Chem. Soc.*, **78**, 5129 (1956); (g) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, **32**, 1372 (1967); (h) D. M. Bailey, J. E. Bowers, and C. D. Gutsche, *ibid.*, **28**, 610 (1963); (i) E. Buchta and S. Billenstein, *Naturwissenschaften*, **51**, 383 (1964); (j) K. Alder and R. Reubke, *Chem. Ber.*, **91**, 1525 (1958); (k) C. W. Jefford, *Proc. Chem. Soc.*, **64** (1963).

(4) R. P. Nelson and R. G. Lawton, *J. Amer. Chem. Soc.*, **88**, 2884 (1966).

(5) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(6) A. F. Ferris, *J. Org. Chem.*, **20**, 780 (1955).

SCHEME III



hindered side of the molecule.[7] It is this stereochemical result which greatly enhances the synthetic utility of this annelation process. Further, the sequence clearly defines the mechanism and stereochemical preference of this type of Michael reaction. Obviously the alkylating agent must reside axially with regard to the cyclopentanone ring during the Michael process and certain aspects of this feature of the reaction become important in the construction of bicyclononanone systems.

The preparation of the unsaturated bromo ester **6** is somewhat inefficient and it is our usual practice to utilize its precursor, ethyl β,β'-dibromoisobutyrate (**10**).[6] Triethylamine dehydrohalogenation *in situ* provided the bromo ester **6** which resulted in the same *endo*-bicyclic ester **8**.

The question of the exact sequence of steps in the annelation synthesis becomes important when one has an annelation agent which is unsymmetrical. Although the proposed alkylation–Michael pathway appeared most plausible, two alternate routes, (A) an N-alkylation–Claisen rearrangement–Michael[8] route and (B) an SN2′–Michael route could not be eliminated. Although the SN2′ pathway is not common, the possibility of its occurrence with **6** is enhanced by the increased electrophilicity of the double bond caused by conjugation with the ester function. Thus, route B could also be looked upon as a Michael–elimination–Michael process. In contrast to more complex reagents, all of the three pathways give the same product using starting material **6**.

Dimethyl γ-bromomesaconate (**11**) was easily prepared by N-bromosuccinimide reaction with mesaconic ester.[9] The structure contains the requisite alkylation and Michael addition sites and an extra ester function which serves as a means to determine additional features of the reaction. Reaction of the bromo diester with the pyrrolidine enamine of cyclopentanone (**7**) in acetonitrile afforded, after hydrolysis of the imine salt, a 51% yield of a major isomer, dimethyl bicyclo[3.2.1]octan-8-one-2-*exo*,3-*endo*-dicarboxylate (**12**) contaminated with a small quantity (<5%) of an inseparable minor isomer later determined to be the 2-*exo*,3-*exo* diester (**13**). Treatment of the diesters with sodium methoxide in methanol afforded a single new isomer (**14**) (Scheme III) which clearly must have both ester functions in the more stable equatorial positions (2-*endo*,3-*exo*).

Sodium borohydride reduction[10] of octanones **12** and **13** gave two γ-lactone esters directly which could be separated by chromatography. There was also obtained a trace quantity of unlactonized alcohol, presumably the C_8 epimer. The facile formation of the γ-lactones **15** and **16** indicated the axial (*exo*) orientation of the 2-carbomethoxy function in both the major and minor isomers. The major isomer was confirmed as **12** by the *t*-butoxide–*t*-butyl alcohol isomerization of the γ-lactone of the major isomer (**15**) to the minor isomer γ-lactone **16**. Methoxide–methanol opened the lactone and isomerized both ester functions to give **17**. Consequently, the relative stereochemistry of the ester functions in the major isomer is *trans* and in the least stable diaxial position.

The stereoselectivity of the reaction in this case eliminates the other two considered pathways. If either alternate path A or B occurred, both possible diastereomeric intermediates **18** and **19** would be expected and the final product should, therefore, consist of a mixture of **12** and **20** (Scheme IV). The ratio of these products would only depend upon a subtle conformation orientation of enamine and ester fragments in the Claisen rearrangement of route A or in the SN2′ step of route B. The absence of significant quantities of **20** in the product indicates the C-alkylation–Michael pathway is preferred in this case.[11] Nevertheless, the C-alkylation–Michael pathway is not unique, and the exact path or paths vary with the structure. An example of an al-

(7) (a) F. Johnson and S. K. Malhotra, *J. Amer. Chem. Soc.*, **87**, 5492 (1965); (b) S. K. Malhotra and F. Johnson, *ibid.*, **87**, 5493 (1965).

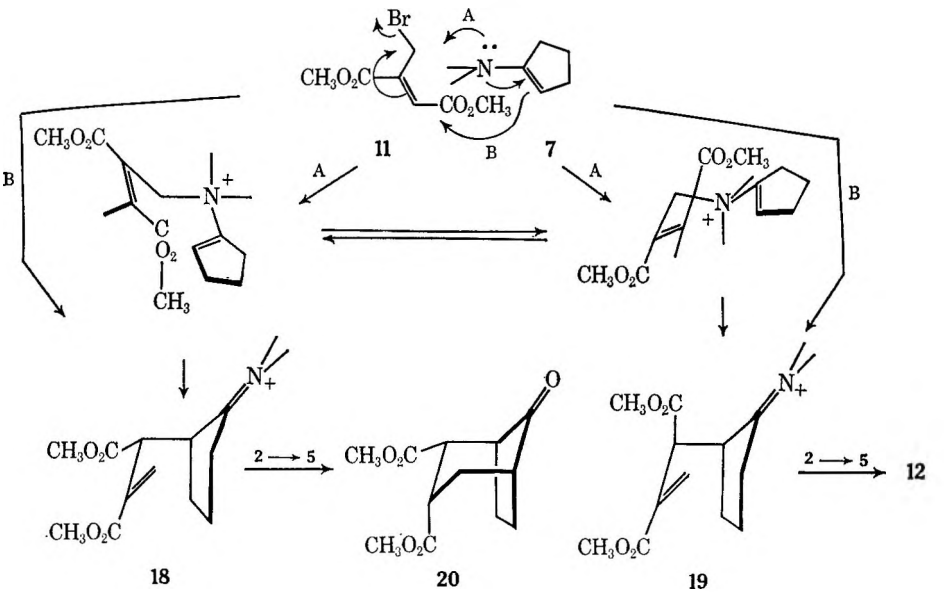
(8) See J. Szmuszkovicz in "Advances in Organic Chemistry: Methods and Results," Vol. 4, R. A. Raphael, E. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 26.

(9) N. R. Campbell and J. H. Hunt, *J. Chem. Soc.*, 1176 (1947).

(10) A. C. Cope, J. M. Grisar, and P. E. Peterson, *J. Amer. Chem. Soc.*, **82**, 4299 (1960).

(11) The intermediate C-alkylation product has been isolated in the condensation of cyclohexanone enamine and dimethyl γ-bromomesaconate. These studies will be detailed in a future paper.

Scheme IV



ternate mechanistic route arose in the synthesis of the strained benzobicyclo[3.2.1]octanone system.

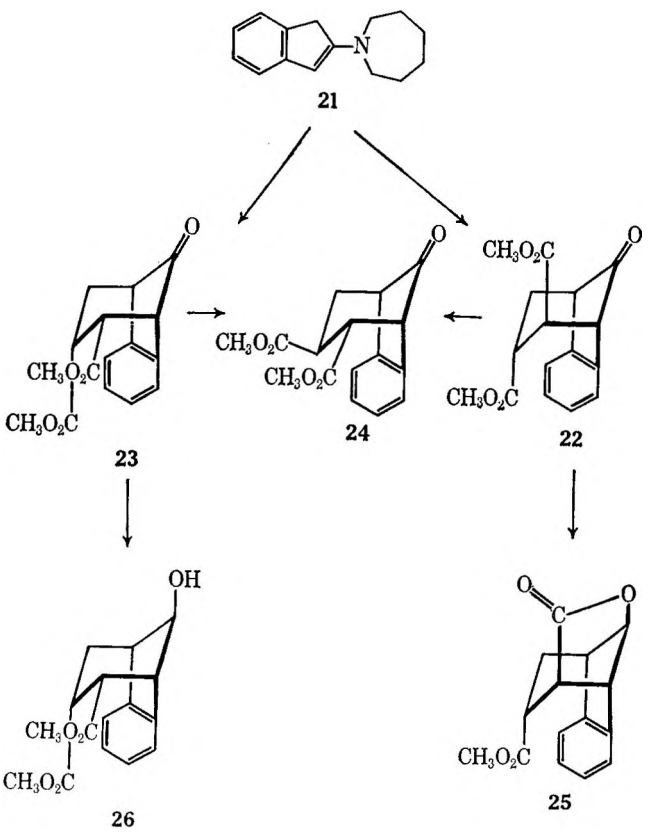
Reaction of the homopiperidine enamine of 2-indanone (**21**) with dimethyl γ-bromomesaconate (**11**) in acetonitrile gave a 10% yield of ring-closed product. The homopiperidine enamine was chosen because this particular enamine had previously been found to give the largest amounts of C-alkylated products with a variety of alkylating agents.[12]

Proton magnetic resonance (pmr) analysis of the product indicated the presence of two isomers since there were four ester methyls at τ 6.21, 6.30, 6.83, and 6.89. The fact that two of the ester absorptions occurred at such high field led to the conclusion that both isomers possessed an *axial* 3-carbomethoxy function which was strongly shielded by the aromatic ring. Separation of the mixture yielded an equal quantity of both crystalline isomers. The isomer assigned structure **22** possessed a single absorption at τ 2.76 for the aromatic protons (methoxyls at 6.21 and 6.83), whereas isomer **23** had the aromatics as multiplets at 2.59 and 2.81 (methoxyls at 6.30 and 6.89). The anisotropic effect of the equatorial 2-carbomethoxy function in **23** on a portion of the aromatic ring accounts for the aromatic multiplets observed. The shielding effect of the aromatic ring on the equatorial ester methoxyl of **23** is also apparent.

Confirmation of this spectral assignment was obtained by chemical techniques used with compound **12**. Treatment of either isomer **22** or **23** with sodium methoxide–methanol afforded a single new isomer **24** (Scheme V) having methyl ester absorptions at τ 6.25 and 6.48. When the isomer **22** was caused to react with sodium borohydride, a γ-lactone (**25**) was formed, whereas borohydride reduction of the isomer **23** gave only alcohol **26**. These data clearly assigned the structures.

Mechanistically, the observed stereochemistry of the two products can be explained by the N-alkylation–rearrangement–Michael route, the SN2′–Michael route, or by a process involving the normal C-alkylation–Michael route combined with either of these alternate routes.

Scheme V



Both the enamine and α-(1-haloalkyl)-unsaturated derivative are able to include many diverse features and the α,α′-annelation procedure provides a general method for the construction of a wide variety of cyclic structures in a single step and under mild conditions. The stereochemistry and conformation of bicyclo[3.3.1]nonan-9-ones[4] constructed by this process as well as the synthesis of tricyclic, tetracyclic, and spiro systems will be developed in later publications.

(12) A. T. Blomquist and E. J. Moriconi, *J. Org. Chem.*, **26**, 3761 (1961).

Experimental Section

Infrared (ir) spectra were taken using a Perkin-Elmer Model 237 spectrophotometer and were determined as thin films or in chloroform solution. Pmr spectra were determined for deuteriochloroform solutions with a Varian A-60 spectrophotometer using tetramethylsilane as an internal reference: s, singlet; d, doublet; t, triplet; q, quadruplet; quint, quintuplet; m, multiplet. Chemical shifts are reported using the τ scale. Melting points were determined in open capillary tubes unless stated otherwise, using a Thomas–Hoover capillary melting point apparatus and are uncorrected. Microanalysis were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Mass spectral analysis were performed by the Morgan Schaeffer Corp., Montreal, Que.

Ethyl Bicyclo[3.2.1]octan-8-one-3-*endo*-carboxylate (8).—To a solution of 1.01 g (0.0074 mol) of the pyrrolidine enamine of cyclopentanone[5] (7) and 0.82 g (0.0080 mol) triethylamine in 10 ml of acetonitrile (dried over calcium hydride) was added dropwise with stirring 2.03 g (0.0074 mol) ethyl β,β'-dibromoisobutyrate[6] dissolved in 10 ml of dry acetonitrile. Heat was generated upon addition and, as the solution turned reddish brown, a solid precipitated. The reaction mixture was heated at reflux for 3.5 hr. Hydrolysis of the iminium ion was accomplished by the addition of 5 ml of 5% aqueous acetic acid followed by a 0.5-hr reflux period. The reaction mixture was cooled and an equal volume of water was added. The aqueous mixture was then extracted several times with ether and the combined extracts were washed with 5% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The resulting ethereal solution was dried over anhydrous magnesium sulfate. Filtration and evaporation of the ether yielded 1.34 g of a pale yellow oil which distilled at 83–88° (0.05 mm). The product consisted of a single isomer as shown by glpc analysis using a 5-ft 20% SE-30 (silicone) column maintained at 200°. Spectral properties follow: ir ($CHCl_3$) 1749, 1726, 1375, 1076, 1040 cm^{-1}; pmr ($CDCl_3$) τ 5.82 (2 H, q), 7.09 (1 H, m), 7.34 (2 H, m), 7.59 (1 H, m), 7.99 (3 H, m), 8.15 (4 H, s), 8.70 (3 H, t).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.30; H, 8.16.

Ethyl Bicyclo[3.2.1]octan-8-one-3-*exo*-carboxylate (9).—9 was prepared by sodium ethoxide epimerization of the *endo* compound. To a solution of 0.012 g (0.0005 g-atom) of sodium in 25 ml of dry ethanol was added with stirring 0.16 g (0.0008 mol) of *endo* compound 8 in 10 ml of ethanol. The reaction mixture was heated at reflux for 1 hr, allowed to cool, and neutralized with 10 ml of 5% aqueous acetic acid. An equal volume of water was added and the resulting mixture was extracted several times with ether. The combined extracts were washed with saturated aqueous sodium bicarbonate and saturated sodium chloride and then dried over anhydrous magnesium sulfate. Filtration and evaporation of the ether yielded 0.12 g of yellow oil. Kugelrohr distillation at 100–110° (bath temperature) (0.1 mm) gave a product consisting of predominately one isomer as shown by pmr analysis. Spectral properties follow: ir ($CHCl_3$) 1765, 1748, 1726, 1453, 1378, 1125, 1105, 1055, 1030 cm^{-1}; pmr ($CDCl_3$) τ 5.94 (2 H, q), 6.49 (1 H, quint), 7.80–8.45 (10 H, broad overlapping multiplets), 8.78 (3 H, t).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.36; H, 8.32.

Dimethyl γ-Bromomesaconate (11)—11 was prepared using the general route designed by Campbell and Hunt.[9] To a solution of 100 g (0.633 mol) of dimethyl mesaconate in 140 ml of carbon tetrachloride was added 133 g (0.633 mol) of N-bromosuccinimide and 5.50 g of benzoyl peroxide. The mixture was irradiated with an incandescent lamp and heated with a heating mantle to maintain a constant reflux. The reaction period was 2 hr. The reaction mixture was cooled and washed repeatedly with water to remove the succinimide. The carbon tetrachloride layer was dried with anhydrous magnesium sulfate, filtered, and rid of solvent under aspirator vacuum. The resulting light green oil was fractionated yielding 116 g (76.9%) of bromo ester 11, bp 123–124° (5 mm) [lit.[9] ethyl ester bp 72° (0.1 mm)]. Spectral properties follow: ir ($CHCl_3$) 3020, 2960, 1725, 1635, 1280 cm^{-1}; pmr ($CDCl_3$) τ 3.18 (1 H, s), 5.30 (2 H, s), 6.10 (3 H, s), 6.19 (3 H, s).

Anal. Calcd for $C_7H_9O_4Br$: C, 35.47; H, 3.79; Br, 33.71. Found: C, 36.07, 35.92; H, 3.83, 3.85; Br, 33.78.

Dimethyl Bicyclo[3.2.1]octan-8-one-2,3-dicarboxylate (12.)—To a solution of 16.9 g (0.123 mol) of the pyrrolidine enamine of cyclopentanone (7) in 90 ml of acetonitrile (dried over calcium hydride) was added dropwise with stirring 29.4 g (0.123 mol) of dimethyl γ-bromomesaconate (11). Heat was generated as the bromo ester was added and the solution turned orange-brown. The reaction mixture (under nitrogen) was maintained at reflux for 2 hr using a heating mantle. Hydrolysis of the resulting iminium ion was effected through the addition of 10 ml of 5% aqueous acetic acid, followed by an additional reflux period of 1 hr. The reaction mixture was processed in the same manner as was used to obtain 8. Evaporation of the ether solvent yielded 21.8 g of an orange viscous oil which exhibited no carbon–carbon double-bond absorptions in the ir. Fractionation of the crude oil gave 15.3 g (51.6%) of dimethyl bicyclo[3.2.1]octan-8-one-2-*exo*,3-*endo*-dicarboxylate (12) with a trace of 13, bp 161–164.5° (1.8 mm). The product appeared to consist of a major isomer as shown by glpc analysis using a 6-ft, 6% LAC-728 (adipate ester) column maintained at approximately 250°. Spectral properties follow: ir ($CHCl_3$) 1747, 1725, 1260, 1175, 1025 (three peaks) cm^{-1}; pmr ($CDCl_3$) τ 6.20 (3 H, s), 6.27 (3 H, s), 8.10 (4 H, m), 7.76 (1 H, m), 7.38 (3 H, m), 6.88 (1 H, m); mass spectrum *m/e* peak at 240.

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.16; H, 6.82.

The 2,4-dinitrophenylhydrazone of 12 was prepared using the procedure of Vogel.[13] The orange-yellow hydrazone was recrystallized from methanol–chloroform yielding purified crystals, mp 206–207°.

Anal. Calcd for $C_{18}H_{20}N_4O_8$: C, 51.53; H, 4.80; H, 13.33. Found: C, 51.58; H, 4.88; H, 13.30.

Epimerization of Dimethyl Bicyclo[3.2.1]octan-8-one-2-*exo*,3-*endo*-dicarboxylate (12) with Sodium Methoxide.—A solution of 6.02 g (0.0251 mol) of dimethyl bicyclo[3.2.1]octan-8-one 2-*exo*,3-*endo*-dicarboxylate and 1.35 g (0.0249 mol) of sodium methoxide in 50 ml of methanol (dried with magnesium) was heated at reflux (heating mantle) for 1.5 hr. The reaction mixture was processed in the same manner as that used to obtain 9. Evaporation of solvent yielded 4.22 g (70.0%) of brown oil which solidified on standing. Recrystallization of the crude crystals from ether gave 3.73 g of white solid, mp 92–94°. Spectral properties follow: ir ($CHCl_3$) 1745, 1730, 1320, 1250 cm^{-1}; pmr ($CDCl_3$) τ 6.30 (3 H, s), 6.71 (q), 7.47 (m), 7.77 (m), 8.10 (m).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.49; H, 6.71. Found: C, 59.35; H, 6.60.

Methyl Bicyclo[3.2.1]octan-8-ol-2-carboxy-3-*endo*-carboxylate γ-Lactone (15) and -3-*exo*-carboxylate γ-Lactone (16).—To a cooled (ice bath) solution of 0.205 g (0.855 mmol) of dimethyl bicyclo-[3.2.1]octan-8-one 2,3-dicarboxylate (12) in 12 ml of methanol was added slowly 0.0337 g (0.880 mmol) of sodium borohydride. The reaction was allowed to stand with occasional stirring at room temperature for 30 min. An approximately equal volume of water was added and the aqueous methanol solution was extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of solvent yielded 0.170 g of crude slightly yellow oil whose ir spectrum possessed the characteristic γ-lactone carbonyl absorption at 1785 cm^{-1}. Column chromatography of 1.52 g of oil, prepared in an analogous experiment over 80 g of silicic acid absorbant using 5% ether in benzene as eluent, yielded 0.302 g of a major γ-lactone (15) followed by 0.0367 g of a minor epimeric γ-lactone (16). There was also obtained C_8 epimeric alcohol.

The major γ-lactone (15) [Kugelrohr 200° (1 mm)] had the following spectral properties: ir ($CHCl_3$) 1785, 1730, 1310, 1150 (three peaks), 1025 cm^{-1}; pmr ($CDCl_3$) τ 6.21 (3 H, s), 5.22 (1 H, t), 6.82 (1 H, m), 7.21 (2 H, m), 7.67 (2 H, m), 8.25 (4 H, m).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85, H, 6.71. Found: C, 62.96; H, 6.76.

The minor γ-lactone (16) had the following spectral properties: ir ($CHCl_3$) 1780, 1730, 1150, 1015 (three peaks) cm^{-1}; pmr ($CDCl_3$) τ 6.25 (3 H, s), 5.22 (1 H, m), 7.07 (m), 7.65 (m), 8.17 (m).

The epimeric alcohol (C_8) had the following spectral properties: ir ($CHCl_3$) 3610 (s), 3450 (b), 1730, 1260 cm^{-1}; pmr ($CDCl_3$) τ 6.34 (6 H, s), 6.78 (2 H, m), 8.25 (m).

(13) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, John Wiley & Sons, Inc., New York, N. Y., 1962, p 344.

Attempted Epimerization of Methyl Bicyclo[3.2.1]octan-8-ol-2-Carboxy-3-carboxylate γ-Lactone (15) with Sodium Methoxide.—To a solution containing 0.0020 g (0.00087 g-atom) of sodium metal dissolved completely in 1 ml of methanol was added 0.0459 g (0.219 mmol) of γ-lactone (**15**). An additional 1 ml of methanol was used as a transfer agent. The mixture was heated in an oil bath to maintain reflux for 0.5 hr. Cooling of the mixture followed by processing as in the epimerization of ketone **8** yielded 0.0449 g (84.9%) of clear oil. The ir spectrum of the crude oil lacked the γ-lactone carbonyl absorption at 1785 cm^{-1}. Alcohol **17** had the following spectral properties: ir ($CHCl_3$) 3610 (s), 3475 (b), 2960, 1730, 1250 cm^{-1}.

Epimerization of Methyl Bicyclo[3.2.1]octan-8-ol-2-carboxy-3-carboxylate γ-Lactone (15) with Potassium *t*-Butoxide.—A solution of 0.110 g (0.476 mmol) of pure γ-lactone **15** and 0.012 g (0.099 mmol) of potassium *t*-butoxide in 4 ml of *t*-butyl alcohol (dried over calcium hydride) was stirred at room temperature for 2 hr. Neutralization of the solution with 5% acetic acid followed by processing as in the procedure used for the epimerization of ketone **8** yielded 0.108 g of oil which contained approximately 18% epimerized material **16** by pmr analysis. The pmr spectrum revealed that the previous ester methyl absorption at τ 6.21 had shifted to 6.25. Spectral properties follow: ir ($CHCl_3$) 1780, 1730, 1150, 1015 (three peaks) cm^{-1}; pmr ($CDCl_3$) τ 5.22 (1 H, m), 6.25 (3 H, s), 6.83 (m), 7.07 (m), 7.65 (m), 8.17 (m).

Dimethyl 6,7-Benzobicyclo[3.2.1]octan-8-one-2,3-dicarboxylates (22 and 23).—To a solution of 8.16 g (0.0422 mol) of the homopiperidine enamine of 2-indanone (**21**)[12,14] in 50 ml of acetonitrile was added 10.0 g (0.0422 mol) of bromomesaconate (**11**). Nitrogen was swept over the reaction mixture throughout the bromo ester addition and during the subsequent 3-hr reflux period. Triethylamine (3 ml, 0.04 mol) was added and the mixture was heated at reflux for another hour. The imine salt was hydrolyzed using 10 ml of 5% acetic acid followed by an additional reflux period of 12.5 hr. Processing of the reaction as in the preparation of keto ester **8** followed by evaporation of solvent gave 6.88 g of brown oil. Fractionation of the oil yielded 1.30 g (10.9%) of dimethyl 6,7-benzobicyclo[3.2.1]octan-8-one-2,3-dicarboxylates (**22** and **23**), bp 168–172° (0.35 mm). The pmr analysis indicated two compounds. The remaining oil was chromatographed over 65 g of acid-washed silicic acid using ether–benzene as eluent. Keto diester **22** (0.275 g) was the first isomer eluted from the column in 4% ether–benzene with keto diester **23** (0.446 g), mp 109.5–111°, being removed with 10% ether–benzene.

Keto diester 23 had the following spectral properties: ir ($CHCl_3$) 3020, 1765, 1740, 1200, 1025 cm^{-1}; pmr ($CDCl_3$) τ 2.59, 2.81 (4 H, m), 6.12 (m), 6.30 (3 H, s), 6.63 (m), 6.89 (ester methyl superimposed on multiplet), 71.6 (m), 7.75 (m).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.68; H, 5.50.

Keto diester 22 had the following spectral properties: ir ($CHCl_3$) 3010, 1775, 1740, 1280 cm^{-1}; pmr ($CDCl_3$) τ 2.76 (4 H, s), 5.88 (1 H, m), 6.21 (3 H, s), 6.28 (1 H, m), 6.66 (m), 6.83 (3 H, s), 7.11 (m), 7.42 (m).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.60; H, 5.55.

Epimerization of Dimethyl 6,7-Benzobicyclo[3.2.1]octan-8-one-2-*exo*,3-*endo*-dicarboxylate (22) with Sodium Methoxide.—To a solution of 0.005 g (0.0002 g-atom) of sodium metal dissolved completely in 2 ml of methanol (dried with magnesium) under nitrogen was added 0.100 g (0.35 mmol) of keto diester **22**. The solution was maintained at reflux using an oil bath for 0.75 hr during which time the solution turned wine red. The reaction mixture was cooled and processed as in the epimerization of bicyclononanone **8**. Evaporation of solvent yielded 0.0813 g (81.3%) of yellow oil which solidified to give white crystals. Recrystallization from ether followed by vacuum drying over concentrated sulfuric acid gave 0.0377 g of purified material, mp 143.5–144.5° (**24**). Spectral properties follow: ir ($CHCl_3$) 3020, 1775, 1740, 1260, 1100 cm^{-1}; pmr ($CDCl_3$) τ 2.72 (4 H, m), 6.25 (3 H, s), 6.48 (3 H, s), 6.55 (m), 6.69 (m), 7.78 (m).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.78; H, 5.46.

Epimerization of Dimethyl 6,7-Benzobicyclo[3.2.1]octan-8-one-2-*endo*,3-*endo*-dicarboxylate (23) with Sodium Methoxide.—In 2 ml of methanol (dried with magnesium) was dissolved 0.005 g (0.0002 g-atom) of sodium metal. To the sodium ethoxide–methanol solution was added 0.0871 g (0.300 mmol) of keto diester **23**. The reaction mixture was heated at reflux for 0.75 hr using an oil bath, cooled, and processed as in the epimerization of dimethyl 6,7-benzobicyclo[3.2.1]octan-8-one-2-*exo*,3-*endo*-dicarboxylate (**22**). Evaporation of solvent gave 0.0607 g (69.6%) of yellow oil which yielded 0.0270 g (44.5%) of white crystals of keto ester **24** upon treatment with ether.

Methyl 6,7-Benzobicyclo[3.2.1]octan-8-ol-2-carboxy-3-*endo*-carboxylate γ-Lactone (25).—To 1.5 ml of methanol was added 0.133 g (0.464 mmol) of keto diester **22**. The resulting solution was treated with 0.0190 g (0.505 mmol) of sodium borohydride which caused a color change in the solution from colorless to yellow. After the solution was allowed to stand at room temperature for 0.5 hr, the reaction was processed as in the reduction of keto diester **12** giving 0.132 g (100% recovery) of a yellow oil. The product consisted of γ-lactone [–C(=O)–, 1785 cm^{-1}] contaminated with unlactonized alcohol [3700, 3620 (sharp), 3330 (broad) cm^{-1}]. More γ-lactone was not formed after heating at 170° for 1.75 hr. Spectral properties follow: ir ($CHCl_3$) 1785, 1730, 1170 cm^{-1}; pmr (major peaks of crude oil) ($CDCl_3$) τ 2.84 (s), 2.91 (s), 5.82 (1 H, t), 6.83 (3 H, s).

Dimethyl 6,7-Benzobicyclo[3.2.1]octan-8-ol-2-*endo*,3-*endo*-dicarboxylate (26.)—A cooled solution (~15°) of 0.148 g (0.513 mmol) of keto diester **23** in 1.5 ml of methanol was treated with 0.0228 g (0.603 mmol) of sodium borohydride. After the reaction mixture ceased bubbling, it was allowed to stand at room temperature for 0.5 hr. Processing as in the reduction of **12** yielded 0.151 g (100%) of oil which solidified on standing (mp 124–124.5°). Ir analysis indicated the presence of an alcohol function [3650 (sharp), 3520 (broad) cm^{-1}]. However, no γ-lactone had formed. Spectral properties follow: ir ($CHCl_3$) 3650 (sharp), 3520 (broad), 3040, 1265, 1200 cm^{-1}; pmr ($CDCl_3$) τ 2.74 (s on m) and 2.93 (m) [4 H], 5.75 (1 H, t), 6.38 (3 H, s), 6.61 (m), 6.99 (3 H, s superimposed on m), 7.55 (m).

Registry No.—**8**, 19530-66-6; **9**, 19530-67-7; **11**, 19530-68-8; **12**, 19530-69-9; **12** (2,4-dinitrophenylhydrazone), 19530-70-2; **13**, 19530-71-3; **14**, 10560-30-2; **15**, 10555-66-5; **16**, 10555-67-6; **17**, 19530-74-6; **22**, 19545-03-0; **23**, 19530-75-7; **24**, 19530-76-8; **25**, 19530-77-9; **26**, 19545-04-1.

(14) J. E. Horan and R. W. Schiessler, *Org. Syn.*, **41**, 53 (1961).

Beckmann Rearrangement and Fission of 2-Arylcyclohexanone Oxime Tosylates. Trapping of Carbonium Ion Intermediates as Pyridinium Cations[1]

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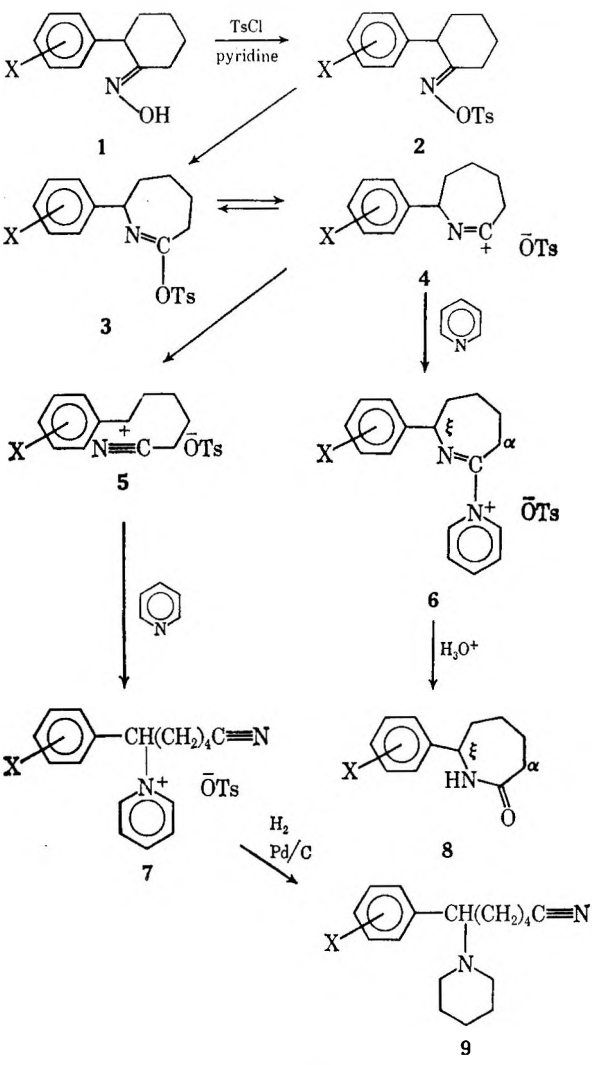
Reaction of *anti*-2-*o*-tolyl-, 2-*p*-tolyl- and 2-(*p*-chlorophenyl)cyclohexanone oximes **1** with tosyl chloride in pyridine at room temperature gave pyridinium salts **6** and **7**, products of the iminyl carbonium ion **4** and of the fission carbonium ion **5**, respectively. The results support a mechanism involving a rate-determining rearrangement step of oxime tosylate **2** to iminol tosylate **3**, or some intermediate closely related to it, followed by a fast ionization and a partitioning of the resulting carbonium ion **4** to the corresponding pyridinium cation **6** and pyridinium cation **7** of the fission reaction. The rearrangement of the oxime tosylate was slowest with *p*-chloro compound **1c** and this compound yielded the smallest amount of fission reaction pyridinium salt **7c**.

In an attempt to isolate 2-*o*-tolylcyclohexanone oxime tosylate **2a** oxime **1a** was treated with tosyl chloride in dry pyridine at room temperature and after a few hours the mixture was poured into about eight times its volume of water. Extraction of the aqueous mixture with ethyl ether and benzene yielded very little organic material besides pyridine. Acidification of the aqueous layer caused cloudiness and extraction with ether yielded lactam **8a** in about 40% yield. The high partitioning in water, prior to acidification, indicated that in our reaction the intermediate leading directly to the lactam was not iminol tosylate **3a**. A more careful investigation of the reaction with the aid of nuclear magnetic resonance (nmr) showed that prior to acidic hydrolysis the main products were pyridinium salts **6a** (product of the carbonium ion **4a**) and pyridinium salt **7a** (product of the fission reaction leading to carbonium ion **5a**). Proof of structure for **6a** rests on nmr and solubility data, but **7a** was characterized from its hydrogenation product **9a** in addition to spectroscopic data. The reaction in pyridine at room temperature was quite fast. It appeared to reach completion in less than 20 min as no subsequent change was noticeable in the nmr spectrum upon standing for 36 hr, with the possible exception of a slight increase in the ratio of **7a** to **6a**. Similar results were obtained with *p*-methyl isomer **1b**. With *p*-chloro oxime **1c** the disappearance of the oxime (or more probably the oxime tosylate) was somewhat slower, the ratio of pyridinium salt **6c** to **7c** was larger, and the yield of the lactam was slightly larger than with the tolyl compounds.

The results are consistent with the sequence of events outlined in Scheme I. Scheme I is also consistent with reported information on the Beckmann rearrangement and fission (or fragmentation) reactions of ketoxime tosylates,[2-6] but to our knowledge this is the first report of the "trapping" of the carbonium ion intermediates of types **4** and **5**.

There are many reports of reactions of arylsulfonyl esters of oximes in pyridine,[2,5,6] but in most cases the work-up did not provide for the detection and isolation

SCHEME I



a, X = *o*-CH_3
b, X = *p*-CH_3
c, X = *p*-Cl

of the pyridinium salts of the fragmentation reactions. The spontaneous rearrangement of benzenesulfonate esters of ketoximes to iminol esters has been shown by Kuhara and coworkers,[7] as far back as 1914. Recently, Grob and coworkers[4] have concluded that the rate-determining step of the rearrangement of oxime tosylates in 80% ethanol involves the isomerization to

(1) This investigation was supported in part by Research Grant MH 12204 from the National Institute of Mental Health, U. S. Public Health Service.

(2) K. Morita and Z. Suzuki, *J. Org. Chem.*, **31**, 233 (1966).

(3) R. K. Hill, R. T. Conley, and O. T. Chortyk, *J. Amer. Chem. Soc.*, **87**, 5646 (1965).

(4) C. A. Grob, H. P. Fischer, W. Raudenbusch, and J. Zergenyi, *Helv. Chim. Acta*, **47**, 1003 (1964).

(5) P. A. S. Smith in "Molecular Rearrangements," part 1, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, p 483 (and references therein).

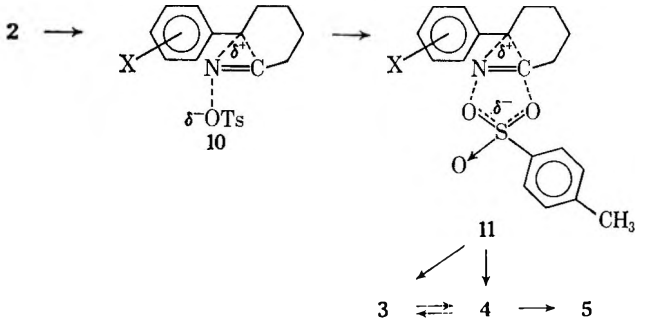
(6) L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, **11**, 1 (1960).

(7) M. Kuhara, K. Matsumiya, and N. Matsunami, *Mem. Coll. Sci., Univ. Kyoto*, **1**, 105 (1914), from ref 5. The original work was not consulted.

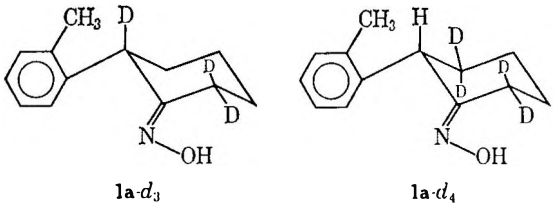
an iminol tosylate which then ionizes to a nitrilium cation,[8] the common intermediate of rearrangement and fission products. They showed that the reaction rates reflect migratory aptitudes and that fission reactions occur after the rate-determining migration step. It follows that the extent of fragmentation, under a given condition, will depend on the energy of activation for the formation of the fission carbonium ion, which in turn can be related to the stability of this carbonium ion. The results of Morita and Suzuki[2] are in agreement with this.

Our own results support the conclusions of Grob and coworkers. A mechanism for the formation of carbonium ions **4** and **5** is depicted in Scheme II but our results do not establish whether the formation of **4** must pass through **3** or whether it could come directly from an intermediate of the nature of **11**, closely related to the transition state.

SCHEME II



For the nmr investigation the reactions were carried out at concentrations of about 12–16% of the oxime in dry pyridine using either 1 mol or 1.1 mol equiv of *p*-toluenesulfonyl chloride (tosyl chloride). The nmr interpretation was strengthened by also carrying out the reaction on the tri- and tetradeuterated oximes **1a**-d_3 and **1a**-d_4.



1a-d_3 **1a**-d_4

Spectrum A, Figure 1, is the 60-MHz nmr spectrum of the reaction mixture in pyridine of 2-*o*-tolylcyclohexanone oxime **1a** with 1.1 mol equiv of tosyl chloride after standing for 36 hr. The spectrum indicates a mixture of pyridinium salts **6a** and **7a** in a ratio of about 3:2, respectively. The signals at τ 7.80, 7.63, and 7.53 are attributed to the aromatic methyl groups of the tosylate ion, and the pyridinium cations **6a** and **7a**, respectively. The broad signals at τ 6.32 and 4.69 (ratio of 2:1) are attributed to the α-methylene and ϵ-methine hydrogens, respectively, of **6a**. The methylene signal at τ 6.32 and the aromatic methyl signal at τ 7.63 integrate to a ratio of approximately 2:3. The signal at τ 0.15 (downfield from the signals of the pyridine) is attributed to the combined α hydrogens of pyridinium cations **6a** and **7a**. This signal integrates to an approximate ratio of 2:6 to the combined signals of all aromatic methyl groups. The chemical shift of this signal is sensitive to moisture. Addition of 5 drops of D_2O causes an upfield shift of 0.3–0.4 ppm. The addition of D_2O also caused the aromatic methyl signals at τ 7.53 and 7.63 to overlap at 7.57. The addition of D_2O also caused a small triplet (separation of about 7 Hz) to appear at τ 3.58. This signal is attributed to the methine hydrogen of **7a**, hidden under the signals of the pyridine prior to addition of D_2O. The signal at τ 0.15 is very indicative of the presence of salts **7a** and **6a** because this signal is not seen with *p*-toluenesulfonic acid nor tosyl chloride in pyridine but such a signal is seen with benzylpyridinium bromide. Additional proof is obtained from the spectra of the following work-up products.

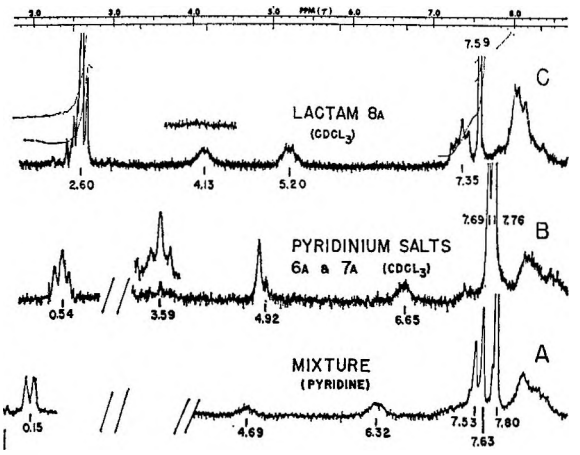


Figure 1.—60-MHz nmr spectra of reaction mixture of **1a** with tosyl chloride in pyridine (A); mixture of pyridinium salts **6a** and **7a** in chloroform-*d* (B); and lactam **8a** in chloroform-*d* (C); all with TMS as internal standard.

The reaction mixture giving spectrum A was mixed with an equal volume of water and the mixture extracted successively with ethyl ether and benzene, removing most of the pyridine. The remaining aqueous layer was extracted several times with chloroform, the chloroform layer washed with water, the chloroform removed at room temperature, and an nmr spectrum of the resulting material was determined in chloroform-*d*, spectrum B. The combined signals of the α hydrogens of pyridinium salts **6a** and **7a** are still in the ratio of 2:6 in relation to the combined aromatic methyl hydrogens, which includes the tosyl group. The signal of the methine hydrogen of **7a** gives the expected triplet at τ 3.59.[9] The signals of the ϵ and α hydrogens of **6a** are at τ 4.92 and 6.65, respectively. The signal at τ 4.92 is partially overlapped with the signal of hydrogen from moisture (shown by addition of D_2O). Salt **7a** was isolated by acid hydrolysis of either the original reaction mixture, or the mixture giving spectrum B, using about 15% *p*-toluenesulfonic acid. In both cases the resulting lactam **8a** was extracted with ether or benzene and **7a** was obtained by extraction of the aqueous layer with chloroform or dichloromethane. Any remaining pyridine was azeotroped at room tem-

(8) The cation is really a resonance hybrid between the nitrilium ion and iminyl carbonium ion structures. In cyclic structures where linearity of the nitrilium structure is prevented the ion will have a greater degree of carbonium ion character.

(9) The spectrum of benzylpyridinium bromide in chloroform-*d* gives a complex doublet at τ 0.40 for the α-pyridinium hydrogens and a singlet at τ 3.72 for the methylene hydrogens.

perature with 2,2,4-trimethylpentane on a rotary evaporator. The nmr spectrum of **7a** in chloroform-*d* lacks the peaks at τ 6.65 and 4.92, seen in spectrum B, but gives a doublet for the pyridinium α hydrogen at τ 0.72 and a triplet for the methine hydrogen at τ 3.67 in the ratio of 2:1 (the positions of these two signals vary with presence of moisture) and singlets of equal intensities at τ 7.69 and 7.80 for the aromatic methyl groups of the **7a** cation and the tosylate anion, respectively. Salt **7a** is somewhat hydroscopic and was not analyzed but an elementary analysis was obtained on its hydrogenation product **9a**. The ir spectra of **7a** and **9a** exhibit a C≡N stretching band at 2240 cm^{-1}.

Spectrum C is that of the lactam **8a** measured in chloroform-*d*. The signals at τ 4.13, 5.20, 7.35, and 7.59 integrate for one, one, two, and three hydrogens, respectively, and are assigned to the NH, the benzylic ϵ-methine hydrogen, the α-methylene hydrogens, and the aromatic methyl hydrogens in that order. The signal at τ 4.13 disappears upon exchange with D_2O (upper curve). The assignment of structure **8a** is unambiguous[10] and is further substantiated by the spectra of the lactams obtained from the deuterated oximes **1a**-d_3 and **1a**-d_4. The structure of lactam **8a** establishes the structure of the starting oxime as having the *anti* configuration.[10] The same is true for **1b** and **1c**.

In the reactions with the deuterated oximes the acid hydrolysis was carried out without removal of the pyridine. Deuterated lactams **8a** and deuterated pyridinium salts **7a** were isolated for nmr analysis. With **1a**-d_3 the nmr spectrum of the reaction mixture differed from spectrum A only in the absence of the signals at τ 4.69 and 6.32 and in the absence of appearance of the triplet around τ 3.58 upon addition of D_2O. The spectrum of salt **7a** lacked the triplet seen at τ 3.67, attributed to the methine hydrogen in the spectrum of nondeuterated **7a**. The spectrum of the lactam differed from spectrum C in the absence of signals at τ 5.20 and 7.35. With tetradeuterated oxime **1a**-d_4 the spectrum of the reaction mixture lacked the signal at τ 6.32 and the signal at 4.69 was now a sharper singlet. This is as expected for **6a** having deuterium on the α and δ carbons. Addition of D_2O caused a singlet to appear in the vicinity of τ 3.58. The spectrum of the moist pyridinium tosylate salt **7a**-d_4, measured in chloroform-*d*, gave a doublet (2 H) at τ 0.75, a sharp singlet (1 H) at 3.70, a complex pattern for the remaining aromatic hydrogens (11 H), two singlets (3 H each) at 7.70 and 7.80, and a broad signal of four hydrogens at about τ 8.5. The data are consistent with structure **7a** having deuterium on C-2 and C-5 of the chain. The most significant differences in the spectrum of the tetradeuterated lactam were the absence of the signal at τ 7.35 in C and a sharpening of the signals at 5.20.

2-*p*-Tolylcyclohexanone oxime **1b** gave results very similar to those of the *ortho* isomer but there was a partial overlap of the signals of the aromatic methyl groups of **6b**, **7b**, and the tosyl group for the reaction mixture in pyridine.

With equal molar quantity of 2-(*p*-chlorophenyl)-cyclohexanone oxime **1c** and tosyl chloride the nmr spectrum measured at 30 min of reaction time had two tosyl methyl signals of almost identical intensities, τ 7.70 and 7.78. After 6.5 hr of total reaction time only one methyl signal was present at τ 7.78. Otherwise the spectrum was quite similar to spectrum A, Figure 1, showing a complex doublet at τ 0.0, and signals in ratio of 1:2 at τ 4.77 and 6.34, respectively. Integration indicated a higher proportion of **6c** compared to **7c** than with the tolyl compounds. The signals at τ 7.70 and 7.78, at 30-min reaction time, are attributed to the aromatic methyl hydrogens of oxime tosylate **2c** and the tosylate anions of **6c** and **7c**. This implies that the rearrangement of **2c** is slower than **2a** and **2b**. This is consistent with the expected lower migratory aptitude of the *p*-chlorobenzyl than methylbenzyl groups. The larger proportion of pyridinium salt **6c** (and subsequent higher yield of the lactam **8c**) is also consistent with the expected lower stability of the carbonium ion **5c** compared to **5a** and **5b**.

Experimental Section

Melting points were determined on a Kofler micro hot stage melting point apparatus. The nmr spectra were determined on a Varian A-60 spectrometer with tetramethylsilane as an internal standard.

anti-2-**Arylcyclohexanone oximes** (**1a**, **1b**, **and 1c**) were prepared from the known 2-*o*-tolyl-, 2-*p*-tolyl-, and 2-(*p*-chlorophenyl)cyclohexanones[11] by a method similar to that of Drefahl and Martin.[12] The preparation of 2-*o*-tolylcyclohexanone oxime **1a** is described as a general example. To a mixture of 9.60 g (0.051 mol) of 2-*o*-tolylcyclohexanone and 7.20 g (0.103 mol) of hydroxylamine hydrochloride in 210 ml of methanol was added a solution of 7.70 g (0.058 mol) of potassium carbonate in 105 ml of water. The mixture was refluxed for 1.5 hr and cooled in ice; 100 ml of ice-cold water was added. The resulting precipitate was collected by suction filtration, washed with two 20-ml portions of water, and recrystallized from 95% ethanol, giving a total recovery of 9.5 g (91%): mp 197–198°; 2-*p*-tolylcyclohexanone oxime **1b** (90%), mp 183–184°; 2-(*p*-chlorophenyl)cyclohexanone oxime **1c** (84%), mp 186–187°.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found for **1a**: C, 76.77; H, 8.39; N, 6.81. Found for **1b**: C, 76.60; H, 8.57; N, 6.72.

Anal. Calcd for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; N, 6.26. Found for **1c**: C, 64.65; H, 6.44; N, 6.03.

ϵ-**Aryl-**ϵ-**caprolactams** (**8a**, **8b**, **and 8c**).—The method described for ϵ-*o*-tolyl-ϵ-caprolactam **8a** was used as a general method for obtaining the lactams but variations in work-up procedures were used for nmr studies of the pyridinium salts **6** and **7** as described in the text.

To a solution of 2.032 g (0.010 mol) of **1a** in 10 ml of anhydrous, freshly distilled, pyridine was added a solution of 2.10 g (0.011 mol) of *p*-toluenesulfonyl chloride in 3 ml of anhydrous pyridine. A yellow color developed. The mixture was cooled intermittently in ice to prevent the temperature from rising above 24° and was then allowed to stand at room temperature for about 36 hr. The yellow solution was poured into 50 ml of 10% HCl[13] and the mixture extracted successively with three portions of ethyl ether and benzene. The combined extracts were washed with 5% sodium bicarbonate, followed by water, filtered through anhydrous sodium sulfate, and dried further over Drierite. Evaporation of the solvent gave 980 mg of yellowish solid which was treated with decolorizing carbon in 2-propanol and recrystallized from 2-propanol, yielding 790 mg (39%) of colorless crystalline material, mp 109–115°. The compound undergoes crystal modification in the region of the melting point. Crystals are seen to melt, resolidify, and remelt at higher temperature.

ϵ-*p*-Tolyl-ϵ-lactam **8b** (47%) had mp 153–154°; mass parent ion 203.1366 (calcd 203.1309).

ϵ-(*p*-Chlorophenyl)-ϵ-lactam **8c** (52%) had mp 172–174°. The ir (KBr disk) of all three lactams show sharp N—H stretching at 3320 cm^{-1} and C=O stretching at 1650 cm^{-1}.

(10) A. C. Huitric, D. B. Roll, and J. R. DeBoer, *J. Org. Chem.*, **32**, 1661 (1967).

(11) A. C. Huitric and W. D. Kumler, *J. Amer. Chem. Soc.*, **78**, 614 (1956).

(12) G. Drefahl and D. Martin, *Chem. Ber.*, **93**, 2497 (1960).

(13) In reactions with **1b** and **1c** corresponding lactams **8b** and **8c** precipitated out as solids at this point and were filtered off.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found for **8a**: C, 76.48; H, 8.47; N, 6.73. Found for **8b**: C, 76.73; H, 8.81; N, 6.82.

Anal. Calcd for $C_{12}H_{14}ClNO$: C, 64.43; H, 6.31; N, 6.26. Found for **8c**: C, 64.35; H, 6.16; N, 6.17.

6-*o*-Tolyl-6-(1-piperidyl)hexanenitrile (9a).—A mixture of 400 mg (0.000915 mol) of 1-(1-*o*-tolyl-5-cyanopentyl)pyridinium *p*-toluenesulfonate (**7a**)[14] and 80 mg of 10% palladium on carbon in 20 ml of absolute ethanol was shaken for 24 hr under 30 psi of hydrogen in a Parr hydrogenator. The catalyst was removed by filtration through Celite and the solvent removed under reduced pressure on a rotary evaporator, giving 340 mg of oily material, ir 2240 cm^{-1} (C≡N). The nmr showed the absence of the pyridine ring, the replacement of the triplet of the methine benzylic hydrogen of the pyridinium salt **7a** (Figure 1) at τ 3.59 by a multiplet at τ 5.50, the increase of the integration of signals above τ 7.0 by ten hydrogens compared to **7a**, and the presence of the tosylate group. The oil was dissolved in 20 ml of chloroform, the solution washed with 10% NaOH, followed by water, and dried (Na_2SO_4). Removal of the solvent gave 220 mg of a yellow oil, ir 2240 cm^{-1} (C≡N). The major differences of the nmr compared to that of the tosylate salt was the absence of signals due to the tosylate group and an upfield shift of the signal of the methine benzylic hydrogen from τ 5.50 to 6.50. The free base was converted into the HCl salt by bubbling HCl in a hexane solution of the base, and the salt recrystallized from 2-propanol, mp 188–191°.

Anal. Calcd for $C_{18}H_{27}N_2Cl$: C, 70.45; H, 8.87; N, 9.15. Found: C, 70.37; H, 8.72; N, 9.09.

Deuterated Oximes 1a-d_3 and 1a-d_4.—The deuterated oximes were prepared from the corresponding deuterated ketones by the method described for nondeuterated **1a**.

2-*o*-Tolylcyclohexanone-2,6,6-d_3 was prepared by base-catalyzed deuterium exchange on 1.5 g of 2-*o*-tolylcyclohexanone in a mixture of 6.2 ml of anhydrous purified dioxane and 3.0 ml of D_2O with trace amount of sodium methoxide as source of base. The mixture was stirred at 90° for 2 hr, cooled, poured into 10 ml of water, extracted with ether, and dried (Na_2SO_4); the ether was removed. The process was carried out three times. After the third exchange the nmr integration indicated that the exchange was essentially complete: yield 1.3 g; mp 54.0–55.0° [lit.[11] (nondeuterated) mp 55.5–56.5°].

2-*o*-Tolylcyclohexanone-3,3,6,6-d_4 was prepared by the method previously reported.[15]

Registry No.—**1a**, 19640-09-6; **1a-d_3**, 19640-10-9; **1b**, 19640-11-0; **1c**, 19640-12-1; **6a**, 19643-00-6; **7a**, 19643-01-7; **8a**, 19643-02-8; **8b**, 19643-03-9; **8c**, 19643-04-0; **9a** (HCl salt), 19643-05-1; tosyl chloride, 98-59-9.

(14) Pyridinium tosylate salt **7a** was obtained by chloroform extraction of the aqueous layer resulting from the lactam formation by hydrolysis of the reaction mixture with 15% *p*-toluenesulfonic acid, as explained in the text.

(15) A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, *Tetrahedron*, **19**, 2145 (1963).

Sulfur-Bridged Carbocycles. II. Extrusion of the Sulfur Bridge[1]

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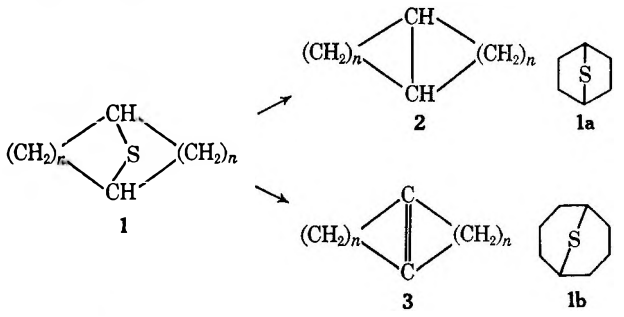
The extrusion of the sulfur bridge from 7-thiabicyclo[2.2.1]heptane (**1a**) and 9-thiabicyclo[3.3.1]nonane (**1b**) and their derivatives, a synthetically useful procedure for the controlled formation of transannular single and double bonds, is described. A novel synthesis of $\Delta^{1,5}$-bicyclo[3.3.0]octene (**8**) has been achieved through the Ramberg–Bäcklund rearrangement of 1-bromo-9-thiabicyclo[3.3.1]nonane 9,9-dioxide (**7**). Thermal extrusion of sulfur dioxide from 7-thiabicyclo[2.2.1]heptane 7,7-dioxide (**4**) and 9-thiabicyclo[3.3.1]nonane 9,9-dioxide (**5**) affords 1,5-hexadiene and bicyclo[3.3.0]octane (**14**), respectively, as major products. Photochemical extrusion of sulfur from **1a** and **1b** in trivalent organophosphorus solvents affords, as the major products, cyclohexene and an equimolar mixture of **14** and cyclooctene, respectively. Related studies on the photochemical extrusion of sulfur from bivalent sulfur compounds in organophosphorus solvents are also described.

We have previously described several convenient synthetic routes to two members of the class of symmetrical sulfur-bridged carbocycles represented by **1**.[1] A variety of other bicyclic and polycyclic sulfur-bridged carbocycles has recently become readily available.[2] It is apparent that, if the bridging sulfur, in any of its valence states, could be extruded from such sulfur-bridged rings with the concomitant formation of a bond between the carbon atoms previously joined to sulfur, affording bicyclic structures **2** or **3**, an interesting synthetic method would be at hand for the controlled formation of transannular single or double bonds.[3] Extension of this procedure to the synthesis of bridgehead- and/or ring-substituted bicyclic or polycyclic structures from the appropriately substituted sulfur-bridged precursors should be possible. The general utility of the proposed synthetic procedure requires the elaboration of suitable methods for the conversion of the C–S–C linkage to a C–C single or double bond.



Advantage has been taken in these studies of several unique and characteristic properties of organically bound sulfur, including its ability to exhibit multiple valence states (thereby making available a variety of sulfur bridges), its ability to stabilize adjacent bridgehead carbanions (making bridgehead substitution possible), and the relative photochemical and thermal lability of the C–S bond.

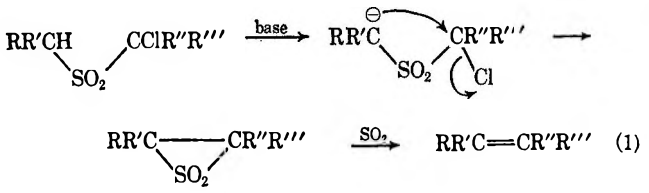
Formation of Transannular Double Bonds. The Ramberg–Bäcklund Reaction.—In 1940, Ramberg and

(1) (a) For paper I of this series, see E. J. Corey and E. Block, *J. Org. Chem.*, **31**, 1663 (1966); (b) also see E. Block, Ph.D. Thesis, Harvard University, 1967 [*Dissertation Abstr.*, **28**, 1849-B (1967)].

(2) (a) For a general survey, see ref 1b; (b) E. D. Weil, K. J. Smith, and R. J. Gruber, *J. Org. Chem.*, **31**, 1669 (1966); (c) F. Lautenschlaeger, *ibid.*, **31**, 1679 (1966); (d) F. Lautenschlaeger, *Can. J. Chem.*, **44**, 2813 (1966); (e) P. Y. Blanc, P. Diehl, H. Fritz, and P. Schlapfer, *Experimentia*, **23**, 896 (1967); (f) F. Lautenschlaeger, *J. Org. Chem.*, **33**, 2620, 2627 (1968).

(3) For a thorough review of the subject of extrusion, see B. P. Stark and A. J. Duke, "Extrusion Reactions," Pergamon Press, New York, N. Y., 1967.

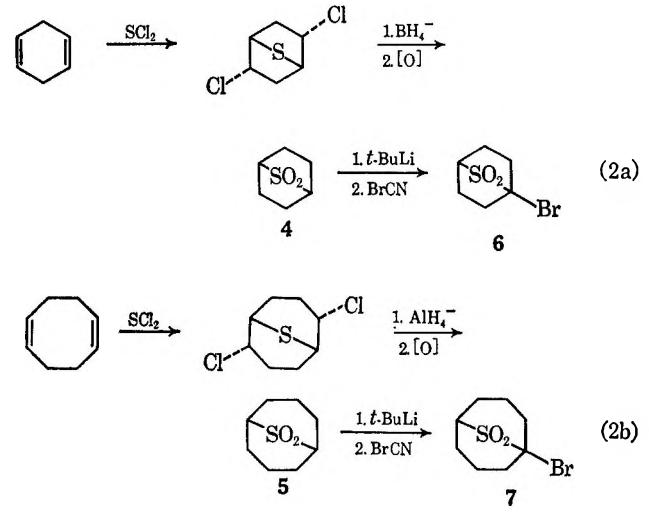
Bäcklund reported that α-halo sulfones, on treatment with aqueous alkali, are transformed into olefins.[4a] Since then the Ramberg–Bäcklund reaction has been studied in considerable detail and is believed to proceed by the sequence illustrated in eq 1.[4b] The reaction is general for molecules containing the structural elements of a sulfonyl group, an α halogen, and at least



(1)

one α-hydrogen atom, and with few exceptions allows the clean replacement of a sulfonyl group by a double bond. The Ramberg–Bäcklund reaction fails in those cases in which the carbanion is geometrically incapable of displacing the α-halogen atom.[4b]

It was of considerable interest to determine if the Ramberg–Bäcklund reaction could be applied to bridgehead halo sulfones such as **6** or **7**. The required bridgehead-substituted sulfones, 1-bromo-7-thiabicyclo[2.2.1]heptane 7,7-dioxide (**6**) and 1-bromo-9-thiabicyclo[3.3.1]nonane 9,9-dioxide (**7**), were conveniently prepared from the corresponding unsubstituted sulfones **4** and **5** by treatment with *t*-butyllithium at low temperatures followed by addition of a source of Br^+, such as cyanogen bromide (eq 2). The



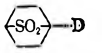
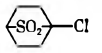
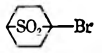
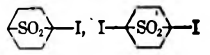
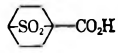
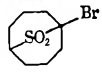
(2a)

(2b)

preparation of the requisite sulfones **4** and **5** has been described in an earlier publication.[1a,5] A variety of other bridgehead-substituted sulfones were prepared (see Table I) by taking advantage of the ability of the sulfone function to stabilize bridgehead anions.[7]

TABLE I

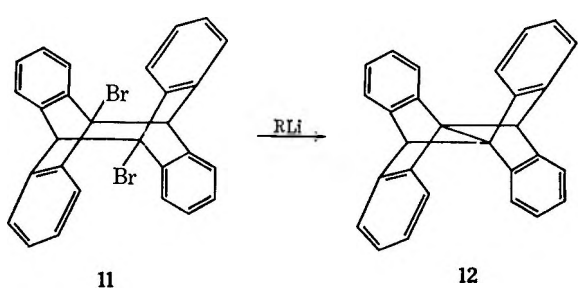
BRIDGEHEAD-SUBSTITUTED SULFONES PREPARED FROM BRIDGEHEAD CARBANIONS

Compound	Reagent	Yield, %
	D_2O	82
	Cl_3CSO_2Cl	72
 (6)	Br_2, BrCN	63, 76
	I_2	60, 2
	CO_2	67
 (7)	BrCN	76

Treatment of bromo sulfone **7** with sodium *t*-pentoxide in tetraglyme at 70° gave the desired transannular Ramberg–Bäcklund rearrangement product, $\Delta^{1,5}$-bicyclo[3.3.0]octene (**8**), in 81% yield. Thus, through a series of several convenient steps, 1,5-cyclooctadiene can be transformed into $\Delta^{1,5}$-bicyclo[3.3.0]octene (**8**) in *ca.* 60% over-all yield. The only previous synthesis of the unsubstituted olefin **8** is a low yield multistep sequence starting with cyclobutanone.[8] Using variously substituted sulfones,[9] a variety of substituted $\Delta^{1,5}$-bicyclo[3.3.0]octenes of known stereochemistry should be preparable.

Treatment of bromo sulfone **6** with base under a variety of experimental conditions led to the disappearance of starting material **6**, but no volatile hydrocarbons, such as the intriguing olefin $\Delta^{1,4}$-bicyclo[2.2.0]-hexene (**9**) or its valence tautomer 1,2-dimethylenecyclobutene (**10**), could be detected. The unsubstituted sulfone **4** is stable under the basic Ramberg–Bäcklund rearrangement conditions. The products of the reaction of bromo sulfone (**6**) with base were water soluble; attempts to characterize the products were not successful.

The novel transannular Ramberg–Bäcklund rearrangement deserves further comment. The conversion of 1-bromo-9-thiabicyclo[3.3.1]nonane 9,9-dioxide (**7**) into $\Delta^{1,5}$-bicyclo[3.3.0]octene (**8**) is postulated to involve backside displacements of a bridgehead halogen (see Scheme I). Another possible example of this unusual type of SN2 reaction was reported by Applequist for the anthracene photodimer system **11** → **12**.[10] It is probable that inversion of carbanion



11 **12**

(4) (a) L. Ramberg and B. Bäcklund, *Arkiv Kemi Mineral. Geol.*, **13A**, No. 27 (1940); *Chem. Abstr.*, **34**, 4725 (1940); B. Bäcklund, Thesis, Uppsala, 1945. (b) For recent reviews of the Ramberg–Bäcklund reaction, see F. G. Bordwell in "Organosulfur Chemistry," M. J. Janssen, Ed., John Wiley & Sons, Inc., New York, N. Y., 1968; L. A. Paquette, *Accounts Chem. Res.*, **1**, 209 (1968).

(5) It has recently come to our attention that the use of the Brown and Bell[6] procedure for the large-scale borohydride reduction of 2,5-bis-*endo*-dichloro-7-thiabicyclo[2.2.1]heptane has resulted in a serious explosion. (L. A. Paquette, personally communicated. We thank Professor Paquette for his communication.) We therefore recommend that the alternate procedure described[1a] for the preparation of 7-thiabicyclo[2.2.1]heptane from 7-oxabicyclo[2.2.1]heptane be used.

(6) H. C. Brown and H. M. Bell, *J. Org. Chem.*, **27**, 1928 (1962).

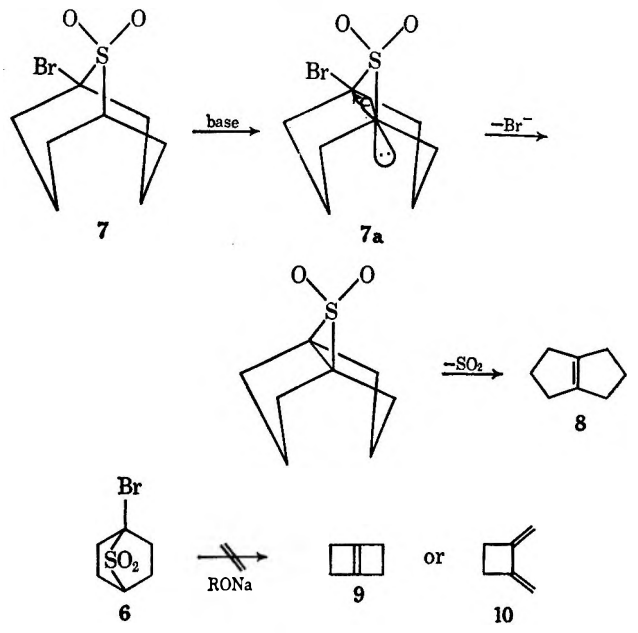
(7) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962.

(8) E. Vogel, *Chem. Ber.*, **88**, 25 (1952).

(9) The preparation of substituted derivatives of 9-thiabicyclo[3.3.1]-nonane and the corresponding sulfone are described in ref 1a, 1b, 2b, and 2d.

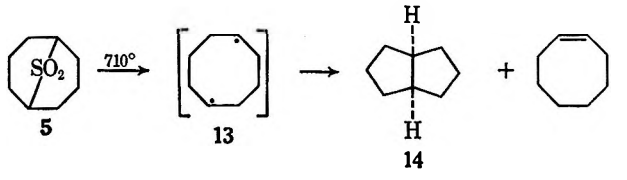
(10) D. E. Applequist, R. L. Little, E. C. Friedrich, and R. E. Wall, *J. Amer. Chem. Soc.*, **81**, 452 (1959); D. E. Applequist and R. Searle, *ibid.*, **86**, 1389 (1964).

SCHEME I

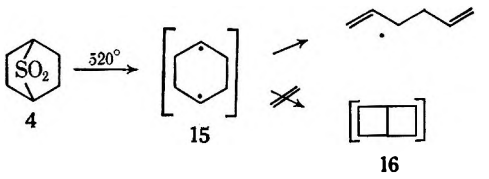


7a is synchronous with transannular bond formation and departure of the bromide ion, as postulated by Applequist for the reaction **11** → **12**.[10] Because of the proximity of the bridgehead carbon atoms in **7** (the C_1–C_5 distance in bicyclo[3.3.1]nonane itself is 2.50 Å[11]), the presence of even a fraction of a negative charge in the rear lobe of the bridgehead carbanion orbital might well lead to considerable transannular repulsive forces which would be relieved by departure of the bromide ion.

Formation of Transannular Single Bonds. Extrusion of Sulfur Dioxide from Bicyclic Sulfones.—Desulfonylation reactions have been the subject of several recent reviews.[3,12] The thermal extrusion of sulfur dioxide occurs readily in those systems in which strain is relieved or aromatization occurs. Sulfur dioxide can be extruded from less reactive sulfones by pyrolysis at temperatures of 600–700°.[12,13] Sublimation of 9-thiabicyclo[3.3.1]nonane 9,9,dioxide (**5**) at 0.1 mm through a quartz tube heated electrically to 710° led to the isolation of *cis*-bicyclo[3.3.0]octane (**14**, 40–50% yield) in addition to minor amounts of cyclooctene (*ca.* 10%). In accord with the proposed mechanism for the pyrolytic extrusion of sulfur dioxide from sulfones,[12] a probable intermediate in this reaction would be diradical **13**.



Sublimation of 7-thiabicyclo[2.2.1]heptane 7,7-dioxide (**4**) at 0.04 mm through a quartz tube at 520° led to the isolation of 1,5-hexadiene in *ca.* 60% yield. Analytical vapor phase chromatography (vpc) failed to reveal significant amounts of bicyclo[2.2.0]hexane (**16**). This hydrocarbon, however, is known to isomerize to 1,5-hexadiene at temperatures above 200°[14] and if formed probably would not survive the pyrolysis conditions. A diradical of the type **15** may be an intermediate in the pyrolysis of sulfone **4**. It is also conceivable that 1,5-hexadiene is formed from sulfone **4** by a concerted mechanism, although this possibility is not very likely in view of the high temperature (520°) necessary to effect the transformation.[15]



Application of this sulfur dioxide extrusion reaction to bicyclic sulfones bearing radical-stabilizing functions at the bridgehead (such as alkyl, aryl, vinyl, or fluorine groups) might permit the synthesis of various bridgehead-substituted hydrocarbons not conveniently synthesized by other methods.

Photochemical Extrusion of Sulfur from Sulfides.—The ultraviolet (uv) spectra of simple dialkyl sulfides reveal two absorption maxima: one at 210–220 mμ with an extinction coefficient of *ca.* 1000 and a second near 230 mμ with an extinction coefficient of less than 200. The stronger, shorter wavelength band is attributed to an $n_s \rightarrow \sigma^*$ transition (*i.e.*, the promotion of a nonbonding electron from an s or sp hybrid orbital on sulfur to an antibonding C–S σ orbital) while the weaker longer wavelength band is ascribed to an $n_p \rightarrow \sigma^*$ transition (the promotion of a nonbonding electron from a p orbital on sulfur to an antibonding C–S σ orbital). Since the energy of a 3p electron is higher than that of a 3s electron, and since the σ^* orbital has a larger p than s character, $n_p \rightarrow \sigma^*$ transitions require less energy (and therefore appear at longer wavelengths), but are less probable and hence give rise to weaker absorption than $n_s \rightarrow \sigma^*$ transitions.[18]

The introduction of strain into cyclic sulfides by decreasing the C–S–C angle results in a bathochromic shift of the long wavelength $n_p \rightarrow \sigma^*$ band.[19] Table II presents several examples of the effect of C–S–C angle strain on the position of the longer wavelength uv maximum in saturated alkyl sulfides.[20] The bathochromic shift is thought to be a consequence of rehybridization of the C–S bonds.[18] Ethylene sulfide may be an anomalous case because of the possibility of

(11) Calculated from the X-ray structural results of W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965).

(12) J. L. Kice in "The Chemistry of Organic Sulfur Compounds," Vol. II, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, New York, N. Y., 1966, p 115.

(13) E. C. Leonard, *J. Org. Chem.*, **30**, 3258 (1965).

(14) S. Cremer and R. Srinivasan, *Tetrahedron Lett.*, No. 21, 24 (1960).

(15) A concerted loss of sulfur dioxide would be a thermally allowed 2 + 2 + 2 process in the terminology of Woodward and Hoffmann[16] if sulfur dioxide is treated as a simple two π-electron system.[17]

(16) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 2046 (1965).

(17) See W. L. Mock, *ibid.*, **88**, 2857 (1966), and S. D. McGregor and D. M. LeMal, *ibid.*, **88**, 2858 (1966), for an application of the Woodward–Hoffmann rules to the pyrolysis of sulfones.

(18) S. F. Mason in "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, p 1. These band assignments may represent an over simplification and in view of recent studies [*e.g.*, P. Salvadori, *Chem. Comm.*, 1203 (1968)] may require modification.

(19) R. E. Davis, *J. Org. Chem.*, **23**, 1380 (1958).

(20) The position of the absorption maximum in alkyl sulfoxides (*ca.* 230 mμ) shows no variation with C–S–C angle strain. Thus, the uv spectrum of 7-thiabicyclo[2.2.1]heptane 7-monoxide was found to be essentially identical with that of dibutyl sulfoxide.

TABLE II
ULTRAVIOLET ABSORPTION SPECTRA OF SATURATED SULFIDES

Compound	Solvent[a]	λ_{max}, mμ[b] (ϵ)	References
$C_2H_5SCH_3$	E	229 (139)	19
	E	229 (183)	19
 [c]	E	235 (sh) (167)	This work
 [d]	E	239 (sh) (87)	This work[e]
	E	239 (54)	19
	I	242 (43)	*f*
	E	247 (43)	This work
	E	257 (40)	19
	E	270 (32)	19
	E	278 (14)	*h*

[a] Solvents: E, ethanol; I, isooctane. [b] Longer wavelength band given; sh, shoulder. [c] Registry number: 281-15-2. [d] Registry number: 6522-54-9. [e] We are grateful to the Hooker Chemical Corp., Niagara Falls, N. Y., for providing us with a sample of 9-thiabicyclo[4.2.1]nonane. [f] American Petroleum Institute Research Project No. 44, Ultraviolet Spectrum No. 843. [g] Registry number: 279-59-4. [h] We are grateful to Professor J. K. Stille of the University of Iowa for the ultraviolet spectrum of 6-thiabicyclo[3.1.1]heptane.

excited states involving the electrons of the C–C as well as the C–S bonds.[19]

Irradiation of simple dialkyl sulfides yields products derived from alkyl and thiyl radicals.[21] The introduction of strain into alkyl sulfides enhances their photochemical reactivity. Thus, both thiacyclobutane and 6-thiabicyclo[3.1.1]heptane undergo ready light-initiated radical polymerization.[22] The complex array of products often obtained from the photolysis of sulfides[23] is a consequence of reactions involving both thiyl and carbon free radicals. By applying the discovery[24] that thiyl radicals can be converted into alkyl radicals by trivalent phosphorus compounds (see eq 3), considerable simplification can be achieved.

$$\mathrm{RSH} \xrightarrow[\text{initiator}]{h\nu \text{ or}} \mathrm{RS}\cdot \xrightarrow{\mathrm{R'_3P}} \mathrm{RS{-}PR'_3} \longrightarrow \mathrm{R}\cdot + \mathrm{R'_3P{=}S} \quad (3)$$

$$\mathrm{R}\cdot + \mathrm{RSH} \longrightarrow \mathrm{RH} + \mathrm{RS}\cdot$$

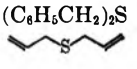
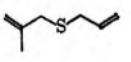
Thus, if the photolysis of a sulfide is carried out in a trivalent organophosphorus solvent (such as a phosphite or phosphine), the only reactive intermediates to be considered should be carbon free radicals (provided that the thiyl radical is desulfurized before it has a chance to react).

$$\mathrm{RSR'} \xrightarrow[\mathrm{R''_3P}]{h\nu} \mathrm{R}\cdot + \mathrm{R'}\cdot + \mathrm{R''_3P{=}S} \quad (4)$$

In fact, irradiation of a solution of 9-thiabicyclo[3.3.1]nonane (**1b**) in isooctyl phosphite gave in 47% total yield a hydrocarbon mixture which consisted of *cis*-bicyclo[3.3.0]octane (**14**, 46%), the product expected from simple intramolecular coupling of the 1,5-cyclooctyl diradical (**13**), in addition to cyclooctene (46%) and cyclooctane (8%).

Table III summarizes the results of irradiating a variety of organic sulfur compounds in trivalent organophosphorus solvents. Certain of these results will be considered in greater detail.

TABLE III
PHOTOLYSIS OF ORGANIC SULFUR COMPOUNDS IN ORGANOPHOSPHORUS SOLVENTS

Reactant	Solvent[a]	Yield, %	Products (relative amounts, %)
	$(R'O)_3P$	47	*cis*-Bicyclo[3.3.0]-octane (46), cyclo-octene (46), cyclooctane (8)
	$(R'O)_3P$	49	Cyclohexene (85), cyclohexane (8), 1,5-hexadiene (6)
	R_3P	49	Cyclohexene (83), cyclohexane (7), 1,5-hexadiene (7)
	$(R_2N)_3P$	*ca.* 4[b]	Cyclohexene (71), cyclohexane (8), 1,5-hexadiene (20)
$(C_6H_5CH_2)_2S$	$(R''O)_3P$	59	Dibenzyl
	$(R'O)_3P$	38	1,5-Hexadiene
	R_3P	68	1,5-Hexadiene (23), 2-methyl-1,5-hexadiene (52), 2,5-dimethyl-1,5-hexadiene (25)
	R'_3P	Traces	1-Pentene (?)
	$(R'O)_3P$		Complex mixture

[a] R = C_4H_9; R' = C_8H_{17}; R'' = CH_3. [b] Photolysis was not carried to completion.

Irradiation of a solution of 7-thiabicyclo[2.2.1]-heptane (**1a**) in trivalent phosphorus solvents gave a mixture of cyclohexene, cyclohexane, and 1,5-hexadiene in relative amounts which varied with the solvent. Thus, for the solvent sequence $(C_7H_{15}O_3)P$, $(C_4H_9)_3P$, and $[(C_4H_9)_2N]_3P$, the relative amount of cyclohexene decreases, the relative amount of 1,5-hexadiene increases, and the relative amount of cyclohexane remains unchanged. Since this solvent sequence represents the order of increasing nucleophilicity at phosphorus,[25] and therefore the order of increasing affinity of the phosphorus solvent for the electrophilic thiyl radical,[26–28] it would appear that the cyclohexene is derived, at least in part, from a thiyl diradical at the

(21) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N. Y., 1966, pp 488–492.

(22) S. F. Birch, R. A. Dean, and N. J. Hunter, *J. Org. Chem.*, **23**, 1026 (1958).

(23) For example, a complex mixture of products is obtained from the photolysis of dibenzyl sulfide: W. H. Laarhoven and Th. J. H. M. Cuppen, *Tetrahedron Lett.*, 5003 (1966); W. Curruthers, *Nature*, **209**, 908 (1966); W. H. Laarhoven, Th. J. H. M. Cuppen, and R. J. F. Nivard, *Rec. Trav. Chim. Pays-Bas*, **86**, 821 (1967).

(24) C. Walling and R. Rabinowitz, *J. Amer. Chem. Soc.*, **81**, 1243 (1959).

(25) See E. H. Amonoo-Neizer, *et al.*, *J. Chem. Soc.*, 4296 (1965).

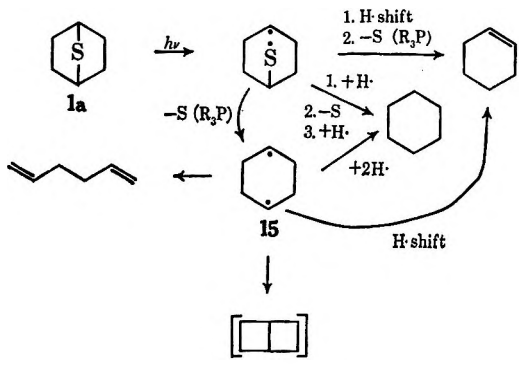
(26) C. Walling, "Free Radicals in Solution," John Wiley & Sons, Inc., New York, N. Y., 1957, pp 318–322.

(27) For an example of the enhanced effectiveness of tris(diethylamino)-phosphine as a desulfurizing agent compared with other phosphines and phosphites, see D. N. Harpp, J. G. Gleason, and J. P. Snyder, *J. Amer. Chem. Soc.*, **90**, 4181 (1968).

(28) For an example of an especially thiophilic organophosphorus heterocycle, see E. J. Corey and J. I. Shulman, *Tetrahedron Lett.*, 3655 (1968).

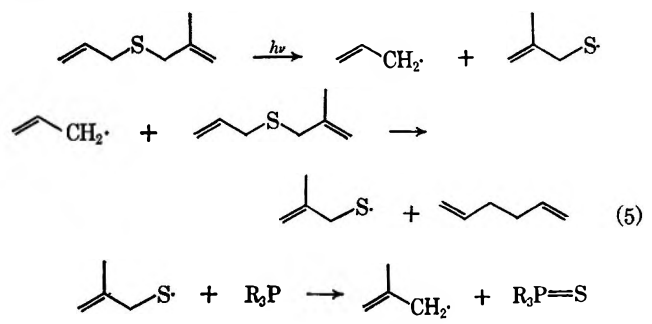
expense of 1,5-hexadiene. Significant quantities of bicyclo[2.2.0]hexane (16) could not be detected. A plausible scheme for the formation of the various products is given in Scheme II. A similar scheme could be written for the photochemical reactions of 9-thiabicyclo[3.3.1]nonane (1b) (omitting the fragmentation reaction characteristic of the 1,4-cyclohexyl diradical).

SCHEME II



Unsuccessful attempts were made to prepare bicyclo[2.2.0]hexane (16) from 7-thiabicyclo[2.2.1]heptane (1a) by irradiation of the blood-red tetracyanoethylene charge-transfer complex of 1a, by irradiation of 1a in the presence of the Lewis acid phosphorus trifluoride, or by warming 1a with the powerful phosphorus nucleophile 2-phenyl-3-methyl-1,3,2-oxazaphospholidine.[29]

A second interesting result recorded in Table III is the completely statistical product distribution obtained from the photolysis of allyl methallyl sulfide. The ratio of the amounts of 1,5-hexadiene, 2-methyl-1,5-hexadiene, and 2,5-dimethyl-1,5-hexadiene obtained in the photolysis is 23:52:25. Consistent with the observed product ratio would be a mechanism involving completely random combination of allylic radicals, a chain mechanism involving attack of an allylic radical at a terminal methylene carbon on unreacted starting material affording a diene and a thiyl radical (eq 5), or some combination of these two mechanisms.



Experimental Section[30]

1-Bromo-7-thiabicyclo[2.2.1]heptane 7,7-Dioxide (6).—A solution of 4.00 g (27.4 mmol) of 7-thiabicyclo[2.2.1]heptane 7,7-dioxide (4) in 200 ml of tetrahydrofuran (distilled from lithium aluminum hydride) was cooled in a nitrogen atmosphere to −78° and treated all at once with 20 ml of 1.97 *M* *t*-butyllithium (39.4 mmol). After stirring at −70° for 30 min, the yellow solution was added in 20-ml portions during 30 min to a vigorously stirred solution of 7 g of cyanogen bromide (66 mmol) in 150 ml of anhydrous ether at −112° in a nitrogen atmosphere. The reaction mixture was stored overnight at −50°, warmed to 0°, and washed several times with 10% aqueous potassium hydroxide and saturated aqueous sodium hydrogen sulfite. The organic phase was dried over anhydrous magnesium sulfate, concentrated to a minimal volume, and treated with excess *n*-pentane to precipitate 5.35 g of crude 6. Recrystallization of the crude solid from methanol gave 4.87 g (76%) of colorless crystals: mp 149–151°; ir $\lambda_{max}^{CHCl_3}$ 7.58, 7.71, 8.70, 8.82 (all intense sulfone bands) in addition to "fingerprint" bands at 9.30 (w), 10.01 (s), 11.06 (br, w), 11.70 (w), 12.06 μ (s); nmr (CF_3COOH) peaks appeared at δ 2.40 (multiplet, eight protons) and 3.25 (singlet, one proton—bridgehead position).

Anal. Calcd for $C_6H_9SO_2Br$: C, 31.99; H, 4.03; Br, 35.51; S, 14.25. Found: C, 31.79; H, 3.98; Br, 35.37; S, 13.82.

1-Bromo-9-thiabicyclo[3.3.1]nonane 9,9-Dioxide (7).—To a suspension of 5.00 g (28.7 mmol) of 9-thiabicyclo[3.3.1]nonane 9,9-dioxide (5) in 350 ml of anhydrous tetrahydrofuran at −78° in a nitrogen atmosphere was added all at once with vigorous stirring 20 ml of 1.97 *M* *t*-butyllithium (39.4 mmol) precooled to Dry Ice temperature. The resulting homogeneous yellow solution was stirred at −78° for 30 min and then added to a vigorously stirred solution of 7.5 g (71 mmol) of cyanogen bromide in 250 ml of anhydrous ether in a nitrogen atmosphere at −112°. The colorless suspension was stored at −50° overnight and then, after warming to −10°, washed several times with saturated aqueous sodium bicarbonate and 10% aqueous potassium hydroxide. The organic phase was dried over anhydrous magnesium sulfate and then concentrated *in vacuo*. Treatment of the residue with excess *n*-pentane followed by recrystallization of the crude solid from boiling methanol afforded 4.11 g (56%) of 7 as colorless needles: mp 182–183° (after several recrystallizations); ir $\lambda_{max}^{CHCl_3}$ 6.75 (m, characteristic band of 3.3.1 system), 6.95 (m), 7.66, 8.91, and 8.99 μ (all intense sulfone bands); nmr (CF_3COOH) peaks appeared at δ 2.5–3.2 (complex methylene multiplet, twelve protons) and 3.59 (bridgehead proton multiplet, one proton).

Anal. Calcd for $C_8H_{12}SO_2Br$: C, 37.95; H, 5.17; Br, 31.57; S, 12.67. Found: C, 38.42; H, 4.73; Br, 31.72; S, 12.77.

1-Chloro-7-thiabicyclo[2.2.1]heptane 7,7-Dioxide.—A solution of 200 mg (1.37 mmol) of bicyclic sulfone 4 in 5 ml of anhydrous tetrahydrofuran was cooled to −78° in a nitrogen atmosphere and treated with *t*-butyllithium (2.3 mmol) in pentane. The yellow solution was stirred for 1 hr at −78° and then added during the course of several minutes to a vigorously stirred solution of 600 mg (3 mmol, 100% excess) of trichloromethyl sulfonyl chloride (recrystallized from hexane prior to use) in 7 ml of anhydrous tetrahydrofuran at −78° in a nitrogen atmosphere. The reaction mixture was slowly warmed to 0° during the course of 2 hr and then stirred for 30 min at 0° with 4 ml of pyridine and 0.5 ml of water to destroy the unreacted sulfonyl chloride. The solution was then diluted with aqueous hydrochloric acid and extracted with several portions of methylene chloride. The organic phase was shaken consecutively with aqueous hydrochloric acid, 2 *N* aqueous copper sulfate, and brine, dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The residue was recrystallized from methylene chloride–*n*-hexane to give 179 mg (72%) of the chloro sulfone as colorless, odorless crystals, mp 146–150°, homogeneous by thin layer chromatography (tlc). The ir spectrum had $\lambda_{max}^{CHCl_3}$ at 7.62, 7.72, 8.70, 8.85 (all intense sulfone bands) and 9.25 (m), 9.91 (s), 10.55 (w), 10.82 (m), 11.61 (m), 12.06 μ (s) ("fingerprint"

(29) E. J. Corey and C. C. Cumbo, unpublished findings.

(30) Elemental analyses were performed by the Scandinavian Microanalytical Laboratories, Herlev, Denmark, and by C. Daessle, Montreal, Canada. Exact molecular weights and mass spectra were determined on an Associated Electrical Industries Ltd., Model MS-9 double-focusing mass spectrometer. All melting points were obtained on a Büchi melting point apparatus and are corrected. Nuclear magnetic resonance (nmr) spectra were obtained on a Varian Associates Model A-60 nmr spectrometer (60 Mc) with tetramethylsilane as internal standard. Spin decoupling at 60 Mc was accomplished using a Varian Associates Model V-6058 spin decoupler in conjunction with the Varian A-60 nmr spectrometer. Infrared (ir) spectra were obtained on a Perkin-Elmer Model 137 sodium chloride spectrophotometer and a Perkin-Elmer Model 237 grating ir spectrometer using polystyrene as a calibration standard. Uv data were obtained using a Perkin-Elmer Model 202 spectrophotometer and Cary Models 11M and 14 spectrophotometers with ethanol as solvent unless otherwise indicated. Vpc was performed on F & M Models 300, 609, and 810 chromatographs.

region bands); the nmr spectrum (CF_3COOH) had peaks at δ 2.0 (multiplet, eight protons) and 3.0 (singlet, one proton) using an external tetramethylsilane standard. The molecular weight determined mass spectrometrically was 180.0010 (calcd for $C_6H_9SO_2Cl$: 180.0013).

1-Iodo-7-thiabicyclo[2.2.1]heptane 7,7-Dioxide.—A solution of 1.10 g of bicyclic sulfone **4** (7.55 mmol) in 50 ml of anhydrous tetrahydrofuran was cooled in a nitrogen atmosphere to −78° and then treated with 10 ml of 1.97 *M* *t*-butyllithium (20 mmol). The clear yellow solution was stirred at −60 to −70° for 45 min and then treated with a saturated solution of iodine in ether until the iodine color remained. The reaction mixture was allowed to warm to −20° and then shaken with saturated aqueous sodium bisulfite solution until the organic layer was colorless. The organic phase was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The solid residue was washed with excess pentane and dried giving 1.55 g of crude product showing two spots on tlc. The spot with the greater R_f value was considerably fainter than the more slowly moving spot; neither spot corresponded to starting material.

Recrystallization of 1.30 g of crude product from boiling carbon tetrachloride gave 0.82 g of colorless crystals homogeneous on tlc analysis (the product corresponding to the more slowly moving spot) and 0.28 g of residue. Preparative tlc of the residue (silica gel, chloroform containing 5% ethyl acetate) gave an additional 0.19 g of the major product (total yield 1.02 g, 60%) and 0.06 g of a second product.

The major product had mp 174–175° and ir $\lambda_{max}^{CHCl_3}$ at 7.65, 7.78, 8.71, and 8.88 (intense sulfone bands) as well as at 9.34 (w), 10.10 (s), 11.75 (w), and 12.09 μ (s). The ir spectrum of this chromatographed product was essentially identical with that of the crude product. The nmr spectrum ($CDCl_3$) showed peaks at δ 1.6–2.7 (complex multiplet, eight protons) and 2.85 (singlet, one proton). The molecular weight determined mass spectrometrically was 271.9358 (calcd for $C_6H_9SO_2I$: 271.9370). The major product was assigned the structure of 1-iodo-7-thiabicyclo-[2.2.1]heptane 7,7-dioxide.

The minor chromatography product had mp 213–215°. The colorless solid had ir $\lambda_{max}^{CHCl_3}$ at 7.55 and 8.75 (intense sulfone bands) as well as at 9.22 (m), 9.95 (m), 10.30 (s), 11.50 (w), and 11.80 μ (w). The nmr spectrum ($CDCl_3$) showed an AB quartet centered at δ 2.53 ($J_1 = 9.5, J_2 = 5.5$ cps). The molecular weight determined mass spectrometrically was 397.8338 (calcd for $C_6H_8SO_2I_2$: 397.8338). The minor product, assigned the structure of 1,4-diiodo-7-thiabicyclo[2.2.1]heptane 7,7-dioxide, was formed in about 2% yield.

7-Thiabicyclo[2.2.1]heptane-1-carboxylic Acid 7,7-Dioxide.—A Solution of 200 mg (1.37 mmol) of bicyclic sulfone **4** in 10 ml of anhydrous tetrahydrofuran was cooled to −78° in a nitrogen atmosphere and treated with *t*-butyllithium (2.3 mmol) in pentane. The yellow solution was stirred for 70 min at −78° and then treated during the course of 6 hr at −78° with gaseous "bone dry" grade carbon dioxide (used from the cylinder without preliminary drying). The reaction mixture was warmed to room temperature, treated with a few milliliters of 10% aqueous potassium hydroxide, extracted several times with ether, filtered, and brought to pH 1 with hydrochloric acid. The aqueous phase was extracted several times with ether and ethyl acetate and the organic extract was dried and concentrated *in vacuo*. The slightly yellow residue was recrystallized from boiling ethyl acetate–carbon tetrachloride giving 171 mg (67% yield) of the title compound as a colorless solid decomposing above 200°: ir λ_{max}^{KBr} at 2.5–4 (broad carboxylic acid bands), 5.86 (carbonyl), 7.64, 7.70, 7.78, 8.74, 8.92 μ (all intense sulfone bands); nmr (CF_3COOH) δ 1.9 (sextet, seven protons) and 2.9 (singlet, single bridgehead proton) using an external tetramethylsilane standard.

Anal. Calcd for $C_7H_{10}SO_4$: C, 44.18; H, 5.30; S, 16.86. Found: C, 44.04; H, 5.18; S, 16.76.

1-Deuterio-7-thiabicyclo[2.2.1]heptane 7,7-Dioxide.—A solution of 435 mg (2.98 mmol) of 7-thiabicyclo[2.2.1]heptane 7,7-dioxide **4** in 20 ml of anhydrous tetrahydrofuran was cooled under nitrogen to −80° and treated dropwise with 2 ml of 2.5 *M* *t*-butyllithium (5 mmol) in pentane. After the yellow solution had stirred for 5 min at −80°, a solution of 1 ml of deuterium oxide in 5 ml of anhydrous tetrahydrofuran was added causing immediate decolorization. The reaction mixture was warmed to room temperature and neutralized with methanolic hydrochloric acid, and the organic layer was decanted from lithium chloride and concentrated *in vacuo*. The residue was taken up in methylene chloride, dried over anhydrous magnesium sulfate, concentrated, and then recrystallized from methylene chloride–carbon tetrachloride–*n*-hexane to give 360 mg (82% yield) of colorless, fluffy needles: mp 248° (with sublimation); ir $\lambda_{max}^{CHCl_3}$ 7.72 and 8.80 (intense sulfone bands) as well as 9.35 (w), 10.20 (w), 11.38 (w), 11.85 (m), and 12.62 μ (w); nmr ($CHCl_3$) δ 2.02 (multiplet, integrated area 8.8) and 2.88 (singlet, broad, integrated area 1).

Deuteration of 9-Thiabicyclo[3.3.1]nonane 9,9-Dioxide (5).—A solution of 400 mg (2.3 mmol) of bicyclic sulfone **5** in 4 ml of anhydrous tetrahydrofuran was added to a solution of 515 mg of potassium *t*-butoxide (4.6 mmol) in 4 ml of *t*-butyl alcohol-OD (93% deuterium by nmr analysis) in a nitrogen atmosphere at 24°. After stirring for 18 hr at 24–29°, 55% of the bridgehead protons had been replaced by deuterium (by nmr analysis); after an additional 2 hr at 50°, 80% of the bridgehead protons had been exchanged. The bridgehead deuterated sulfone could be isolated in 90% yield from the basic solution.

$\Delta^{1,6}$-Bicyclo[3.3.0]octene (8).—In a 25-ml three-necked flask equipped with a stirring bar, a rubber septum, and a wide-bore three-way stopcock leading to a liquid nitrogen trap was placed 1.0 g of 55% sodium hydride in mineral oil (23 mmol). The sodium hydride was washed three times with pentane, and 10 ml of tetraglyme (freshly distilled from lithium aluminum hydride) and 1.08 ml of *t*-amyl alcohol (10 mmol, distilled from calcium hydride) were added. The suspension was warmed to 70° with stirring and, when hydrogen evolution ceased, evacuated to 0.02 mm for 30 min. The reaction mixture was cooled to 30° and 1.00 g (4 mmol) of bromo sulfone **7** was added all at once. The reaction mixture was placed under nitrogen and, with vigorous stirring, warmed to 70° for 1 hr to convert the *t*-amyl alcohol formed from the acidic proton of bromo sulfone **7** into alkoxide. After cooling to 30°, the system was connected by means of the three-way stopcock to the liquid nitrogen trap and the system was evacuated to 0.1 mm. The temperature of the reaction mixture was gradually raised to 70° and kept at this temperature for 1 hr. At the end of 1 hr, 0.34 g (81%) of the colorless bicyclic olefin **8** was collected in the liquid nitrogen trap. The liquid, having a heavy, sweet odor, had $n^{25}D$ 1.4803 (lit.[31] $n^{25}D$ 1.4802) and was homogeneous on several different vpc columns, having practically the same retention time as cyclooctene. The mass spectrum indicated the molecular formula C_8H_{12}. The ir spectrum (neat) was very simple, showing no bands characteristic of unsaturation as expected for a symmetrical tetrasubstituted double bond.[32] The nmr spectrum showed a sharp singlet at δ 2.15 in benzene and at 2.18 in deuteriochloroform (lit.[33] δ 2.12 in carbon tetrachloride).

Attempted Preparation of $\Delta^{1,4}$-Bicyclo[2.2.0]hexene (9).—A solution of 450 mg of recrystallized bromo sulfone **6** (2 mmol) in 8 ml of anhydrous tetraglyme was added dropwise to a freshly prepared solution of 5 mmol of sodium *t*-amyloxide in tetraglyme at 70° under high vacuum using the apparatus described for the preparation of bicyclic olefin **8**. *t*-Amyl alcohol (164 mg, 93% yield based on bromo sulfone **6**), characterized by ir spectroscopy and demonstrated to be homogeneous by vpc (on a column giving excellent separation of *t*-amyl alcohol and C_6 hydrocarbons and olefins), was isolated in the liquid nitrogen trap.

Bromo sulfone **6** could be recovered in good yield after being exposed for 10.5 hr to refluxing 6 *N* aqueous sodium hydroxide.

Treatment of 0.9 g of bromo sulfone **6** with a solution of 1 g of potassium *t*-butoxide in 7 ml of *t*-butyl alcohol at reflux for 12 hr gave an orange solution from which 0.1 g of 7-thiabicyclo[2.2.1]-heptane 7,7-dioxide (**4**) could be isolated by concentration *in vacuo* followed by extraction of the residue with ether and concentration of the extract. From the acidified residue there could be isolated 0.3 g of a water-soluble red-brown viscous oil having complex ir and nmr spectra. This product was not further investigated.

Pyrolysis of 9-Thiabicyclo[3.3.1]nonane 9,9-Dioxide (5).—The pyrolysis apparatus used consisted of a 40-cm-long quartz tube (7-mm inside diameter) sealed at one end and wrapped in the middle 20-cm section with nichrome wire which in turn was wrapped with asbestos tape as insulation. The open end of the tube contained a standard taper joint. A thermocouple was held

(31) A. C. Cope, *et al.*, *J. Amer. Chem. Soc.*, **82**, 4306 (1960).

(32) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley & Sons, New York, N. Y., 1963, p 58.

(33) H. Krieger, *Suomen Kemistilehti*, **B38**, 260 (1965).

against the quartz tube by the nichrome wire. The standard taper joint of the pyrolysis tube could be connected to a trap. Recrystallized bicyclic sulfone **5** (0.50 g, 2.9 mmol) was placed in the bottom of the pyrolysis tube and the entire system was evacuated to 0.1 mm. The pyrolysis zone was warmed electrically to 710°, the trap was cooled in liquid nitrogen, and the sulfone **5** was sublimed into the pyrolysis zone during the course of 1.5 hr by immersing the sealed 10-cm portion of the quartz tube in an oil bath warmed to 135–140°. A yellow oil (0.18 g) was collected in the low temperature trap (volatile gases such as sulfur dioxide and hydrogen sulfide were removed by warming the distillate on a steam bath). The product showed a single major peak on vpc analysis (using a 10-ft 25% TCEP on Chromosorb P column) having the same retention time as authentic *cis*-bicyclo[3.3.0]octane (**14**). The yield of **14**, as estimated from vpc analysis of the crude product, was 40–50%. Minor amounts (*ca.* 5%) of a product having the same vpc retention time as cyclooctene were also obtained. The major product was further characterized by the ir spectrum of product purified by vpc; the ir spectrum of the vpc sample was identical with that of authentic *cis*-bicyclo[3.3.0]octane (**14**). When the pyrolysis was carried out at 590° (temperature of pyrolysis zone) some hydrocarbon **14** was formed in very low yield. At this temperature most of the sulfone **5** simply sublimed through the pyrolysis zone and could be recovered unchanged.

Pyrolysis of 7-Thiabicyclo[2.2.1]heptane 7,7-Dioxide (4).—Using the pyrolysis apparatus described above, 0.500 g of sulfone **4** was sublimed at 0.04 mm into the pyrolysis zone, heated electrically to 520°, during 75 min by warming the sealed end of the quartz tube to 110°. A yellow oil (0.188 g) was isolated in the low temperature trap. Vpc analysis indicated the presence of one major product, characterized as 1,5-hexadiene by ir spectroscopy, formed in 56% yield, in addition to a minor unidentified product, possessing a much greater retention time than 1,5-hexadiene. No significant amounts of bicyclo[2.2.0]hexane (**16**) could be detected by vpc analysis on a silver nitrate column. Lower pyrolysis temperatures led only to sublimation of sulfone **4** through the pyrolysis zone without undergoing any reaction.

Photochemical Studies. General Procedure.—A solution of the sulfide in an organophosphorus solvent was placed in a 10-ml quartz tube. The reaction mixture was repeatedly evacuated and flushed with argon to remove oxygen. Irradiation using vycor filtered light from a 450-W Hanovia medium pressure mercury lamp (Model 450L) was carried out for the indicated time period while the reaction mixture was maintained at 5–10° by a circulating water bath. The progress of the reaction was followed by ir or nmr spectroscopy. After completion of the reaction, the volatile products were isolated from the high boiling solvent by flash distillation. The distillate was collected at liquid nitrogen temperatures and analyzed by vpc combined with spectroscopic methods.

A key to the analytical methods used to identify the various reaction products follows: (a) comparison of ir spectrum of crude distillate with that of an authentic spectrum; (b) comparison of the nmr spectrum of the crude distillate with that of an authentic spectrum; (c) comparison of the vpc retention time with that of an authentic compound; (d) comparison of the ir spectrum of the vpc fraction with that of an authentic spectrum; (e) comparison of the nmr spectrum of the vpc fraction with that of an authentic spectrum; (f) comparison of the mass spectrum of the vpc fraction with that of an authentic spectrum.

Photolysis of 7-Thiabicyclo[2.2.1]heptane (1a). A. In Isooctyl Phosphite.—Irradiation of 400 mg (3.5 mmol) of sublimed **1a** in 6 ml of redistilled isooctyl phosphite for 18 hr gave a yellow solution (no precipitate) from which 140 mg (49% yield) of a colorless volatile fraction was isolated. Analysis of the volatile product on an 8-ft vpc column (30% saturated silver nitrate in triethylene glycol on Chromosorb P) at 0° showed the following products: 8% cyclohexane (a, c, d), 85% cyclohexene (a, c, d), 6% 1,5-hexadiene (a, c, f) (in order of increasing retention times), and several minor products (<1% of each) some of which were derived from the solvent (according to mass spectral analysis).

B. In Tributylphosphine.—Irradiation of 400 mg of **1a** in 6 ml of freshly distilled tributylphosphine for 17 hr gave a yellow solution (no precipitate) from which 140 mg (49% yield—corrected for aliquots taken) of a colorless volatile fraction was isolated. Analysis of the volatile product on the silver nitrate vpc column at 0° indicated the following composition: 7% cyclohexane (c), 83% cyclohexene (a, b, c), 7% 1,5-hexadiene (a, b, c), and several minor products (<1% each).

C. In Tris(dibutylamino)phosphine.—Irradiation of 400 mg of **1a** in 6 ml of distilled tris(disbutylamino)phosphine for 60 hr gave a yellow solution (no precipitate) which still contained considerable starting material (about 85% according to nmr analysis).[34] Analysis of the volatile fraction (69 mg, mainly **3**) indicated the following highly volatile components: 8% cyclohexane (c), 71% cyclohexene (b, c), 20% 1,5-hexadiene (c, d), and 2% unidentified product.

D. In the Presence of an Equivalent of Tetracyanoethylene.—Irradiation of the blood-red charge-transfer complex ($\lambda_{max}^{CH_3CN}$ 410–460 mμ) from equimolar amounts of **1a** and TCNE (doubly sublimed) gave no indication of reaction involving **1a**.

E. In the Presence of Phosphorus Trifluoride.—Irradiation of **1a** in trioctyl phosphine in the presence of phosphorus trifluoride gave a brown precipitate but no evidence of reaction involving **1a**.

In none of the above photolyses could the presence of bicyclo[2.2.0]hexane (**16**) be unequivocally established; if it were formed it constituted less than 1% of the hydrocarbon products.

Photolysis of 9-Thiabicyclo[3.3.1]nonane (1b). A. In Isooctyl Phosphite.—Irradiation of 800 mg (5.63 mmol) of sublimed **1b** in 6 ml of distilled isooctyl phosphite for 20 hr gave a yellow solution (no precipitate) from which 293 mg (47% yield) of a colorless volatile fraction was isolated. Vpc analysis on the silver nitrate column at 24° gave the following results: 46% *cis*-bicyclo[3.3.0]octane (**14**) (d, e, f), 8% cyclooctane (c, d, f), 46% cyclooctene (b, c, d) (in order of increasing retention times), and trace amounts (<1%) of products presumably derived from the solvent.

B. In Tris(dibutylamino)phosphine.—Irradiation of **1b** in tris(dibutylamino)phosphine for 6 days did not lead to appreciable quantities of products derived from **1b**.

Photolysis of Diallyl Sulfide.—Irradiation of 400 mg of diallyl sulfide (3.5 mmol) in 6 ml of trioctylphosphine for 72 hr gave 173 mg of a colorless volatile fraction which analyzed for 60% 1,5-hexadiene (a, b, c) (38% yield) and 37% *n*-octane (a, b, c) derived from the solvent.

Photolysis of Allyl Methallyl Sulfide.—Irradiation of 504 mg (3.93 mmol) of redistilled allyl methallyl sulfide (this was prepared from the reaction of methallyl chloride and sodium allyl mercaptide at 0°; mass measurement indicated a molecular weight of 128; and the nmr spectrum was in full accord with indicated structure) in 6 ml of redistilled tributylphosphine for 18.5 hr gave a colorless solution (no precipitate) from which 253 mg of colorless distillate (60% yield) was isolated. Analysis of the distillate on an 8-ft TCEP vpc column at 60° gave the following composition: 23% 1,5-hexadiene (b, c), 52% 2-methyl-1,5-hexadiene (b, c), and 25% 2,5-dimethyl-1,5-hexadiene (b, c) (in order of increasing retention times; product composition corrected by calibration of the column with a mixture of known composition).

Photolysis of Benzyl Sulfide.—A solution of 748 mg of benzyl sulfide (3.34 mmol) in 6 ml of distilled trimethyl phosphite was irradiated for 72 hr (the reaction was over after 17 hr). Removal of the solvent at 25° (0.01 mm), followed by treatment of the residue with methanol, gave 377 mg (59% yield) of a yellow solid, mp 41–50°, which after recrystallization twice from *n*-pentane (the solid was colorless after recrystallization) had mp 50.2–52.6°, undepressed on admixture with authentic dibenzyl. It had an ir spectrum identical with that of authentic dibenzyl. The residue from the precipitation of the crude dibenzyl consisted principally of trimethyl thiophosphate.

Photolysis of Thiacyclohexane.—Irradiation of 394 mg (3.86 mmol) of thiacyclohexane in 6 ml of trioctylphosphine for 72 hr and analysis of the product by the usual procedure indicated mainly unreacted starting material and products arising from solvent decomposition. In addition, trace amounts of other products, possibly 1-pentene and *n*-pentane, were found on vpc analysis.

Registry No.—**6**, 19669-15-9; **7**, 19669-16-0; 1-chloro-7-thiabicyclo[2.2.1]heptane 7,7-dioxide, 19643-36-8; 1-iodo-7-thiabicyclo[2.2.1]heptane 7,7-dioxide,

(34) Compounds containing P–N bonds are not completely transparent below 250 mμ and thus filter out a portion of the effective radiation, slowing the photolysis considerably.

19643-37-9; 1,4-diiodo-7-thiabicyclo[2.2.1]heptane 7,7-dioxide, 19643-38-0; 7-thiabicyclo[2.2.1]heptane-1-carboxylic acid 7,7-dioxide, 19643-39-1; 1-deuterio-7-thiabicyclo[2.2.1]heptane 7,7-dioxide, 19643-40-4.

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The Chemistry of Ylides. XIX. β-Carbonyl Sulfonium Ylides[1]

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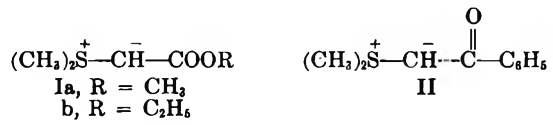
The preparation, isolation, and physical and chemical properties of dimethylphenacylidenesulfurane (II) and dimethyl(carbomethoxymethylene)sulfurane (Ia) are described. Both ylides exhibit decreased nucleophilicity and basicity as a result of the delocalization of the carbanion electrons through the carbonyl groups, the decrease being larger for II. Spectroscopic methods and chemical reactions (alkylation, acylation, and reaction with carbonyl compounds and nitrosobenzene) served to illustrate the differences. The mechanism of the thermal decomposition of sulfonium ylides to cyclopropanes appears to involve a carbenic moiety.

This paper reports the details of our work on a group of stabilized, isolable sulfonium ylides, the β-carbonyl ylides Ia and II, part of the results having been reported in a preliminary communication.[3] At the time this work was undertaken no carboalkoxy sulfonium ylides or β-keto sulfonium ylides were known. In fact, very few isolable sulfonium ylides had been prepared or studied, most of the chemistry of sulfonium ylides having been elaborated utilizing complex solutions of the ylides.[4] We feel it is important actually to isolate and characterize ylides to describe accurately their properties and behavior.



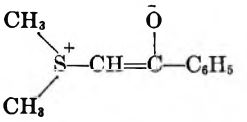
Ia, R = CH_3
b, R = C_2H_5

II

Since our preliminary report on the chemistry of the phenacylide II, several groups[5,6] have reported the results of their similar studies. Nozaki, *et al.*,[7] have studied the related S-methyl-S-phenylphenacylide. Several groups[5,8-11] have reported on the chemistry of Ib while Casanova and Rutolo[12] recently reported on the properties of Ia.

Dimethylphenacylidenesulfurane (II).—The crystalline ylide II was prepared from dimethylphenacylsulfonium bromide in ethanol solution by proton abstraction with triethylamine. The anhydrous ylide, mp 67–68°, was converted into a hydrate of mp 57–58° upon standing exposed to the atmosphere or upon standing in a solvent to which a few drops of water had been added. Payne,[13] Trost,[6] and Ratts[5a] all have reported similar behavior for II. The water was detectable in the nuclear magnetic resonance (nmr) spectrum (δ 3.38) and the infrared (ir) spectrum (3260 cm^{-1}).

The ylide II could be converted into the starting sulfonium salt (ylide conjugate acid) upon treatment with hydrogen bromide. The sulfonium salt showed a pK_a of 7.68 in 95% ethanol solution.[14] Nmr studies showed the methyl groups of the ylide (δ 2.92) to be more highly shielded than those of the conjugate acid (3.05). In addition, the methine proton of II (δ 4.31), as expected, appeared at higher field than the methylene protons of the ylide conjugate acid (5.74). The carbonyl group of the ylide conjugate acid absorbed at 1665 cm^{-1} in the ir while that of the ylide II absorbed at 1508 cm^{-1}, indicating considerable enolate character for the ylide (*i.e.*, considerable contribution of structure III). The stability of the phenacylide undoubtedly is largely due to the delocalization provided the carbanion by the adjacent carbonyl group. X-Ray crystallographic studies of the analogous phosphonium phenacylides have provided significant evidence to this effect.[15] The broadened methine peak at δ 4.31 indicates the contribution of the two geometric isomers of III.[5a,16]



III

The shielding effects of various carbon and sulfur substituents for a series of sulfonium ylides are presented in Table I. Interestingly, the nmr spectra of the closely related phenacylides $(CH_3)(C_6H_5)S{=}CHCOC_6H_5$ and $(C_6H_5)_2S{=}CHCOC_6H_5$ revealed that the presence of one or two phenyl groups on sulfur had the effect of deshielding both the methine protons (δ 4.55 and 4.75, respectively) and the remaining methyl

(1) For part XVIII in this series, see A. W. Johnson and H. L. Jones, *J. Amer. Chem. Soc.*, **90**, 5232 (1968).

(2) Author to whom inquiries should be directed at the University of North Dakota.

(3) A. W. Johnson and R. T. Amel, *Tetrahedron Lett.*, 819 (1966).

(4) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, pp 310–344.

(5) (a) K. W. Ratts and A. N. Yao, *J. Org. Chem.*, **31**, 1185 (1966); (b) *ibid.*, **31**, 1689 (1966).

(6) (a) B. M. Trost, *J. Amer. Chem. Soc.*, **88**, 1587 (1966); (b) *ibid.*, **89**, 138 (1967).

(7) (a) H. Nozaki, K. Kondo, and M. Takaku, *Tetrahedron Lett.*, 251 (1965); (b) *Tetrahedron*, **22**, 2145 (1966).

(8) A. J. Speziale, C. C. Tung, K. W. Ratts, and A. N. Yao, *J. Amer. Chem. Soc.*, **87**, 3460 (1965).

(9) K. W. Ratts and A. N. Yao, *J. Org. Chem.*, **33**, 70 (1968).

(10) G. B. Payne, the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, Abstracts of Organic Division, no. 158; *J. Org. Chem.*, **32**, 3351 (1967).

(11) H. Nozaki, D. Tunemoto, S. Matubara, and K. Kondo, *Tetrahedron*, **23**, 545 (1967).

(12) J. Casanova and D. A. Rutolo, *Chem. Comm.*, 1224 (1967).

(13) G. B. Payne, private communication.

(14) A. W. Johnson and R. T. Amel, *Can. J. Chem.*, **46**, 461 (1968).

(15) (a) F. S. Stephens, *J. Chem. Soc.*, 5640 (1956); (b) A. J. Speziale and K. W. Ratts, *J. Amer. Chem. Soc.*, **87**, 5603 (1965).

(16) F. J. Randall and A. W. Johnson, *Tetrahedron Lett.*, 2841 (1968).

Table I

Nmr Spectra of Sulfonium Salts and Ylides

Compound	Solvent[a]	δ_{CH_3S}[b]	$\delta_{CH \text{ or } CH_2}$
$(CH_3)_2S^+—CH_2COC_6H_5$ (1)	B	3.05	5.74
$(C_4H_9)_2S^+—CH_2COC_6H_5$ (2)	B		5.90
$(CH_3)(C_6H_5)S^+—CH_2COC_6H_5$ (3)	B	3.42	5.92
$(C_6H_5)_2S^+—CH_2COC_6H_5$ (4)	B		6.65
$(CH_3)_2S^+—CH_2COOCH_3$ (5)	C	3.16	4.48
$(CH_3)_2S=CHCOC_6H_5$ (6)	A	2.92	4.31
$(CH_3)(C_6H_5)S=CHCOC_6H_5$ (7)	A	3.10	4.55
$(C_6H_5)_2S=CHCOC_6H_5$ (8)	A		4.75
$(CH_3)_2S=C(COC_6H_5)_2$ (9)	A	3.07	
$(CH_3)_2S=CHCOOCH_3$ (10)	A	2.78	2.87
$(CH_3)_2S=C(COC_6H_5)(COOCH_3)$ (11)	A	2.86	

[a] A, $CDCl_3$; B, $(CD_3)_2SO$; C, trifluoroacetic acid. [b] δ, parts per million downfield from tetramethylsilane.

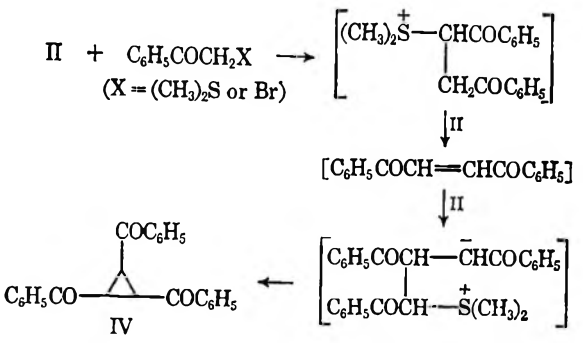
protons (3.10), all relative to the absorptions for II. The same effect was observed for the respective ylide conjugate acids. We interpret these observations as being due to the inductive electron withdrawal by phenyl relative to methyl. This is additional evidence for our generalization[14] that, when attached to an onium atom (sulfonium, phosphonium, arsonium), the inductive withdrawal effect more than counterbalances any conjugative donation effect of a phenyl group. It supports previous evidence based on basicity studies and our recent ^{19}F nmr evidence.[1]

Although stable in the atmosphere at room temperature, the phenacylide II was found to be subject to thermal decomposition. Heating the pure ylide in tetrahydrofuran solution afforded a 47% yield of *trans*-1,2,3-tribenzoylcyclopropane (IV). The same product could be obtained in nearly quantitative yield by treating the ylide II with either its conjugate acid (dimethylphenacylsulfonium bromide) or with phenacyl bromide. Trost[6] has reported the conversion of II into IV using ultraviolet (uv) irradiation or cupric sulfate catalyst. Much earlier, Krollpfeiffer[17] reported the conversion of the conjugate acid of II into IV by treatment with aqueous base.

The alkylation–elimination route from II to IV is proposed to proceed as shown in Scheme I. Each of the individual steps proposed has adequate analogy. The first step, the alkylation, was demonstrated in this work (see below) and is well known for phosphonium ylides. The E2 elimination of methyl sulfide also is known, although all attempts to isolate dibenzoylethylene from this reaction have failed, indicating that its consumption is more rapid than its formation. The Michael-type addition of an ylide to an α,β-unsaturated ketone has been widely explored with phosphonium ylides[18] and the specific reaction shown has been effected by Trost[6] and Nozaki, *et al.*,[7] in very high yield.

Trost[6] has proposed that photolytic decomposition of the phenacylide II proceeded *via* the generation of a carbene, the latter being trapped by the phenacylide to form dibenzoylethylene, which then was converted into IV as shown in Scheme I. The conversion of dibenzoylethylene into IV probably does not occur *via* carbene attack on the olefin owing to the reduced nucleophilicity of the latter.[19] Carrying out the reaction in cyclohexene, however, Trost was able to isolate benzoylnorcarane, presumably the result of trapping the carbene with the more nucleophilic cyclohexene.

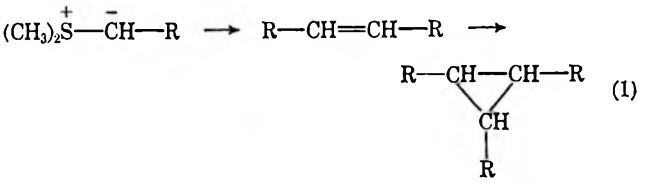
Scheme I



We also were able to carry out the photochemical conversion of the phenacylide II into IV. Furthermore, we were able to trap the carbene intermediate with dimethylbenzylamine to afford, initially, an ammonium ylide (V) which underwent a Steven's rearrangement[20] to the amine (VI). An authentic sample of the ylide V was prepared from its conjugate acid (VII) and was found to afford the amine VI (Scheme II). Ratts and Yao[5b] had reported the trapping of the carbene from the analogous *p*-nitrophenacylide using triphenylphosphine, isolating the corresponding phosphonium ylide. We were unable to trap the benzoylcarbene with triphenylphosphine.

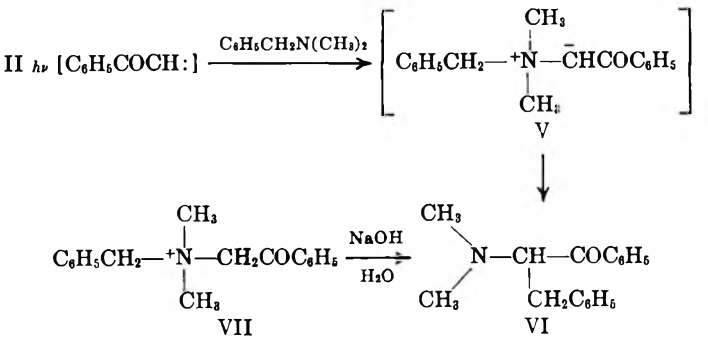
We proposed[3] that the thermal decomposition of the phenacylide II reported herein proceeds by way of a carbenoid pathway shown in Scheme III. Our observation does appear to be a bona fide thermal decomposition and not an alkylation–elimination reaction as counterproposed by Trost.[6b] Water, the presence of which might permit the formation of the conjugate acid and potential alkylating agent, dimethylphenacylsulfonium hydroxide, was demonstrated to be absent by nmr and ir spectroscopy. Furthermore, intentional addition of a small amount of water to the thermal decomposition reaction mixture had no effect on the course of the reaction. No sulfonium salt could be detected.

Previously, we had reported[21] that diphenylsulfonium benzylide thermally decomposed to stilbene. Further work[22] has shown the same decomposition to occur with dimethylsulfonium benzylide and dimethylsulfonium *p*-nitrobenzylide. A carbenoid pathway also has been proposed for these cases. Accordingly, the nature of the substituents on the ylidic carbon seems to control whether the thermal decomposition proceeds only to the olefin stage (as for the benzylides) or on to the cyclopropane stage (as for the phenacylides) (eq 1). We

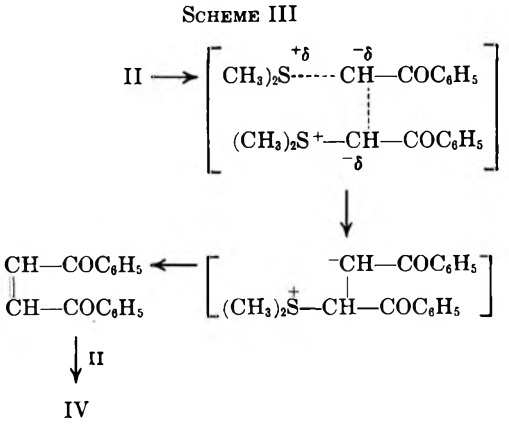


(17) F. Krollpfeiffer and H. Hartmann, *Chem. Ber.*, **83**, 90 (1950).
(18) Reference 4, pp 116–120, 336–338.
(19) F. Serratosa and J. Quintana, *Tetrahedron Lett.*, 2245 (1967).
(20) T. S. Stevens, E. M. Creighton, A. B. Gordon, and M. MacNicol, *J. Chem. Soc.*, 3193 (1928).
(21) A. W. Johnson, V. J. Hruby, and J. L. Williams, *J. Amer. Chem. Soc.*, **86**, 918 (1964).
(22) R. T. Amel, doctoral dissertation submitted in partial fulfillment of the degree requirements, University of Saskatchewan, Oct 1967.

SCHEME II

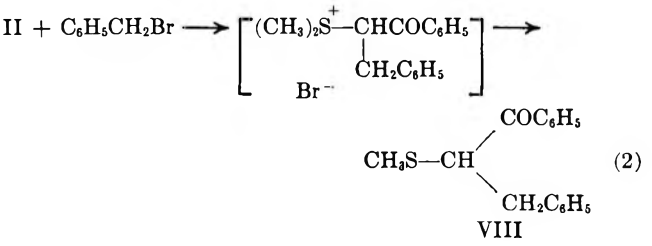


SCHEME III



have proposed that the ylide-to-olefin step involves a carbenoid mechanism where R = phenyl, *p*-nitrophenyl, or benzoyl (see Scheme III). The second step obviously must not be carbenoid but must involve nucleophilic attack of the ylide on the olefin. Such an attack (Michael addition) would be expected to proceed only where R is a group which provides significant stabilization for the carbanion intermediate (*e.g.*, a benzoyl group). Were the second step carbenoid, the cyclopropane would be expected to be obtained from stilbene (R = phenyl) but not from dibenzoylethylene (R = benzoyl) owing to the reduced nucleophilicity of the latter. The failure to obtain triphenylcyclopropane where R = phenyl implies that carbenoids are trapped by ylide before they could react with the stilbene, presumably owing to the greater nucleophilicity of the ylide.

The nucleophilicity of the phenacylide II was demonstrated by several reactions. The ylide was C alkylated with benzyl bromide although the product VIII was obtained only in 16% yield (eq 2). The sul-



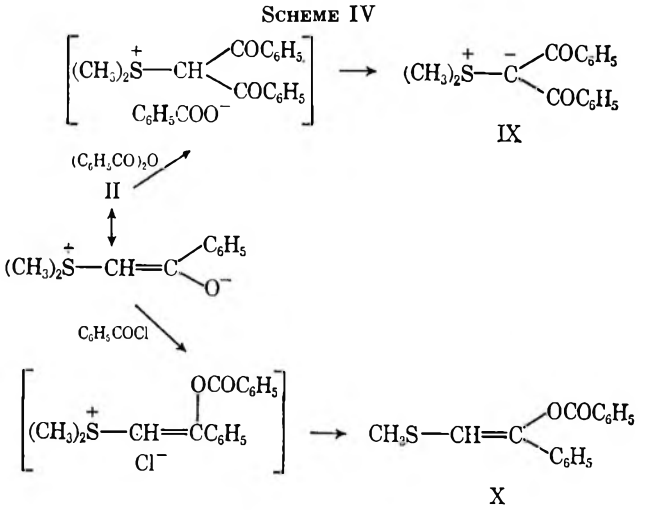
(2)

fonium salt apparently was demethylated by the bromide ion. Ratts and Yao[5b] reported low yields in a similar methylation and also observed subsequent demethylation.

The course of the acylation of the phenacylide II varied with the nature of the acylating agent. Treatment with benzoic anhydride afforded the highly stabilized ylide, dimethyl(dibenzoylmethylene)sulfurane (IX), the result of a C acylation and proton abstraction. The new ylide (IX) was extremely nonbasic, exhibiting a pK_a of 0.79, and was hydrolyzable to dimethylphenacylsulfonium chloride and benzoic acid. Acylation of II with benzoyl chloride resulted in an O acylation, affording the enol benzoate (X) of α-methylmercaptoacetophenone. The structure was proven by its nmr spectrum (methyl singlet at δ 2.31, vinyl singlet at 6.47, and aromatic multiplet at 7.2–8.3, with an integrated area ratio of 3:1:10), its ir spectrum (ν_{CO} 1735 cm^{-1}), its elemental analysis, and an oxidative hydrolysis to methylphenacyl sulfone and benzoic acid. Nozaki, *et al.*,[7b] subsequently reported identical results.

The course of the acylation reaction is illustrated in Scheme IV. The pattern of O acylation and C acylation is identical with that reported by Chopard, *et al.*,[23]

SCHEME IV



for triphenylphosphonium phenacylides and by Krohnke, *et al.*,[24] for pyridinium phenacylide. Carroll and O'Sullivan[25a] have reported that the monoanion of methylphenacyl sulfone also underwent O acylation with benzoyl chloride while Konig and Metzger[25b] found that phenacylidenedimethyloxysulfurane (prepared *in situ*) underwent C acylation with benzoyl

(23) P. A. Chopard, R. J. G. Searle, and F. H. Devitt, *J. Org. Chem.*, **30**, 1015 (1965).

(24) F. Krohnke, *Chem. Ber.*, **68**, 1177 (1935); F. Krohnke, K. Gerlach, and K. E. Schnalke, *ibid.*, **95**, 1118 (1962).

(25) (a) N. M. Carroll and W. I. O'Sullivan, *J. Org. Chem.*, **30**, 2830 (1965); (b) H. Konig and H. Metzger, *Chem. Ber.*, **98**, 3733 (1965).

chloride. Because acylation with benzoyl chloride appears to be a kinetically controlled reaction[23] it may be argued that in the series of phenacylides shown in Chart I the extent of C or O acylation is reflective of the

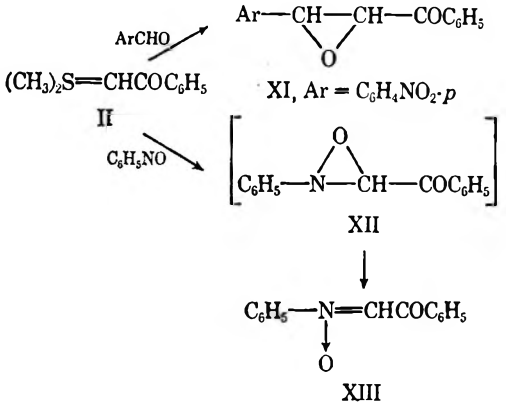
Chart I

Phenacylides	Direction of
$CH_3—SO_2C^-HCOC_6H_5$	1. increasing positive charge on sulfur
$(CH_3)_2S^+—C^-HCOC_6H_5$	2. increasing $p\pi$–$d\pi$ overlap
$(CH_3)_2S^+(O)—C^-HCOC_6H_5$	3. decreasing enolate character

extent of delocalization of the carbanion by the two competing electron sinks attached, the vacant 3d orbitals of sulfur and the carbonyl group. The observations coincide with theoretical predictions,[26] the anion with the least $p\pi$–$d\pi$ stabilization having more enolate character and therefore undergoing O acylation. On this basis it could be predicted that the unknown acylation of the monoanion of methylphenacyl sulfoxide with benzoyl chloride would be an O acylation owing to the relatively insignificant $p\pi$–$d\pi$ overlap of the carbanion with sulfur.

One of the interests in sulfonium ylides stems from their reaction with carbonyl compounds to form epoxides, a reaction discovered by us ten years ago.[27] When the current work was undertaken only one stabilized ylide, the fluorenylide, had been found to react with carbonyls. Since then, Ratts and Yao[5b] reported the formation of a 1-carbamido-2-phenyloxirane from benzaldehyde and $(CH_3)_2S{=}CHCON(C_2H_5)_2$. We have now found that the phenacylide II reacts with *p*-nitrobenzaldehyde, although in low yield, to afford a known epoxide (XI). In addition, the phenacylide underwent a similar reaction with nitrosobenzene, presumably first forming the nonisolable oxazirane (XII)[28] which rearranged to the stable nitrone (XIII) (Scheme V). The

Scheme V



latter gave the expected nmr spectrum (vinyl singlet at δ 8.37 and aryl multiplet at 7.2–8.0, area ratio of 1:10) and ir spectrum (ν_{CO} 1650 cm^{-1} ν_{NO} 1510 and 1310 cm^{-1}) and could be hydrolyzed with aqueous sodium hydroxide to mandelic acid.

In its reactions the isolable phenacylide exhibited typical ylide characteristics although they were modified somewhat in degree and kind from the normal, mainly owing to the ambident character of the anionic portion of the ylide.

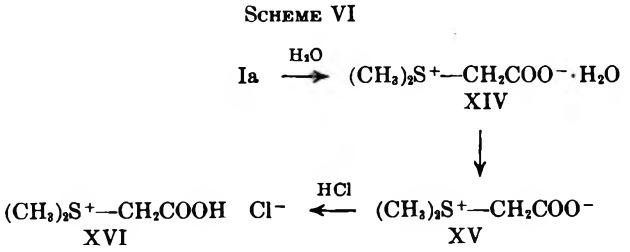
Dimethyl(carbomethoxymethylene)sulfurane (Ia).—The ester ylide (Ia) was prepared by proton abstraction with sodium hydride in tetrahydrofuran solution from dimethyl(carbomethoxymethyl)sulfonium bromide. The ylide was obtained as a clear, pale yellow viscous oil whose melting point was about 20°. Casanova and Rutolo[12] have since reported a melting point of 19–21°. The ylide was reconverted into its conjugate acid (the sulfonium salt) by treatment with aqueous acid.

The ylide showed carbonyl absorption in the ir region at 1620 cm^{-1}, typically shifted to longer wavelength compared with the absorption of the sulfonium salt (1735 cm^{-1}), owing to the adjacent carbanion. The nmr spectra of the ylide and its sulfonium salt precursor (see Table I) indicated that ylide formation led to an increased shielding of all protons α to the sulfur atom. The fact that the methine proton was more shielded than that of the phenacylide II testifies to the less extensive delocalization afforded the carbanion by the ester groups of Ia compared with the ketone group of II. The increase in shielding of the S-methyl group through conversion of the sulfonium salt to phenacylide II was 0.13 ppm while the increase in converting the sulfonium salt into the ester ylide Ia was 0.38 ppm. Apparently there is more $p\pi$–$d\pi$ overlap between a carbanion and sulfur in the ester ylide Ia than in the phenacylide II, as expected on structural grounds.

Casanova and Rutolo[12] have demonstrated and discussed the nmr evidence (two sets of parallel absorptions) for the contribution of two geometric forms of an enolate structure for the ester ylide Ia. The observations and conclusions are analogous to those made earlier for the corresponding phosphonium ylide.[29]

The ester ylide Ia decomposed slowly at room temperature either in solution or upon exposure to the atmosphere to afford dimethylthetin hydrate (XIV). The hydrate could be dehydrated to dimethylthetin (XV) and the latter could be converted into dimethylthetin chloride (XVI) (Scheme VI). These substances

Scheme VI



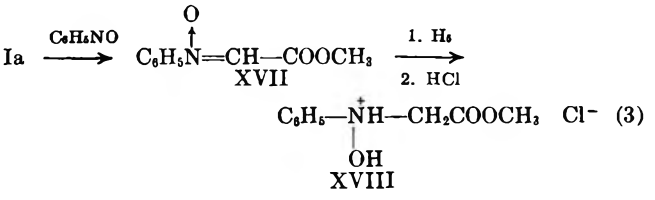
were identified by nmr and ir spectra and by comparison with authentic samples. The decomposition of the ylide Ia propably proceeded by conversion into the sulfonium hydroxide in the presence of water followed by hydrolysis of the ester group. This reaction interfered with many of our subsequent studies. Ratts and Yao[9] recently have reported the same decomposition.

We have been unable to obtain epoxides or any other recognizable products from the reaction of the ester ylide with *p*-nitrobenzaldehyde. Other workers also have been unable to cause ester ylides to react with

(26) D. P. Craig and E. A. Magnusson, *J. Chem. Soc.*, 4895 (1956).
(27) A. W. Johnson and R. B. LaCount, *Chem. Ind.* (London), 1440 (1958); *J. Amer. Chem. Soc.*, **83**, 417 (1961).
(28) A. W. Johnson, *J. Org. Chem.*, **28**, 252 (1963).
(29) H. J. Bestmann, G. Joachim, I. Lengyel, S. F. M. Oth, J. Mereny, and J. Weitkamp, *Tetrahedron Lett.*, 3335 (1966).

carbonyl compounds. However, Speziale, *et al.*,[8] were able to cause Ib to react with a Schiff base, a reaction presumably proceeding *via* a three-membered ring (aziridine) intermediate and a mechanism analogous to epoxide formation. Furthermore, Ratts and Yao[6b] were able to obtain epoxides from the reaction of an amido ylide, $(CH_3)_2S{=}CHCON(C_2H_5)_2$, with aldehydes. The failure to observe an analogous reaction using the ester ylide Ia is difficult to explain, especially in view of its supposed increased nucleophilicity relative to the phenacylide II.

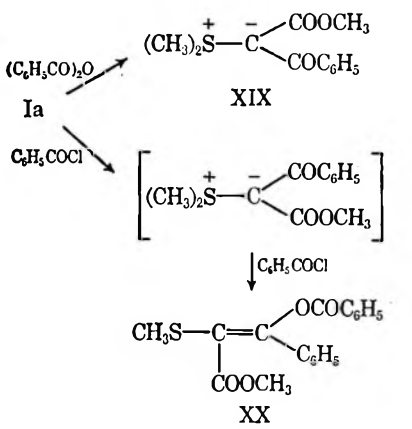
An attempt to obtain a nitrone from the reaction of Ia with nitrosobenzene led to somewhat inconclusive results. The expected nitrone (XVII) apparently was obtained but as a noncrystalline oil. Accordingly, the substance was hydrogenated over palladium on charcoal and a hydrochloride of mp 165–167°, presumably XVIII, was thereby obtained (eq 3). It showed ir



absorption at 1750 cm^{-1} and nmr absorption at δ 3.70 (singlet), 4.11 (singlet), 6.9–7.5 (multiplet), and 9.90 (singlet) in a ratio of 3:1.9:5.2:2.5. Addition of a small amount of D_2O to the sample resulted in the disappearance of the δ 9.90 peak, indicating it was due to acidic protons. A comparison spectrum of N,N-dimethylhydroxylamine hydrochloride also showed absorption at very low field. However, we were unable to obtain a satisfactory elemental analysis for the presumed XVIII. Benzoylation of XVIII afforded a benzoate with nmr absorption at δ 3.75 (singlet), 4.61 (singlet), and 7.0–7.5 (multiplet) in a ratio of 2.8:2.0:10.3.

The nucleophilicity of the ester ylide Ia was demonstrated by other reactions. Treatment with benzoic anhydride led to C acylation and the formation of a new ylide (XIX). The nmr spectrum [(δ 2.86 (singlet), 3.38 (singlet), and 7.0–7.4 (multiplet) in the ratio 5.9:3.0:5.1], ir spectrum (ν_{CO} 1675 and 1545 cm^{-1}), pK_a determination (1.06), and elemental analysis confirmed the assignment of structure. Acylation of Ia with a half-equivalent quantity of benzoyl chloride also afforded XIX but use of a full equivalent of benzoyl chloride produced the enol ester (XX) (Scheme VII).

SCHEME VII

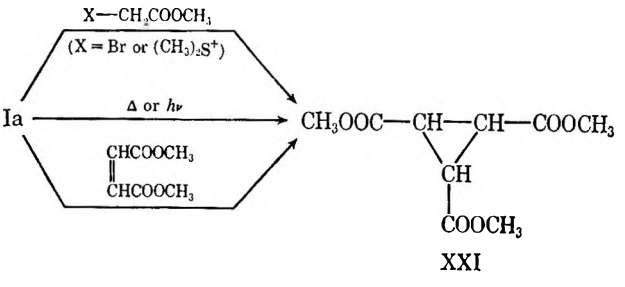


The nmr spectrum [δ 2.28 (singlet), 3.66 (singlet), and 7.2–8.3 (multiplet) in the ratio of 3:3:10.1], ir spectrum (ν_{CO} 1740 and 1720 cm^{-1}), and elemental analysis confirmed the assigned structure. In a separate experiment XIX was O acylated with benzoyl chloride to form XX. These observations provide striking evidence of the difference in the extent of delocalization of the carbanion electrons through the two α carbonyl groups. The complete absence of O acylation of the ester ylide Ia or any of its derivatives is consistent with the supposed larger carbon nucleophilicity and basicity, the larger amount of pπ–dπ overlap, and the larger shielding of protons on the S-methyl and ylide carbon groups, all for the ester ylide Ia when compared with the phenacylide II.

The ester ylide Ia could be thermally decomposed in tetrahydrofuran solution in the presence of cupric sulfate to afford *trans*-1,2,3-tricarbomethoxycyclopropane (XXI). The same product was obtained upon photochemical decomposition but in very low yield. We were unable to trap any carbene (:CHCOOCH$_3$) that may have been formed although attempts were made using cyclohexene, triphenylphosphine, and dimethylbenzylamine. In most instances considerable dimethylthetin hydrate (XIV) was obtained along with the cyclopropane trimer (XXI).

Reaction of the ester ylide Ia with methyl bromoacetate or with the ylide conjugate acid afforded the trimer XXI. Presumably this reaction proceeded *via* an alkylation–elimination route similar to that illustrated for the phenacylide II in Scheme I. Additional evidence for this proposal was obtained by the observation that the ylide reacted with methyl maleate, probably *via* conjugate addition, to afford XXI in high yield (see Scheme VIII). This reaction more recently has been reported by Payne[10] and by Casanova and Rutolo.[12]

SCHEME VIII



It is clear that the ester ylide Ia is, in general, more nucleophilic and basic than the phenacylide II. Its failure to react with carbonyl compounds is inexplicable. Solution of this problem would provide a convenient alternative to the Darzen glycidic ester homologation route, one of the original goals of this research. There appears to be more pπ–dπ overlap in the ester ylide Ia than in the phenacylide II owing to the less stabilizing role of the ester carbonyl group compared with that of the ketonic carbonyl group.

Experimental Section

General.—Melting points are uncorrected. Analyses were by Alfred Bernhardt Microanalytical Laboratory, Mülheim (Ruhr), Germany. Nmr spectra were recorded on Varian A-60 and A-60A spectrometers using tetramethylsilane (TMS) as an internal standard with chemical shifts reported as parts per million down-

field from TMS. Vapor phase chromatographic analyses were carried out using an Aerograph 90-P-3 chromatograph with a column of Apiezon L on Chromosorb W. Areas were determined by planimetry. Photochemical reactions were effected using a Hanovia low pressure quartz lamp.

Phenacylidenedimethylsulfurane (II).—Stirring a mixture of 19.9 g (0.1 mol) of phenacyl bromide and 30 ml of methyl sulfide for 3 hr afforded, after washing with ether, 23.95 g (92%) of phenacyldimethylsulfonium bromide which recrystallized from ether–ethanol as colorless microcrystals, mp 139–140° (lit.[30] mp 145°), ν_{CO} 1680 cm^{-1}. The nmr spectrum in $(CD_3)_2SO$ showed a methyl singlet at δ 3.05 (area 6), a methylene singlet at 5.74 (area 2), and an aromatic multiplet at 7.6–8.2 (area 5.1). The pK_a, determined as previously described,[14] was 7.68.

Anal. Calcd for $C_{10}H_{13}OSBr$: C, 45.98; H, 5.03; S, 12.28; Br, 30.59. Found: C, 45.84; H, 4.98; S, 12.35; Br, 30.91.

To a solution of 2.61 g (10 mmol) of sulfonium salt in 50 ml of 95% ethanol stirring at 10° was added 2.8 ml (20 mmol) of triethylamine. After 2 hr the solution was quenched with water and extracted with chloroform. Evaporation of the chloroform and crystallization of the residual oil from benzene afforded ylide II of mp 57–58° in 79% yield (lit. mp 56–57,[5a] 55–57,[13] 57–59°[6a]): ν_{H_2O} 3260 cm^{-1}, ν_{CO} 1508 cm^{-1}; nmr absorption in $(CD_3)_2SO$ at δ 2.82 (methyl singlet, area 6.1), 4.43 (methinyl singlet, area 1.0), 7.2–8.0 (aromatic multiplet, area 5.0), and 3.38 (water). Extended drying in a vacuum system in the presence of P_2O_5 afforded an apparently anhydrous, but quite hygroscopic, sample of colorless ylide, mp 67–68° (lit. 78–79,[6b] 77–79°[13]), with nmr absorption in $CDCl_3$ solution at δ 2.92, 4.31, and 7.27–8.

Anal. Calcd for $C_{10}H_{12}OS$: C, 66.63; H, 6.71; S, 17.79. Found: C, 65.85; H, 6.64; S, 18.23.

Treatment of the ylide II with aqueous hydrochloric acid, evaporation of the solution to dryness, and recrystallization of the residue from ethanol–ether afforded colorless crystals of phenacyldimethylsulfonium chloride of mp 138–139° (lit.[30] mp 139°).

Thermolysis of Phenacylidenedimethylsulfurane (II).—A carefully purified sample of 0.45 g (2.5 mmol) of ylide II, shown to be free of water, phenacyl bromide, and its conjugate acid, all by nmr spectroscopy (limit of detection about 1%), was dissolved in 15 ml of THF and heated under reflux for 24 hr. Chromatography on alumina and then crystallization afforded 0.28 g of unreacted ylide and 0.05 g (47% based on ylide consumed) of *trans*-1,2,3-tribenzoylcyclopropane (IV) which crystallized from ethanol as colorless crystals, mp 218.5–219.5° (lit.[17,31] mp 215°), ν_{CO} 1665 cm^{-1}.

Anal. Calcd for $C_{24}H_{18}O_3$: C, 81.34; H, 5.12. Found: C, 81.50; H, 5.55.

Repetition of the thermolysis with the addition of an equimolar quantity of N,N-dimethylbenzylamine and anhydrous cupric sulfate afforded a 7% yield of IV and <1% dimethyl(α-benzyl)-phenacylamine (VI). The yields and identities were established using vpc, but IV also was isolated, crystallized, and shown to be identical with an authentic sample by admixture melting point and a comparison of ir spectra. Thermolysis in the presence of 0.5 equiv of water afforded a trace amount of IV.

Dimethyl(α-benzyl)phenacylamine (VI).—To a solution of 4.7 g (50 mmol) of N,N-dimethylbenzylamine in 30 ml of benzene was added 10 g (50 mmol) of phenacyl bromide. Stirring at ambient temperatures, followed by evaporation of the solvent, afforded an oil which crystallized from ether–ethanol to afford 10.15 g (61%) of N,N-dimethylbenzylphenacylammonium bromide (VII) as a colorless powder, mp 164–165° (lit.[20] mp 167–168°).

Dissolution of the ammonium salt VII in water, then addition of aqueous sodium hydroxide sufficient to raise the pH of the solution to 11, followed by heating on a steam bath for 1 hr, afforded a yellow oil which solidified. Crystallization of the oil afforded a 79% yield of the amine VI as yellow needles, mp 77–79° (lit.[20] mp 77–79°).

Photolysis of Phenacylidenedimethylsulfurane (II).—A solution of 2.43 g (13.5 mmol) of II and 2.02 g (15 mmol) of N,N-dimethylbenzylamine in 25 ml of THF, all in a Vycor flask, was irradiated for 21 hr. Concentration to a volume of 10 ml and then vpc analysis indicated the presence of 3% amine VI and 6% cyclopropane IV. The latter subsequently was isolated and characterized.

Formation of *trans*-1,2,3-Tribenzoylcyclopropane (IV). A. From the Phenacylide II and Phenacyl Bromide.—A solution of 0.39 g (2.2 mmol) of ylide II and 0.11 g (0.54 mmol) of phenacyl bromide in 15 ml of THF was heated under reflux for 25 hr. Removal of the solvent *in vacuo* and crystallization of the residual oil from ethanol afforded 0.18 g (94%) of IV, mp 218–219°.

B. From the Phenacylide II and Phenacyldimethylsulfonium Bromide.—A solution of 0.33 g (1.8 mmol) of sulfonium salt and 0.12 g (0.45 mmol) of ylide II in 15 ml of THF was heated under reflux for 24 hr. Removal of the solvent *in vacuo* and crystallization of the residual oil from ethanol gave 0.15 g (93%) of IV, mp 219–220°.

Alkylation of the Phenacylide II with Benzyl Bromide.—A solution of 1.19 g (6.6 mmol) of ylide II in 10 ml of THF became milky upon the addition of 0.8 ml (6.6 mmol) of benzyl bromide. Stirring at room temperature for 18 hr afforded a precipitate of 0.46 g (27%) of phenacyldimethylsulfonium bromide which was removed by filtration. Evaporation of the filtrate left an oil which crystallized from hexane–chloroform to afford 0.19 g (16% based on ylide consumed) of α-methylthio-β-phenylpropiophenone (VIII) as colorless crystals, mp 62–62.5°, ν_{CO} 1670 cm^{-1}. The structure was confirmed by oxidation with hydrogen peroxide in acetic acid to afford α-methylsulfonyl-β-phenylpropiophenone as a colorless powder: mp 137–138° (lit.[25a] mp 137–138°); ν_{CO} 1670 cm^{-1}, ν_{SO_2} 1310 and 1122 cm^{-1}.

Acylation of Phenacylidenedimethylsulfurane (II). A. With Benzoic Anhydride.—A solution of 0.65 g (3.6 mmol) of ylide II and 0.82 g (3.6 mmol) of benzoic anhydride in 10 ml of THF was stirred at room temperature for 43 hr. The resultant precipitate was removed by filtration and crystallized from chloroform–hexane to afford 0.25 g (24%) of dibenzoylmethylenedimethylsulfurane (IX) as colorless crystals: mp 211–212°; ν_{CO} 1582 cm^{-1}; pK_a 0.79; nmr absorption in $CDCl_3$ at δ 3.07 (methyl singlet, area 6.0) and 6.9–7.5 (aromatic multiplet, area 10.5).

Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.84; H, 5.63; S, 11.28. Found: C, 71.17; H, 6.18; S, 11.20.

Upon concentration the filtrate from the reaction mixture afforded 0.29 g (67%) of benzoic acid, mp 121–122°.

Hydrolysis of 0.34 g of IX in 25 ml of water and 5 ml of 5 *N* hydrochloric acid afforded 0.08 g (55%) of benzoic acid, mp 121–122°, and 0.10 g (39%) of phenacyldimethylsulfonium chloride, mp 129–130°, identified by admixture melting point and comparison of ir spectra.

B. With Benzoyl Chloride.—A solution of 0.72 g (4 mmol) of ylide II in 10 ml of THF became milky upon the addition of 0.5 ml (4.3 mmol) of benzoyl chloride. After stirring at room temperature for 22 hr a small amount (0.04 g) of phenacyldimethylsulfonium chloride was removed by filtration. Removal of the solvent from the filtrate *in vacuo* left a precipitate which was recrystallized from hexane–chloroform to afford 0.82 g (76%) of the enol benzoate (X) of α-methylthioacetophenone as colorless crystals: mp 75–76°; ν_{CO} 1735 cm^{-1}; nmr absorption in $CDCl_3$ at δ 2.31 (methyl singlet, area 3), 6.47 (vinyl singlet area, 1), and 7.2–8.3 (aromatic multiplet, area 10).

Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.12; H, 5.18; S, 11.86. Found: C, 71.09; H, 5.02; S, 11.56.

Heating 0.12 g of the enol benzoate X with 0.6 ml of 50% hydrogen peroxide in 10 ml of acetic acid afforded 0.1 g (18%) of benzoic acid, mp 119–120°, and 0.3 g (30%) of methylphenacyl sulfone: mp 105–106° (lit.[32] mp 106–107°); ν_{CO} 1680 cm^{-1}, ν_{SO_2} 1302 and 1119 cm^{-1}.

Reaction of Phenacylidenedimethylsulfurane (II) with Electrophiles. A. *p*-Nitrobenzaldehyde.—A solution of 1.75 g (9.7 mmol) of ylide II and 1.5 g (10 mmol) of *p*-nitrobenzaldehyde in 50 ml of THF was heated under reflux for 27 hr. Removal of the solvent *in vacuo* and chromatography of the remaining oil on alumina afforded 0.42 g (28%) of *p*-nitrobenzyl alcohol, mp 88° (formed by reduction of the aldehyde on alumina[33]), and 0.25 g (10%) of 1-(4-nitrophenyl)-2-benzoyloxirane (XI) which crystallized from carbon tetrachloride as colorless crystals: mp 149.5–150.5° (lit.[34] mp 150°); ν_{CO} 1675 cm^{-1}; nmr absorption in $CDCl_3$ at δ 4.28 (two methinyl doublets, area 2) and 7.3–8.4 (aromatic multiplet, area 9).

B. Nitrosobenzene.—To a greenish blue solution of 0.54 g (5 mmol) of nitrosobenzene and 1.30 g (5 mmol) of phenacyldi-

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methylsulfonium bromide in 55 ml of 90% ethanol–water held at −10° was added 0.4 g (10 mmol) of sodium hydroxide dissolved in 10 ml of water. An exothermic reaction resulted and the solution became yellow. After the ice bath was removed and the solution was allowed to stand at room temperature for 25 hr, water slowly was added to the cloud point. Cooling overnight afforded a yellow precipitate which recrystallized from ethanol to afford 0.64 g (57%) of the nitrone XIII as yellow crystals: mp 108.5–110° (lit.[35] mp 109–110°); ν_{CO} 1650 cm^{-1}, ν_{NO} 1510 and 1310 cm^{-1}; nmr absorption in $CDCl_3$ at δ 8.37 (vinyl singlet, area 0.8) and 7.2–8.0 (aromatic multiplet, area 10). Hydrolysis of a sample of XIII in 8 ml of 1 *N* sodium hydroxide afforded, after extraction with ether and sublimation, 0.07 g of mandelic acid, mp 118–120° (lit.[35] mp 118–119°), ν_{CO} 1720 cm^{-1}.

Carbomethoxymethylenedimethylsulfurane (Ia).—Stirring a mixture of 10 ml (0.1 mol) of methyl bromoacetate and 10 ml of methyl sulfide for 1.5 hr produced a colorless precipitate which, after being washed with ether, afforded 21.6 g (100%) of carbomethoxymethyldimethylsulfonium bromide. Recrystallization from ether–ethanol gave a pure sample: mp 81–82°; ν_{CO} 1735 cm^{-1}; nmr absorption in trifluoroacetic acid at δ 3.21 (S-methyl singlet area 6), 4.01 (O-methyl singlet, area 3), and 4.57 (methylene singlet, area 1.95).

Anal. Calcd for $C_5H_{11}O_2SBr$: C, 27.91; H, 5.16; S, 14.91; Br, 37.15. Found: C, 27.80; H, 5.29; S, 14.70; Br, 37.08.

To 1.10 g (5 mmol) of the sulfonium bromide in 10 ml of THF was added 0.30 g (6 mmol) of 50% sodium hydride in mineral oil from which the mineral oil had been removed by washing with hexane. After stirring for 3 hr at room temperature the gray color of the sodium hydride suspension had been replaced by the yellowish suspension of sodium bromide. Removal of the precipitate and evaporation of the solvent left 0.42 g (63%) of crude, yellowish oily ylide Ia which solidified below 20° but could not be crystallized. It showed ν_{CO} 1620 cm^{-1} and nmr absorption in $CDCl_3$ at δ 2.78 (S-methyl singlet) and 2.87 (methine singlet, combined area 7), as well as at 3.55 (O-methyl singlet, area 3).

Passing gaseous hydrogen bromide through a solution of the oily ylide in ether afforded the conjugate acid bromide, mp 80–82°, identified by admixture melting point and comparison of ir spectra. A similar reaction but using gaseous hydrogen chloride afforded carbomethoxymethyldimethylsulfonium chloride: mp 107–108°; ν_{CO} 1735 cm^{-1}; nmr absorption in trifluoroacetic acid at δ 3.16 (S-methyl singlet, area 5.9), 4.00 (O-methyl singlet, area 3), and 4.48 (methylene singlet, area 2).

Anal. Calcd for $C_5H_{11}O_2SCl$: C, 35.18; H, 6.50; S, 18.79; Cl, 20.78. Found: C, 35.05; H, 6.57; S, 18.60; Cl, 20.93.

Allowing the ylide Ia, formed from 10 g (46 mmol) of sulfonium salt, to stand exposed to the atmosphere in THF solution led to the appearance of a precipitate which was recrystallized from ethanol–ether to afford 2.5 g (39%) of dimethylthetin hydrate (XIV) as colorless crystals: mp 67–69°; ν_{CO} 1625 cm^{-1}; nmr absorption in $(CD_3)_2SO$ at δ 2.80 (S-methyl singlet, area 6) and 3.91 (methylene singlet, area 2). Drying the hydrate over P_2O_5 afforded dimethylthetin (XV): mp 143.5–144.5°; ν_{CO} 1625 cm^{-1}; nmr absorption in $(CD_3)_2SO$ at δ 2.80 and 3.90.

Anal. Calcd for $C_4H_8O_2S$: C, 39.97; H, 6.72; S, 26.68. Found: C, 40.01; H, 6.30; S, 26.64.

Addition of dilute hydrochloric acid to XV or XIV produced dimethylthetin chloride (XVI) which crystallized from ethanol–ether as colorless crystals: mp 134.5–135.5°; ν_{KO} 1720 cm^{-1}; nmr absorption in $(CD_3)_2SO$ at δ 3.15 (S-methyl singlet, area 6.1), 4.90 (methylene singlet, area 1.9), and 13.75 (carboxyl proton singlet, area 1.1). This substance was identical with a sample prepared by the direct combination of methyl sulfide and chloroacetic acid, as evidenced by admixture melting point and a comparison of nmr and ir spectra. This sample was then converted into dimethylthetin and its hydrate by treatment with sodium hydride.

Reaction of Ester Ylide Ia with Nitrosobenzene.—Addition of 1.54 g (14.3 mmol) of nitrosobenzene to a solution of 14.3 mmol of ester ylide Ia in 30 ml of THF gave a yellow solution after standing for 4 hr at room temperature. Removal of the solvent, addition of water, extraction with ether, drying, and then concentrating the ethereal solution afforded a yellow oil which could not be crystallized. Accordingly, the oil was dissolved in 150 ml of methanol and hydrogenated over 1 g of 10% palladium on carbon for 11 hr. Removal of the catalyst and solvent left a noncrystallizable oil which was converted into a hydrochloride. The latter crystallized from ether–ethanol as colorless crystals which were then sublimed: mp 165–167°; ν_{CO} 1750 cm^{-1}; nmr absorption in $(CD_3)_2SO$ at δ 3.70 (methyl singlet, area 3), 4.11 (methylene singlet, area 1.9), 6.9–7.5 (aromatic multiplet, area 5.2), and 9.90 (NH and OH singlet, area 2.5). Addition of D_2O caused the δ 9.90 peak to vanish and a new peak to appear at 4.71 (HOD and HOH).

Anal. Calcd for $C_9H_{12}NO_3Cl$: C, 49.65; H, 5.57; N, 6.44; Cl, 16.29. Found: C, 53.47; H, 6.08; N, 7.14; Cl, 17.48.

Treatment of the hydrochloride with benzoyl chloride afforded a benzoate which crystallized from hexane–chloroform as colorless crystals: mp 63–65°; ν_{CO} 1750 and 1650 cm^{-1}; nmr absorption at δ 3.75 (methyl singlet, area 2.8), 4.61 (methylene singlet, area 2), and 7.0–7.5 (aromatic multiplet, area 10.3).

Acylation of the Ester Ylide Ia. A. With Benzoic Anhydride.—A solution of 35 mmol of ylide Ia and 7.90 g (35 mmol) of benzoic anhydride in 80 ml of THF was stirred at room temperature for 15 hr. The reaction was quenched with 50 ml of water and washed with ether [from which 3.95 g (95%) of benzoic acid was obtained], and the aqueous layer was concentrated to afford a yellow precipitate (6.91 g, 83%). Sublimation afforded pure carbomethoxybenzoylmethylenedimethylsulfurane (XIX) as a colorless powder: mp 129–131°; ν_{CO} 1675 and 1545 cm^{-1}; nmr absorption in $CDCl_3$ at δ 2.86 (S-methyl singlet, area 5.9), 3.38 (O-methyl singlet, area 3), and 7.0–7.4 (aromatic multiplet, area 5.1).

Anal. Calcd for $C_{12}H_{14}O_3S$: C, 60.50; H, 5.92; S, 13.43. Found: C, 60.43; H, 5.82; S, 13.52.

B. With Benzoyl Chloride.—Addition of 0.64 ml (5.5 mmol) of benzoyl chloride to a solution of 11 mmol of ester ylide Ia in 50 ml of benzene caused a precipitate to form. After stirring for 24 hr at room temperature, the precipitate [0.94 g (100%) of carbomethoxymethyldimethylsulfonium chloride] was removed by filtration. Addition of hexane to the filtrate resulted in the precipitation of 1.24 g (95%) of XIX, mp 127–128°, identified by admixture melting point and comparison of ir spectra.

Repetition of the experiment using 15.4 mmol of benzoyl chloride afforded the by-product, carbomethoxymethyldimethylsulfonium chloride, and an oil. Chromatography of the oil on alumina followed by crystallization from hexane–chloroform gave 1.7 g (34%) of the enol benzoate (XX) of α-methylthio-α-carbomethoxyacetophenone as colorless prisms: mp 74–74.5°; ν_{CO} 1740 and 1720 cm^{-1}; nmr absorption in $CDCl_3$ at δ 2.28 (S-methyl singlet, area 3), 3.66 (O-methyl singlet, area 3), and 7.2–8.3 (aromatic multiplet, area 10.1).

Anal. Calcd for $C_{18}H_{16}O_4S$: C, 65.85; H, 4.91; S, 9.74. Found: C, 65.71; H, 4.85; S, 9.92.

The benzoylcarbomethoxymethylenedimethylsulfurane (XIX). 2.23 g, 9.4 mmol, in 50 ml of benzene was converted by 1.1 ml (9.4 mmol) of benzoyl chloride into 1.46 g (48%) of XX, mp 74–75°, identified by admixture melting point and comparison of ir spectra.

Preparation of *trans*-1,2,3-Tricarbomethoxycyclopropane (XXI). A. Thermolysis of the Ester Ylide Ia.—A solution of 9.6 mmol of the ylide Ia in 20 ml of THF to which was added 0.14 g of cupric sulfate was heated under reflux for 122 hr. The solution was concentrated to 10 ml and then analyzed by vpc. A 19% yield of the cyclopropane XXI was detected.

B. Photolysis of the Ester Ylide Ia.—A solution of 7.9 mmol of the ylide Ia in 15 ml of THF was irradiated for 56 hr in a Vycor flask. Concentration of the solution and then vpc analysis indicated that a 5% yield of the cyclopropane XXI was formed. Repetition of the experiment but with the addition of an equimolar quantity of triphenylphosphine afforded a 13% yield of cyclopropane XXI and a 62% yield of dimethylthetin hydrate (XIV), mp 68–69°. A portion (42%) of the triphenylphosphine was recovered along with a 27% recovery of triphenylphosphine oxide.

C. Reaction of Ester Ylide Ia with Carbomethoxymethyldimethylsulfonium Bromide.—A solution of 4.67 mmol of ester ylide Ia and 0.42 g (1.95 mmol) of conjugate acid bromide in 13 ml of THF was heated under reflux for 24 hr. Concentration of the solution and vpc analysis indicated the formation of a 28% yield of the cyclopropane XXI.

D. Reaction of Ester Ylide Ia with Methyl Bromoacetate.—A solution of 4.67 mmol of ester ylide Ia and 0.30 g (1.95 mmol) of methyl bromoacetate was heated under reflux for 24 hr. Concentration and vpc analysis indicated the formation of a 24% yield of the cyclopropane XXI.

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E. Reaction of the Ester Ylide Ia with Methyl Maleate.—A stirred solution of 9.2 mmol of ester ylide Ia and 1.32 g (9.2 mmol) of methyl maleate was heated under reflux for 17 hr. Concentration and vpc analysis indicated the formation of a 71% yield of cyclopropane XXI. The latter was isolated by evaporation of the solvent and sublimation of the residual oil to afford XXI as a colorless powder, mp 54–56° (lit.[36] mp 56–57°), ν_{CO} 1720 cm^{-1}.

Anal. Calcd for $C_9H_{12}O_6$: C, 50.00; H, 5.59. Found: C, 50.11; H, 5.73.

Registry No.—1, 19023-61-1; 2, 19023-62-2; 3, 19023-63-3; 4, 19023-64-4; 5, 19643-11-9; 6, 5697-33-6; 7, 19643-13-1; 8, 19643-14-2; 9, 19643-15-3; 10, 19643-16-4; 11, 19643-17-5; Ia, 18915-90-7; II, 5633-34-1; VIII, 14679-98-2; IX, 5633-35-2; X, 5633-68-1; XI, 5633-36-3; XIII, 5492-70-6; XIV, 19643-24-4; XV, 4727-41-7; XVI, 10132-50-0; XIX, 19643-27-7; XX, 19643-28-8; phenacyldimethylsulfonium bromide, 5667-47-0; carbomethoxymethyldimethylsulfonium bromide, 19643-31-3; carbomethoxymethyldimethylsulfonium chloride, 19643-32-4.

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Polarity Effects in the Solvolysis of Cyclohexane Derivatives. The Importance of Field Effects in Determining Relative Reactivities[1,2]

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The rates of acetolysis of 4-substituted cyclohexyl methanesulfonates are shown to be dependent upon the polarity and conformation of the substituent as well as the conformation of the leaving methanesulfonate group. Rates of solvolysis for *cis*- and *trans*-4-chlorocyclohexyl methanesulfonate and for *cis*- and *trans*-4-bromocyclohexyl methanesulfonate have been calculated using a field effect model by employing the observed ground-state conformer populations (as determined by infrared spectroscopy) and the appropriate bond dipoles. The good agreement of the kinetic data with rate constants calculated employing a purely field effect model indicates the absence, or at least the very small role, of "through-the-bond" inductive effects.

Some years ago investigations in these laboratories showed that the solvolysis of 4-methoxycyclohexyl tosylate occurs with methoxyl participation.[4,5] In developing a comprehensive interpretation of the nature of the products, one of the questions which was very difficult to answer was the expected rate in the absence of participation. We did not reach a definitive conclusion at this point in our earlier publications. One approach, in order to gain further information at this point, is to examine the rate of solvolysis of substituted cyclohexane derivatives with polar substituents, which should be expected *not* to participate in any transannular sense. Chloro and cyano substituents satisfy this criterion very well. It is therefore the purpose of the present report to examine the solvolysis of such systems. In the course of this study it became apparent that the influence of the polarity of the substituent causes a very substantial perturbation of the conformational equilibria of the starting materials, the cyclohexyl sulfonates, and that in addition field effects are particularly important in determining the relative reactivities of the pairs of isomers.

Results

The preparation of the requisite compounds was in general unexceptional. Treatment of 1,4-epoxycyclohexane with concentrated hydrochloric acid[6] afforded *trans*-4-chlorocyclohexanol (1) in excellent yield. The configuration of 1 is confirmed by the studies of Heine,[7] who demonstrated the formation of 1,4-epoxycyclohexane in the reaction of 1 with base. From 1, tosylate 2 and methanesulfonate 3 were prepared. Treatment of 1 with sodium acetate in dimethylformamide afforded an authentic sample of *cis*-4-chlorocyclohexanol (4), from which tosylate 5 and methanesulfonate 6 were prepared. Solvolysis of 2 and of 5 in acetic acid showed that the *cis* isomer solvolyzes more slowly than the *trans* isomer. Examination of the products from each of these solvolyses showed that they were the normal products; *i.e.*, there was no evidence for any participation. This result shows that the polar influence of the chloro substituent vitiates the general rule that *trans*-4-substituted cyclohexane derivatives will generally react more slowly than *cis* isomers, for the reason that the *cis* isomer will have a higher population of that conformation with the reacting moiety in the axial position.

In order to determine the source of this inversion of relative reactivities, we have examined the conformational population of a number of derivatives of 4-chlorocyclohexanol. During the course of this study, Takeoka[8] reported that 1 is 28% in the diaxial conformation in carbon disulfide solution. It is known that both 1,4-dichlorocyclohexane and 1,4-dibromocyclohexane are predominantly in the diaxial conformation in a variety

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(2) A portion of this work has been published in a preliminary form: D. S. Noyce, B. N. Bastian, and R. S. Monson, *Tetrahedron Lett.*, 863 (1962).

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of solvents.[9] We find, from an examination of the infrared spectrum, that *trans*-4-chlorocyclohexyl acetate appears to be 73% in the diaxial conformation in carbon disulfide solution, while *cis*-4-chlorocyclohexyl acetate appears to be a 46:54 mixture of two conformations. These results were obtained from measurements using the 752- and 717-cm^{-1} bands representing equatorial and axial carbon–chlorine stretching vibrations, respectively. In the case of **2**, such an examination of the ground-state conformation was precluded by the intense aromatic absorptions in this region of the spectrum. In the hope that the spectrum could be simplified by a change to an aliphatic sulfonate, we turned our attention to the examination of the methanesulfonates. The results of these studies will be elaborated below.

An analogous preparative sequence was used to obtain both *trans*-4-bromocyclohexanol (**7**), trans-4-bromocyclohexyl tosylate (**8**), and *trans*-4-bromocyclohexyl methanesulfonate (**9**). Reduction of 4-bromocyclohexanone afforded a mixture rich in *cis*-4-bromocyclohexanol (**10**) which was largely separated by fractionation. Tosylate **11** and methanesulfonate **12** were prepared.

The synthesis of the cyanocyclohexanols started with the known isomers of the hydroxycyclohexanecarboxylic acids. As each hydroxy acid was converted smoothly into a distinctive cyanocyclohexanol, we consider this method of preparation adequate proof of configuration for the cyanocyclohexanols. *trans*-4-Cyanocyclohexanol (**13**), *cis*-4-cyanocyclohexanol (**14**), *trans*-3-cyanocyclohexanol (**15**), and *cis*-3-cyanocyclohexanol (**16**) were prepared in this fashion, and converted into the respective sulfonate esters.

Conformational Relationships.—The use of the methanesulfonates provided opportunity to examine directly the conformational situation of the reacting systems. We have shown[10] that the methanesulfonate group has an A value of 0.56, and that two bands in the region 900–950 cm^{-1} are characteristic for axial and equatorial methanesulfonates. Using the bands at 936 cm^{-1} (equatorial sulfonate) and the band at 909 ± 3 cm^{-1} (axial sulfonate) which were shown to have nearly identical extinction coefficients,[10] we obtain the results for the conformational populations given in Table I.

TABLE I

OBSERVED CONFORMATIONAL POPULATIONS OF THE 4-HALOCYCLOHEXYL METHANESULFONATES IN CARBON TETRACHLORIDE SOLUTION

Compd	% equatorial OMs	% axial OMs
3	39.8	60.2
6	63.6	36.4
9	37.0	63.0
12	62.9	37.1

It is to be noted that the *trans* isomers are predominantly in the diaxial conformation, similar to the 1,4-dihalocyclohexanes.[9]

(9) K. Kozima and T. Yoshino, *J. Amer. Chem. Soc.*, **75**, 166 (1953).
(10) D. S. Noyce, B. E. Johnston, and B. Weinstein, *J. Org. Chem.*, **34**, 463 (1969).

Kinetic Results

The results of measurement of the rate of acetolysis of the several compounds prepared in this study are given in Table II.

TABLE II

RATES OF ACETOLYSIS OF SUBSTITUTED CYCLOHEXYL SULFONATES

Compd	Concn of sulfonate, M[a]	Temp,[b] °C	10^5k, sec^{-1}
2	0.03	75.00	4.58 ± 0.6
	0.03	90.00	28.5 ± 0.6
5	0.03	75.00	2.07 ± 0.03
	0.03	90.00	12.1 ± 0.2
3	0.05	70.00	3.11 ± 0.05
	0.05	90.00	30.3 ± 0.7
6	0.05	70.00	1.31 ± 0.02
	0.05	90.00	14.5 ± 0.2
8	0.05	89.97	24.2 ± 0.7
11	0.05	89.97	12.1 ± 0.2
9	0.05	70.00	2.56 ± 0.09
	0.05	90.00	27.1 ± 0.08
12	0.05	70.00	1.27 ± 0.01
	0.05	90.00	12.4 ± 0.1
13-OTs	0.05	90.00	9.32 ± 0.05
14-OTs	0.05	90.00	8.14 ± 0.12
15-OTs	0.05	90.00	5.89 ± 0.1
16-OTs	0.05	90.00	3.84 ± 0.1

[a] All solvolyses were carried out in acetic acid with added acetic anhydride and sodium acetate, both at twice the concentration of the sulfonate. [b] Temperatures all ±0.03°.

The rates of solvolysis of the compounds studied in this report are uniformly less than the rates for cyclohexyl itself. This is, of course to be expected for compounds containing electron-withdrawing substituents. It is of interest to examine the rate ratios (k_{trans}/k_{cis}) for each of these pairs. The data are summarized in Table III, along with additional data reported previously from these laboratories[4,11] and by Mori.[12,13]

TABLE III

RATE RATIOS FOR SOLVOLYSIS OF SUBSTITUTED CYCLOHEXYL SULFONATES

Substituted cyclohexyl	Sulfonate group	Temp, °C	k_{trans}/k_{cis}	Ref
4-Chloro	OTs	90	2.34	*a*
	OMs	90	2.09	*a*
4-Bromo	OTs	90	2.02	*a*
	OMs	90	2.19	*a*
4-Cyano	OTs	90	1.13	*a*
4-Methoxy	OTs	75	4.18	*b*
4-Acetoxy	OTs	99.8	2.50	*c*
4-Tosyloxy	OTs	99.8	2.18	*d*
3-Cyano	OTs	90	1.53	*a*
3-Methoxy	OTs	75	1.49	*b*
3-Methoxy-carbonyl	OTs	75	4.7	*e*

[a] Present study. [b] Reference 4. [c] Reference 12. [d] Reference 13. [e] Reference 11.

For the 4-substituted cyclohexyl sulfonates the *trans* isomer typically solvolyzes about twice as rapidly as the *cis* isomer. This generalization helps to clarify the ex-

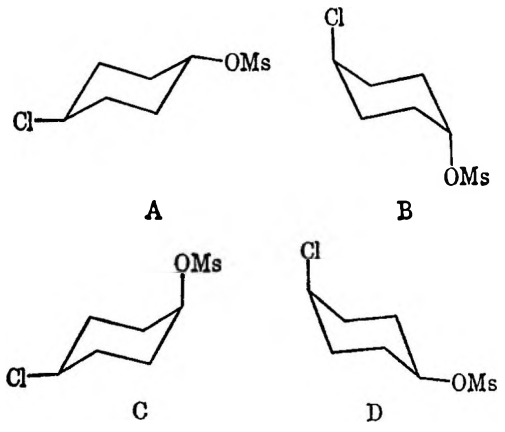
(11) D. S. Noyce and H. I. Weingarten, *J. Amer. Chem. Soc.*, **79**, 3103 (1957).
(12) N. Mori, *Bull. Chem. Soc. Jap.*, **33**, 1332 (1960).
(13) N. Mori, *ibid.*, **34**, 110 (1961).

tent of methoxyl participation in *trans*-4-methoxycyclohexyl tosylate.[5]

In the limited number of cases of 3-substituted cyclohexyl sulfonates, the *trans* isomers solvolyze more rapidly than the *cis* isomers. This is a more "normal" ratio, and shows that a major portion of the inversion in rate for the 4-substituted cyclohexyl sulfonates comes from the reversal of the ground-state conformational populations (see Table I).

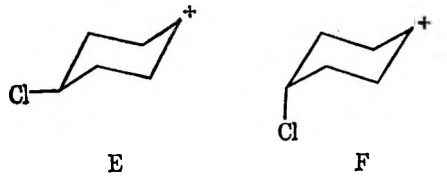
In order to establish more clearly the role of electrostatic interactions in the solvolysis of 4-chlorocyclohexyl methanesulfonate, we have carried out calculations based on a Kirkwood–Westheimer model.

Models for the two conformations of **3** (A and B) and of **6** (C and D) were used. Distances and geometry



were taken from standard sources.[14] Using a relatively high group moment for the methanesulfonoxy group,[15,16] conformation B is slightly more than 1 kcal more stable than conformation A on electrostatic grounds alone. Conformations C and D are of essentially equal energy, in agreement with the experimental observations. For conformations A and B, the addition of this dipole–dipole interaction to the normal steric terms which are encompassed in the A values results in a satisfactory explanation of the conformational equilibria which we have observed for **3** (*cf.* Table I).

Calculations were also carried out on models for the transition states for solvolysis, E and F. The method



of calculation followed that used and recently described by Wilcox and Leung.[17,18] The extent to which charge was developed at C-1 was varied in subsequent calculations. The most usual model assumes that X, the fractional positive charge, is 0.50.[19] We observe somewhat more satisfactory fit of experimental results with calculation when X is set at 0.8.

For models E and F, there is greater electrostatic repulsion in E than in F which amounts to nearly 0.9 kcal/mol. From the calculations of the ground-state energies, and electrostatic interactions in the transition state, one may then predict the rates of acetolysis for the halogen-substituted cyclohexyl methanesulfonates, by using observed rates for *trans*-4-methylcyclohexyl methanesulfonates and *cis*-4-*t*-butylcyclohexyl methanesulfonate[10] as models for pure, unperturbed equatorial and axial rates. Table IV summarizes these comparisons.

TABLE IV
COMPARISON OF CALCULATED AND EXPERIMENTAL ACETOLYSIS RATES AT 70°

Cyclohexyl methanesulfonate	10^6k, sec^{-1} Calcd	Exptl	$k_{calcd}/k_{exp\ tl}$
3	2.14	3.11	0.69
6	1.37	1.31	1.05
9	2.52	2.56	0.98
12	1.60	1.27	1.26

The very satisfactory agreement between the observed rates of acetolysis of **3**, **6**, **9**, and **12** with those calculated using a field effect model indicates the absence, or at least the very small role, of a "through-the-bond" inductive effect. If inductive effects were dominant, then conformers of the same methanesulfonate conformation would be expected to show the same reactivity. The results of the present study show that this is not the case, and that an axial bromine or chlorine is rate enhancing relative to equatorial bromine or chlorine by a factor of 3.2 or 2.04, respectively. Field effect calculations predict ratios of 3.5 and 3.02, respectively.

In making these calculations we were greatly assisted by Professor C. F. Wilcox of Cornell University, who generously made his FIELD computer program available to us.[11] We also wish to thank Professor Wilcox for his counsel in carrying through these calculations.[20]

The composition of solvolysis product mixtures are given in Table V.

TABLE V
COMPOSITION OF SOLVOLYSIS PRODUCT MIXTURES

Compd solvolyzed	Products formed,[a] mol % A	B	C	D	E	F
2	83.8	N.D.[b]	14.9	1.3		
5	70.7	N.D.	<0.5	29.3		
3	87.5	N.D.	11.1	1.4		
6	81.4	N.D.	1.1	17.5		
9	80.5	2.3	15.3	2.0		
12	74.6	4.4	1.1	19.9		
15-OTs	61.4	8.1			23.5	6.9
16-OTs	51.6	12.6			<1.0	35.8

[a] Products formed: A = 4-ene; B = 3-ene; C = *cis*-4-acetate; D = *trans*-4-acetate; E = *cis*-3-acetate; F = *trans*-3-acetate. [b] N.D. = not determined. The isolated chlorocyclohexene had an infrared spectrum essentially identical with that of authentic 4-chlorocyclohexene.

(14) E. L. Eliel, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, p 454.

(15) *Cf.* the dipole moment of dimethyl sulfone[16] of 4.44 D.

(16) V. Baliah and Sp. Shanmuganathan, *Trans. Faraday. Soc.*, **55**, 232 (1959).

(17) C. F. Wilcox and C. Leung, *J. Amer. Chem. Soc.*, **90**, 336 (1968).

(18) The energy of interaction between a dipole at C-4 and a charge at C-1 were calculated by computing the energies of an array of charges embedded in a cavity of dielectric constant 2, in turn embedded in a continuous medium of higher dielectric constant (6.62 for acetic acid). Calculations were made using both the molecular volume as calculated by Traube's rules [J. Traube, *Samml. Chem. Chem.-Tech. Vortr.*, **4**, 255 (1899)] and also estimating the radius of the cavity by Tanford's method [C. Tanford, *J. Amer. Chem. Soc.*, **79**, 5348 (1957)].

(19) S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

(20) The calculations were made at the Computer Center, University of California, using an IBM 7094 computer. We wish to thank the center for making computer time available to us.

Experimental Section[21]

trans-4-**Chlorocyclohexanol** (1).—Treatment of 1,4-epoxycyclohexane with concentrated hydrochloric acid at room temperature for 8 days, following the procedure of Bennett and Niemann,[6] afforded *trans*-4-chlorocyclohexanol, mp 84–85°, in 72% yield (lit.[6,22] mp 82–83°).

trans-4-**Chlorocyclohexyl acetate** was prepared from *trans*-4-chlorocyclohexanol in the usual manner: bp 93.5–93.7° (4.5 mm); $n^{25}D$ 1.4644; distinguishing ir bands at 8.97, 9.90, and 13.78 μ.

Anal. Calcd for $C_8H_{13}ClO_2$: C, 54.39; H, 7.42; Cl, 20.07. Found: C, 54.52; H, 7.37; Cl, 20.10.

trans-4-**Chlorocyclohexyl 3,5-dinitrobenzoate**, prepared in the usual manner,[23] crystallized from ethyl acetate in lustrous white plates, mp 158.8–159.8°.

Anal. Calcd for $C_{13}H_{13}ClN_2O_6$: C, 47.58; H, 3.99; Cl, 10.79; N, 8.52. Found: C, 47.75; H, 4.12; Cl, 10.68; N, 8.46.

trans-4-**Chlorocyclohexyl** *p*-**toluenesulfonate** (2) was prepared from *p*-toluenesulfonyl chloride and *trans*-4-chlorocyclohexanol in pyridine. Isolation in the usual manner afforded *trans*-4-chlorocyclohexyl *p*-toluenesulfonate, mp 74.6–76.0°. A sample for analysis and for the kinetic runs was prepared by additional crystallization from hexane–carbon tetrachloride, mp 76.1–76.9°.

Anal. Calcd for $C_{13}H_{17}ClO_3S$: C, 54.06; H, 5.94; Cl, 12.28; S, 11.10. Found: C, 54.06; H, 6.15; Cl, 12.40; S, 10.88.

trans-4-**Chlorocyclohexyl methanesulfonate** (3) was prepared following the procedure of Truce, Campbell, and Norbell[24] in nearly quantitative yield. Crystallization from ligroin (bp 90–120°) gave pure material, mp 88.5–89.0°.

Anal. Calcd for $C_7H_{13}ClO_3S$: C, 39.53; H, 6.16; S, 15.08. Found: C, 39.31; H, 5.94; S, 15.03.

cis-4-**Chlorocyclohexanol** (4).—*trans*-4-Chlorocyclohexyl tosylate was heated with sodium acetate in dimethylformamide (steam bath, 72 hr) to afford *cis*-4-chlorocyclohexyl acetate in 27% yield, after distillation and chromatography on alumina: bp 80–81° (1 mm); $n^{25}D$ 1.4675; distinguishing ir bands at 9.07, 11.53 and 13.92 μ. Vapor phase chromatography on a silicone oil–Chromosorb column revealed that the material is greater than 96% *cis* isomer. The *cis*-4-chlorocyclohexyl acetate was reduced with lithium aluminum hydride to afford *cis*-4-chlorocyclohexanol, which slowly crystallized, mp 23.8–25.6° (from hexane).

Reduction of 4-chlorocyclohexanone with lithium aluminum hydride afforded a mixture of *cis*- and *trans*-4-chlorocyclohexanols (60% *cis*) which was separated by distillation at reduced pressure with a spinning-band column to afford a larger sample of *cis*-4-chlorocyclohexanol, which crystallized slowly and was 97% *cis* by vpc.

cis-4-**Chlorocyclohexyl 3,5-dinitrobenzoate**, prepared in the usual manner,[23] was crystallized from ethyl acetate–hexane, mp 158.2–159.6° (mmp 132–136° with *trans* isomer).

Anal. Calcd for $C_{13}H_{13}ClN_2O_6$: C, 47.58; H, 3.99; Cl, 10.79; N, 8.52. Found: C, 47.47; H, 4.05; Cl, 10.83; N, 8.59.

cis-4-**Chlorocyclohexyl tosylate** (5), prepared in the usual manner, was crystallized from hexane, mp 66.0–67.0°.

Anal. Calcd for $C_{13}H_{17}ClO_3S$: C, 54.06; H, 5.94; Cl, 12.28; S, 11.10. Found: C, 53.88; H, 6.08; Cl, 12.14; S, 10.98.

cis-4-**Chlorocyclohexyl methanesulfonate** (6) was prepared by treating a mixture of *cis*-4-chlorocyclohexanol and methanesulfonyl chloride in benzene, cooled to 0°, with a 10% excess of triethylamine. The precipitated triethylamine hydrochloride was removed by filtration, and the solvent and excess triethylamine were removed under reduced pressure. The residual oil slowly crystallized from anhydrous methanol at −78° and was then crystallized twice from cyclohexane to give *cis*-4-chlorocyclohexyl methanesulfonate, mp 44.2–44.7°.

Anal. Calcd for $C_7H_{13}ClO_3S$: C, 39.53; H, 6.16; S, 15.08. Found: C, 39.37; H, 5.95; S, 14.88.

trans-4-**Bromocyclohexanol** (7).—1,4-Epoxycyclohexane (217 g) was mixed with 48% aqueous hydrobromic acid (391 g), and the solution stirred at 50°. After 3 days, the solution separated into two layers. The reaction was discontinued after 6 days. The mixture was saturated with sodium chloride and extracted with ether. The ethereal solution was washed with sodium bicarbonate solution, then water, then dried over anhydrous sodium sulfate. The ether was evaporated and a small amount of unreacted oxide (*ca.* 10 g) was distilled under reduced pressure from the residue, which then solidified upon standing. Two recrystallizations from hexane gave 233 g (59%) of *trans*-4-bromocyclohexanol as white plates, mp 81–82° (lit.[6] mp 81.0–81.5°).

Anal. Calcd for $C_6H_{11}BrO$: C, 40.24; H, 6.28; Br, 44.67. Found: C, 40.22; H, 6.11; Br, 44.73.

In the case of 4-bromocyclohexanol, the reaction of 1,4-epoxycyclohexane with hydrogen bromide is not so stereospecific as with HCl.

trans-4-**Bromocyclohexyl 3,5-dinitrobenzoate** was prepared in the usual way.[23] Recrystallization from ethanol–ethyl acetate gave white plates, mp 164–165°.

Anal. Calcd for $C_{13}H_{13}BrN_2O_6$: C, 41.82; H, 3.49; Br, 21.44; N, 7.50. Found: C, 42.06; H, 3.72; Br, 21.23; N, 7.34.

trans-4-**Bromocyclohexyl tosylate** (8) was prepared in the usual manner. Six crystallizations from hexane afforded pure material, mp 85–86°.

Anal. Calcd for $C_{13}H_{17}BrO_3S$: C, 46.85; H, 5.14; Br, 23.98; S, 9.62. Found: C, 46.97; H, 5.11; Br, 23.91; S, 9.48.

trans-4-**Bromocyclohexyl Methanesulfonate** (9).—*trans*-4-Bromocyclohexanol (10.00 g) and methanesulfonyl chloride (6.40 g) were cooled to 0° in benzene (50 ml) and a 10% excess of triethylamine in benzene (6.40 g of triethylamine in 25 ml of benzene) was added over 30 min, with stirring. The precipitate of triethylamine hydrochloride (7.85 g, 102%) was filtered off, and the solvent and excess triethylamine were removed by distillation at reduced pressure, leaving a residual white solid (13.5 g, 0.052 mol, 94%). This solid was recrystallized twice from hexane to give pure *trans*-4-bromocyclohexyl methanesulfonate (7.60 g, 52.8%), mp 83.5–84.0°.

Anal. Calcd for $C_7H_{13}BrO_3S$: C, 32.70; H, 5.10; S, 12.47. Found: C, 32.58; H, 5.08; S, 12.32.

cis-4-**Bromocyclohexanol** (10).—*trans*-4-Bromocyclohexanol was oxidized with sodium dichromate in 10% sulfuric acid. After 2 hr at 50° the reaction solution was cooled and extracted with ethyl ether, and the extract was washed with sodium bicarbonate solution and with water. The dried ether solution of 4-bromocyclohexanone was used directly for reduction with lithium aluminum hydride. Addition of this solution to a slurry of lithium aluminum hydride in ethyl at −78° was carried out over 100 min. The reaction mixture was allowed to return to room temperature over 90 min and then heated briefly. After work-up in the usual fashion distillation at reduced pressure afforded a yellow oil (76% over-all yield from *trans*-4-bromocyclohexanol), which proved to be a mixture of 57% *cis*- and 43% *trans*-4-bromocyclohexanol by vpc. Careful refractionation of this material at reduced pressure gave samples of *cis*-4-bromocyclohexanol of up to 97% *cis* content (by vapor phase chromatography), bp 94° (20 mm).

cis-4-**Bromocyclohexyl 3,5-dinitrobenzoate** was prepared in the usual way, and the product recrystallized from ethanol: mp 163–164°; mmp 137–140° with *trans* isomer.

Anal. Calcd for $C_{13}H_{13}BrN_2O_6$: C, 41.82; H, 3.49; Br, 21.44; N, 7.50. Found: C, 41.81; H, 3.65; Br, 21.47; N, 7.56.

cis-4-**Bromocyclohexyl Tosylate** (11).—The oily *cis*-4-bromocyclohexenol was dissolved in pyridine and treated with *p*-toluenesulfonyl chloride in the usual way. The product was recrystallized six times from hexane: mp 79–80°; mmp 57–62° with *trans* isomer.

Anal. Calcd for $C_{13}H_{17}BrO_3S$: C, 46.85; H, 5.14; Br, 23.98; S, 9.62. Found: C, 46.57; H, 5.16; Br, 24.18; S, 9.38.

cis-4-**Bromocyclohexyl Methanesulfonate** (12).—A *cis*-rich mixture of *cis*- and *trans*-4-bromocyclohexanols (containing 85.1% *cis* isomer by vpc) was treated with methanesulfonyl

(21) Melting points are corrected; boiling points are uncorrected. Analyses are by the Microanalytical Laboratory, University of California.

(22) E. A. Fehnel, S. Goodyear, and J. Berkowitz, *J. Amer. Chem. Soc.*, **73**, 4978 (1951).

(23) S. M. McElvain, "The Characterization of Organic Compounds," The MacMillan Co., New York, N. Y., 1956, p 199.

(24) W. E. Truce, R. W. Campbell, and J. R. Norbell, *J. Amer. Chem. Soc.*, **86**, 288 (1964).

chloride and a 10% excess of triethylamine in benzene. After work-up as described above a pale yellow viscous oil was obtained, which did not crystallize. Several drops were dissolved in a minimal amount of methylcyclohexane at 60°, and the solution was seeded with a small crystal of *trans*-4-bromoeyclohexyl methanesulfonate and cooled. The main portion of the product was then taken up in minimal methylcyclohexane at 60°, filtered hot, cooled in an ice bath, and seeded with some seed crystals formed above. This process induced crystallization as a partially crystalline mass. The material was allowed to stand for 1 hr in the ice bath, whereupon the mass was broken up with a spatula, filtered cold, and air dried, obtaining crude *cis*-4-bromocyclohexyl methanesulfonate (mp 25–40°, mostly at 37–40°. Three further recrystallizations from methylcyclohexane as above gave pure *cis*-4-bromocyclohexyl methanesulfonate (45% yield), mp 44.5–45.0°.

Anal. Calcd for $C_7H_{13}BrO_3S$: C, 32.70; H, 5.10; S, 12.47. Found: C, 32.89; H, 5.23; S, 12.55.

cis-4-Carboxamidocyclohexanol.—*cis*-4-Hydroxycyclohexanecarboxylic acid lactone[25] (17.1 g) was mixed with concentrated aqueous ammonium hydroxide (200 ml) and stirred at room temperature. Dissolution of the solid lactone occurred after 30 min and stirring was continued for an additional 2.5 hr. Ammonia and water were removed under reduced pressure and the white solid residue was recrystallized from acetonitrile: mp 140–143°; yield 14.6 g (75%).

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.74; H, 9.10; N, 9.80. Found: C, 58.46; H, 8.82; N, 9.62.

cis-4-Carboxamidocyclohexyl Acetate.—*cis*-4-Carboxamidocyclohexanol (13.6 g) was stirred at room temperature with 100 ml of pyridine and 100 ml of acetic anhydride for 24 hr. Volatile materials were removed by vacuum distillation, and the residue was recrystallized from benzene–hexane, giving white plates: mp 137–139°; yield 13.4 g (76%).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.43; H, 8.11; N, 7.57. Found: C, 58.45; H, 7.93; N, 7.54.

cis-4-Cyanocyclohexyl Tosylate.—*cis*-4-Carboxamidocyclohexyl acetate (13.4 g) was dissolved in thionyl chloride (50 ml) and refluxed for 1 hr. Excess thionyl chloride was removed on an aspirator. The infrared spectrum of the residue showed complete conversion of the amide into *cis*-4-cyanocyclohexyl acetate, as evidenced by the disappearance of the amide band at 6.08 μ and the appearance of the strong nitrile band at 4.46 μ. The oily product was then stirred with aqueous sodium hydroxide (400 ml, 0.2 *N*) for 11 hr at room temperature. The mixture was then continuously extracted with ether overnight. Evaporation of the ether left an oil whose infrared spectrum showed complete conversion of the acetate to *cis*-4-cyanocyclohexanol (**14**), as evidenced by the disappearance of the acetate band at 5.78 μ and the appearance of the hydroxyl band at 2.88 μ. Treatment of this oil with pyridine and *p*-toluenesulfonyl chloride in the usual way gave a solid tosylate which was recrystallized from cyclohexane affording white needles: mp 105–106°; yield 5.4 g (20.7%).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.21; H, 6.13; N, 5.02; S, 11.47. Found: C, 60.02; H, 5.91; N, 5.36; S, 10.22.

trans-4-Carboxamidocyclohexyl Acetate.—*trans*-4-Acetoxycyclohexanecarboxylic acid (8.1 g), prepared by the method of Campbell and Hunt,[26] was combined wth redistilled thionyl chloride (20 ml) and the mixture refluxed for 1 hr. Excess thionyl chloride was removed and the oily residue poured slowly into 50 ml of concentrated aqueous ammonia. The white solid precipitate was recrystallized from chloroform–cyclohexane giving crystals: mp 198–200°; yield 3.9 g (48%).

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.43; H, 8.11; N, 7.57. Found: C, 58.22; H, 8.19; N, 7.55.

trans-4-Cyanocyclohexyl Tosylate.—*trans*-4-Carboxamidocyclohexyl acetate (10.6 g) was mixed with purified thionyl chloride (40 ml) and the solution refluxed for 1 hr. Excess thionyl chloride was removed on an aspirator and the residual oil stirred with aqueous sodium hydroxide solution (200 ml, 0.4 *N*) for 40 hr at room temperature. The mixture was then continuously extracted with ether and the ether evaporated. The infrared spectrum of the crystalline product showed complete conversion of *trans*-4-acetoxycyclohexanecarboxamide into *trans*-4-cyanocyclohexanol (**13**), as evidenced by the disappearance of the amide and acetate bands at 6.13 and 5.78 μ, respectively, and the appearance of the strong nitrile band and the hydroxyl band at 4.46 and 2.89 μ, respectively. The white solid was dissolved in pyridine and treated with *p*-toluenesulfonyl chloride in the usual way. The product was recrystallized from cyclohexane: mp 95–96°; yield 4.9 g (24%).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.21; H, 6.13; N, 5.02; S, 11.47. Found: C, 60.07; H, 6.36; N, 5.21; S, 11.64.

cis-3-Carboxamidocyclohexanol.—The lactone of 3-hydroxycyclohexanecarboxylic acid[27] (63 g, mp 117–119°) was treated with 220 ml of concentrated aqueous ammonia at room temperature for 2 hr. After cooling in ice, the precipitated solid was collected and an additional crop obtained by concentration of the filtrate under reduced pressure. The crude amide was crystallized from ethyl acetate: mp 176–178.5°; yield 75%.

Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15. Found: C, 58.51; H, 8.97.

cis-3-Carboxamidocyclohexyl acetate was prepared by treatment of the amide with acetic anhydride and pyridine at room temperature for 20 hr. The white crystalline solid obtained upon removal of the excess pyridine and acetic anhydride under vacuum was crystallized from 1:1 benzene–ligroin (bp 60–90°): mp 131.5–133°; yield 68%.

Anal. Calcd for $C_9H_{15}NO_3$: C, 58.43; H, 8.11. Found: C, 59.09; H, 7.97.

cis-3-Cyanocyclohexyl Acetate.—*cis*-3-Carboxamidocyclohexyl acetate (48.5 g) was added to 90 ml of redistilled thionyl chloride and heated under reflux for 2 hr. Excess thionyl chloride was removed under reduced pressure to give a residual oil which solidified on chilling. The crude *cis*-3-cyanocyclohexyl acetate was crystallized twice from ethanol–water, mp 39–41°.

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84. Found: C, 64.48; H, 7.92.

cis-3-Cyanocyclohexyl Tosylate.—*cis*-3-Cyanocyclohexyl acetate was hydrolyzed to *cis*-3-cyanocyclohexanol with 0.2 *N* NaOH, and the progress of the reaction was monitored by infrared. After 22 hr, the ester band was absent. Crude *cis*-3-cyanocyclohexanol (**16**) was isolated by continuous extraction with ether, and concentration of the ether extracts. The crude alcohol was treated directly with *p*-toluenesulfonyl chloride in the usual manner to afford *cis*-3-cyanocyclohexyl tosylate, mp 67–68° (from CCl_4).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.21; H, 6.13. Found: C, 60.03; H, 5.97.

trans-3-Carboxamidocyclohexyl Acetate.—*trans*-3-Hydroxycyclohexanecarboxylic acid[28] was converted into *trans*-3-acetoxycyclohexanecarboxylic acid by treatment with acetic anhydride and pyridine. The crude *trans*-3-acetoxycyclohexanecarboxylic acid was treated with thionyl chloride and the crude acid chloride poured into concentrated aqueous ammonium hydroxide, in a fashion similar to that described for the *trans*-4 isomer above. The precipitated solid was crystallized twice from benzene to give *trans*-3-carboxamidocyclohexyl acetate, mp 105–106°, whose infrared spectrum was consistent with the assigned structure.

trans-3-Cyanocyclohexyl Tosylate.—*trans*-3-Carboxamidocyclohexyl acetate (21 g) was refluxed with 41.5 ml of redistilled thionyl chloride for 2 hr. Excess thionyl chloride was removed, and 17 g (85%) of *trans*-3-cyanocyclohexyl acetate was collected by distillation at 123–125° (5 mm). This ester was hydrolyzed with 0.2 *N* NaOH, and the progress of the hydrolysis was monitored on aliquots by infrared. After 20 hr hydrolysis was complete. The crude *trans*-3-cyanocyclohexanol (**15**) was isolated by extraction with ether. The crude *trans*-3-cyanocyclohexanol was converted into the tosylate in the usual way. The crude tosylate crystallized very slowly, and was purified by crystallization from ether, mp 47–48° (11 g, 40% over-all yield from *trans*-3-carboxamidocyclohexyl acetate).

Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.21; H, 6.13; N, 5.02; S, 11.46. Found: C, 60.12; H, 6.15; N, 4.93; S, 11.34.

Kinetic Method.—The usual sealed ampoule technique was used. As all the kinetic measurements were carried out in acetic acid, with solutions containing approximately twice the concentration of the initial sulfonate ester, the progress of the reactions was followed by titration with perchloric acid in acetic

(25) D. S. Noyce, G. L. Woo, and B. R. Thomas, *J. Org. Chem.*, **25**, 260 (1960).

(26) N. R. Campbell and J. H. Hunt, *J. Chem. Soc.*, 1379 (1950).

(27) D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.*, **74**, 5912 (1952).

(28) D. S. Noyce and H. I. Weingarten, *ibid.*, **97**, 3098 (1957).

acid either to the bromphenol blue end point or potentiometrically.

Product Analysis.—The products formed under the conditions of the kinetic measurements were determined for each of the compounds studied. The products represented a normal product distribution (large excess of inversion over retention, predominant formation of olefin) for a typical solvolysis of cyclohexyl compounds. The detailed results are presented in Table V.

Registry No.—**2**, 19556-66-2; **3**, 19556-67-3; **4**, 19556-68-4; **4** (3,5-dinitrobenzoate derivative), 19556-69-5; **5**, 19556-70-8; **6**, 19556-71-9; **8**, 19556-72-0; **9**, 19556-73-1; **10**, 19556-74-2; **10** (3,5-dinitrobenzoate derivative), 19594-76-4; **11**, 19556-75-3; **12**, 19556-76-4; *trans*-4-chlorocyclohexyl acetate, 19556-77-5; *trans*-4-chlorocyclohexyl 3,5-dinitrobenzoate, 19556-78-6; *trans*-4-bromocyclohexyl 3,5-dinitrobenzoate, 19556-96-8; *cis*-4-carboxamidocyclohexanol, 19556-97-9; *cis*-4-carboxamidocyclohexyl acetate, 19556-98-0; *cis*-4-cyanocyclohexyl tosylate, 19556-99-1; *trans*-4-carboxamidocyclohexyl acetate, 19557-00-7; *trans*-4-cyanocyclohexyl tosylate, 19557-01-8; *cis*-3-carboxamidocyclohexanol, 19557-02-9; *cis*-3-carboxamidocyclohexyl acetate, 19557-03-0; *cis*-3-cyanocyclohexyl acetate, 19557-04-1; *cis*-3-cyanocyclohexyl tosylate, 19557-07-4; *trans*-3-carboxamidocyclohexyl acetate, 19557-05-2; *trans*-3-cyanocyclohexyl tosylate, 19557-06-3.

Polarity Effects on the Acetolysis of Substituted 1-Decalyl Methanesulfonates[1]

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All four stereoisomers of 4-cyano-1-decalol containing the *trans*-decalin moiety have been synthesized and characterized. The rates of acetolysis of the methanesulfonates of these compounds have been measured. *trans*-4α-Cyano-1β-decalyl methanesulfonate (equatorial cyano and equatorial methanesulfonate) solvolyzes 3.2 times faster than *trans*-4α-cyano-1β-decalyl methanesulfonate (axial cyano and equatorial methanesulfonate) in agreement with calculations based on a direct field effect model. In contrast, an inductive effect operating through the bonds would predict identical rates for these two compounds. The field effect model, based upon 70% charge separation at the transition state, predicts the reaction rates quite well for three of the four compounds in this study. The fourth compound, *trans*-4β-cyano-1α-decalyl methanesulfonate (axial cyano and axial methanesulfonate), reacts about twice as rapidly as predicted; this is probably the result of a complex mechanism for the axial methanesulfonate, as has been postulated in similar systems, involving participation of the adjacent ring juncture hydrogen (which is tertiary, axial, and in an antiperiplanar orientation to the leaving sulfonate group).

In the preceding paper, we have shown that the solvolysis of 4-halocyclohexyl methanesulfonates is most satisfactorily explained on the basis of a field effect.[2] However, the conformational mobility of simple cyclohexane systems adds an additional degree of uncertainty to this conclusion, and it seemed desirable to examine the effect of the polarity of substituents on reaction rate in conformationally rigid systems. For this purpose we have chosen to investigate the reactivity of a selected group of *trans*-decalin derivatives.

Condensation of 1-(1-acetoxyvinyl)cyclohexene with acrylonitrile produced a mixture of 4α-cyano- and 4β-cyano-1-acetoxy-$\Delta^{1,10}$-octalins. Mild hydrolysis afforded a mixture of four isomeric 4-cyano-1-decalones. The two major components of this mixture, *trans*-4α-cyano-1-decalone (**1**,[3] 65%), and *trans*-4β-cyano-1-decalone (**2**, 33%), were separated and purified. The two minor components (2% of the total mixture) were assigned the *cis*-4-cyano-1-decalone structures by virtue of their conversion into a mixture of **1** and **2**. The structure of **1** and **2** was established by hydrolysis to the known *trans*-4α-carboxy-1-decalone (**3**) and comparison with an authentic sample prepared by the method of Nazarov, Kucherov, and Segal.[4] This establishes that the cyano group is in the 4 position rather than the 3 position, which would have resulted from addition in the reverse direction in the Diels–Alder reaction. The assignment of configuration to **1** and **2**, respectively, comes from a consideration of their nmr spectra. *trans*-4β-Cyano-1-decalone has a peak for one proton at δ 2.93, in good agreement with the δ 2.91 chemical shift observed for the equatorial hydrogen atom adjacent to the cyano group in *cis*-4-*t*-butyl-1-cyanocyclohexane.[5] The peak for the hydrogen atom adjacent to the cyano group in **1** is not separated from the complex multiplet due to the ring protons. The corresponding peak for the axial hydrogen atom adjacent to the cyano group in *trans*-4-*t*-butyl-1-cyanocyclohexane is also obscured by the ring protons.[5]

Pure samples of *trans*-4α- and *trans*-4β-cyano-1-decalones were each reduced with aluminum isopropoxide; from **1** a 50:50 mixture of two alcohols was obtained, and from **2**, a 70:30 mixture of two different alcohols was formed. The mixtures of alcohols were separated by chromatography on alumina. The structures of these alcohols were established on the basis of their origins and their nmr spectra. The chemical shifts of the nmr peaks are listed in Table I with the chemical shifts of the peaks for known compounds in the cyclohexane series which are "conformationally pure." The methanesulfonates of these alcohols were then formed by standard methods. The structures of

(1) Supported in part by grants from the National Science Foundation, GP-1572 and GP-6133X.

(2) D. S. Noyce, B. N. Bastian, P. T. S. Lau, R. S. Monson, and B. Weinstein, *J. Org. Chem.*, **34**, 1247 (1969).

(3) Nomenclature in this paper will use the steroid conventions and numbering, with the hydrogen at C-10 in the β orientation. All the compounds in the present study are *dl* mixtures. Only one enantiomorph is shown in Scheme I for convenience.

(4) I. N. Nazarov, V. F. Kucherov, and G. M. Segal, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1241 (1956).

(5) N. L. Allinger and W. Szkrybalo, *J. Org. Chem.*, **27**, 4601 (1962).

TABLE I

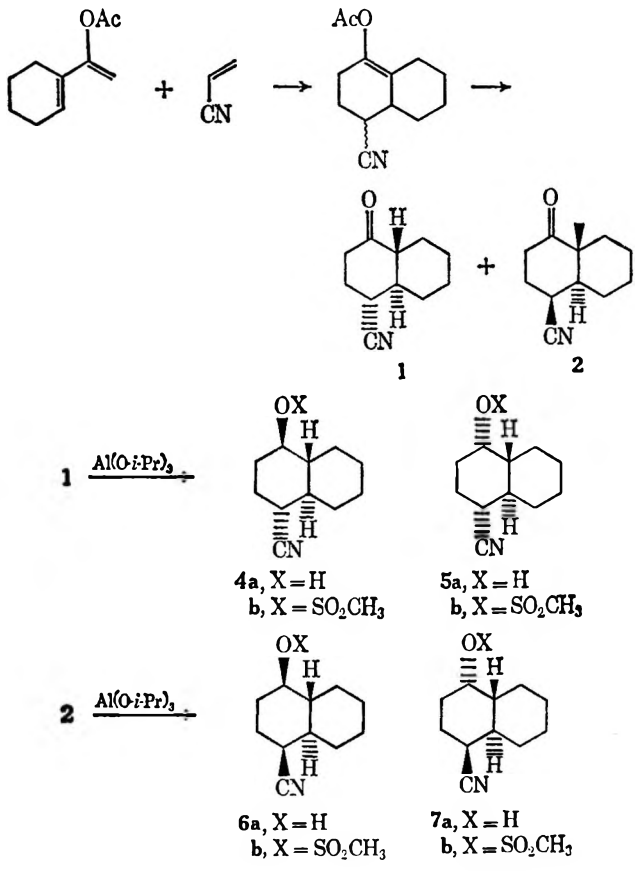
SIGNIFICANT NMR PEAKS FOR ASSIGNMENT OF STRUCTURE

Compd	Confign[a] CN	Confign[a] OX	δ[b] Eq H (CHCN)	Eq H (CHOH)	Ax H (CHOH)	Eq H (CHOMs)	Ax H (CHOMs)
2	Ax		2.93 (7)				
4a	Eq	Eq			3.21 (15)		
4b	Eq	Eq					4.29 (16)
5a	Eq	Ax		3.73 (7)			
5b	Eq	Ax				4.70 (7)	
6a	Ax	Eq	2.73 (7)		3.17 (15)		
6b	Ax	Eq	2.77 (7)				4.28 (16)
7a	Ax	Ax	2.95 (7)	3.78 (7)			
7b	Ax	Ax	2.83 (7)			4.73 (7)	
cis-4-*t*-Butyl-1-cyanocyclohexane[c]	Ax		2.91				
trans-1β-Decalol		Eq			3.13 (15)		4.17 (16)
cis-4-*t*-Butylcyclohexanol[d]		Ax		3.93 (7)		4.88 (7)	
trans-4-*t*-Butylcyclohexanol[d]		Eq			3.37 (15)		4.45 (16)

[a] Axial or equatorial, OH or OSO_2CH_3 (OMs). [b] The values are chemical shifts in parts per million from TMS (internal) in chloroform solution. Values in parentheses are peak widths at half-height in cycles per second. [c] Reference 5. [d] From ref. 8.

the methanesulfonates were also supported by comparison of the nmr spectra with the nmr spectra of known compounds in the cyclohexane series (see Table I). These reactions are summarized in Scheme I.

SCHEME I



Kinetic Results.—The four isomers all solvolyzed smoothly in acetic acid giving good first-order behavior. The rates of solvolysis are substantially less than the rates of solvolysis of the corresponding decalols as would be expected. The rates of acetolysis of both *trans*-1α-decalyl tosylate and *trans*-1β-decalyl tosylate have been measured.[6,7] Extrapolation of these measured rates to 90°, in conjunction with our previous comparisons of tosylates and methanesulfonates,[8] predicts a rate for *trans*-1α-decalyl methanesulfonate (axial sulfonate) of 3.2×10^{-3} sec^{-1} and for *trans*-1β-decalyl methanesulfonate (equatorial sulfonate) of 7.8×10^{-5} sec^{-1}. The rate ratio (axial/equatorial) of 40 is not the usual factor of about 3. However, other instances of axial sulfonates with an adjacent equatorial substituent showing accelerated rates are well documented. The rate ratio in the menthyl series ($k_{neomenthyl}/k_{menthyl}$) is 77,[9] presumably revealing an enhanced rate due to participation by the neighboring axial hydrogen; for the 2-methylcyclohexyl tosylate, the rate ratio is 71.[6]

Our rate measurements are summarized in Table II and derived thermodynamic data are given in Table III.

Discussion

Observed Reaction Rates.—The kinetic results listed in Table II indicate that the orientation of the cyano substituent does affect the reaction rates, as predicted if a field effect were important. The relative rates for the isomeric compounds in this study are listed in Table IV. The relative rates of the equatorial methanesulfonates differ by a factor of 3, while the relative rates of the axial methanesulfonates differ by only 20%. To a first approximation these ratios should be independent of the leaving group, depending only on the relative energies of the carbonium ions.

The solvolysis of **5b** and **7b** may well be complicated by participation, and therefore this ratio is less instructive. The equatorial methanesulfonate solvolyses (*i.e.*, **4b** and **6b**) should not be complicated by participation.

The similar compound, menthyl *p*-toluenesulfonate, reacts through a normal solvolysis.[9] Therefore, the solvolysis rates of the *trans*-4-cyano-1-decalyl methanesulfonates, which have equatorial methanesulfonate groups, should be useful for studying polar effects on acetolysis rates. The resulting rate ratio for this pair of compounds, k_{4b}/k_{6b} (Table IV) shows that there is a substantial difference in the rates due to the change in the orientation of the substituent dipole.

(6) W. Hückel and H. D. Säurland, *Ann.*, **592**, 190 (1955).

(7) I. Moritani, S. Nishida, and M. Murakami, *J. Amer. Chem. Soc.*, **81**, 3420 (1959).

(8) D. S. Noyce, B. E. Johnston and B. Weinstein, *J. Org. Chem.*, **34**, 463 (1969).

(9) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

TABLE II

KINETICS OF THE ACETOLYSES OF 4-SUBSTITUTED *trans*-1-DECALYL METHANESULFONATES

Compd[a]	Config[b] –CN	Config[b] –O Ms	Temp, °C	$k_1 \times 10^6$, sec^{-1}
4b	Eq	Eq	90.00	2.64 ± 0.04
			110.00	23.0 ± 0.8
6b	Ax	Eq	90.00	0.813 ± 0.020
			110.00	7.25 ± 0.020
5b	Eq	Ax	70.00	5.65 ± 0.34
			90.00	51.7 ± 0.5
7b	Ax	Ax	70.00	7.27 ± 0.32
			90.00	64.7 ± 0.8

[a] **4b** is *trans*-4α-cyano-1β-decalyl methanesulfonate. **6b** is *trans*-4β-cyano-1β-decalyl methanesulfonate. **5b** is *trans*-4α-cyano-1α-decalyl methanesulfonate. **7b** is *trans*-4β-cyano-1α-decalyl methanesulfonate. [b] Axial or equatorial configuration of methanesulfonate group (–OMs) or cyano group (–CN).

TABLE III

ACTIVATION PARAMETERS

Compd[a]	$\Delta H^{\ddagger}$, kcal	$\Delta S^{\ddagger}$, eu
4b	29.2 ± 0.3	−4.1 ± 0.7
6b	29.5 ± 0.3	−5.5 ± 0.7
5b	26.7 ± 0.2	−5.0 ± 0.6
7b	26.4 ± 0.2	−5.5 ± 0.7

[a] **4b** is *trans*-4α-cyano-1β-decalyl methanesulfonate. **6b** is *trans*-4β-cyano-1β-decalyl methanesulfonate. **5b** is *trans*-4α-cyano-1α-decalyl methanesulfonate. **7b** is *trans*-4β-cyano-1α-decalyl methanesulfonate.

TABLE IV

RELATIVE ACETOLYSIS RATES OF THE *trans*-4-CYANO-1-DECALYL METHANESULFONATES

Temp, °C	Equatorial –OMs k_{4b}/k_{6b}	Axial –OMs k_{5b}/k_{7b}
70.00		0.80
90.00	3.25	0.78
110.00	3.17	

Calculated Reaction Rates.—Interaction energies between the substituent dipole and the reaction center were calculated as in the Kirkwood–Westheimer treatment.[10] The dipoles were treated as point charges on the cyano carbon atom and nitrogen atom rather than as point dipoles[10] since the length of the dipole is the same order of magnitude as distances between the dipoles and the reaction centers. This type of treatment predicts that the interaction will have a $1/R$ dependence rather than $1/R^2$ dependence as in the point dipole approximation. The use of the point charge models has been suggested elsewhere,[11-13] but has not been used extensively because of the increased complexity of the calculations. Calculations which have been carried out applying both point charge and point dipole models to a system do not produce appreciably different results.[11,14]

The choice of a model for the cavity is somewhat more difficult. Ideally the cavity should have a shape and volume which are similar to the shape of the molecule and the volume which it occupies in the solvent. In order to treat the problem mathematically a simplified model for this cavity must be chosen. Kirkwood and Westheimer[10] treat this cavity as an ellipsoid with the point dipole and the reactive center at the foci. The volume of the cavity can be approximated using Traube's rules,[15] based on extensive studies of the volume changes associated with the solution of compounds. Tanford[16] has suggested the use of a spherical model with a radius which is 1.0 Å greater than the distance from the center of the molecule to the furthest point charge. This type of treatment centers the cavity at the center of the molecule, while still maintaining all substituents within the cavity. This 1.0-Å distance has been comprised to the minimal distance between the substituent and the nearest solvent molecule.

The Traube radius for a cyanodecalyl methanesulfonate is 4.62 Å, compared with the Tanford radius (relative to the center of the ring) of 5.15 Å for a compound with an equatorial cyano group and 4.46 Å for a compound with an axial cyano group. The Traube radius for cyclohexyl methanesulfonate is 4.16 Å. This latter model is impractical since it would place the equatorial nitrogen atom on the surface of the sphere, when in reality, the solvent molecules are limited in their approach by steric interactions.

The dipole moments used in this study were taken from standard sources. The calculated interaction energies for the ground states and carbonium ions (**8** and **9**) of the compounds in this study, based on these

8 **9**

models, are listed in Table V. The corresponding calculations for the 4-hydrogen compounds are included, since corrections for the effect of the hydrogen dipole should be applied if the calculated rates for the unsubstituted compounds are to be used as standards for the reaction rates in the absence of a dipole effect. As seen in Table V the calculated interactions are quite insensitive to the model for the cavity and the radius. The effective dielectric constants are very close to 2.0, the internal dielectric constant, as can be seen by comparing the calculated interaction energies using cavity models, with the corresponding energies for a continuous medium with a dielectric constant of 2.0. Therefore, the medium effect is small (relative to a solvent such as water, $D = 78$) and the choice of a model for the cavity is less important. Methods E and F place the limits of the cavity at or very near the nitrogen atom. This type of treatment is impractical for two reasons: the

(10) J. G. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506 (1938).
(11) H. D. Holtz and L. M. Stock, *J. Amer. Chem. Soc.*, **86**, 5188 (1964).
(12) J. D. Roberts and R. A. Carboni, *ibid.*, **77**, 5554 (1955).
(13) M. J. S. Dewar and P. J. Grisdale, *ibid.*, **84**, 3539 (1962).
(14) H. D. Holtz and L. M. Stock, *ibid.*, **87**, 2404 (1965).
(15) J. Traube, *Samml. Chem. Chem.-Tech. Vortr.*, **4**, 225 (1899).
(16) C. Tanford, *J. Amer. Chem. Soc.*, **79**, 5348 (1957).

Table V

Calculated Field Effect Energies[a]

Compd[b]	Method[c] A	B	C	D	E	F
8	6.09	5.45	5.37	5.26	5.04	5.03
9	6.53	6.12	6.01	6.16	5.98	6.02
4b	0.51	0.60	0.58	0.60	0.60	0.59
6b	0.75	0.75	0.75	0.75	0.75	0.77
5b	0.28	0.28	0.27	0.28	0.27	0.28
7b	0.37	0.52	0.52	0.52	0.52	0.54

[a] These calculations were carried out using the FIELD computer program, supplied to us by Professor C. F. Wilcox of Cornell University, to whom we are indebted. This program evaluates the first eleven Legendre polynomials for each interaction (see ref 10). The values are listed in kilocalories. [b] Compounds 4b–7b are the 4-cyano-1-decalyl methanesulfonates, as depicted in Scheme I. Compounds 8 and 9 are the two carbonium ions derived from these compounds. [c] Method A is calculated on the basis of a continuous medium, $D = 2.0$; methods B and C use Tanford radii, centered at the middle of the ring and the middle of the C_9–C_{10} bond, respectively. Methods D and E use the Traube radii for decalin compounds centered in the middle of the ring and in the middle of the C_9–C_{10} bond. Method F used the Traube radii for the cyclohexane molecules centered in the ring.

bulk of the substituent prevents the solvent continuum from beginning near the center of charge, and the mathematical treatment used for these calculations begins to break down when a charged species is placed near the surface of the cavity, owing to nonconvergence of the Legendre polynomial function.

All of the calculation methods listed in Table V predict that *trans*-4β-cyano-1-decalyl carbonium ion **9** is less stable than *trans*-4α-cyano-1-decalyl carbonium ion **8**. These calculations predict that 4α-cyano compounds will react faster than the 4β-cyano compounds, as has been observed for the equatorial methanesulfonates.

For quantitative calculations the charge separation in the transition state has been treated as a variable between 50 and 100%. The effect of the negatively charged ion on the transition state energy has been assumed to be negligible. This assumption is based on the predicted lengthening of the carbon–oxygen bond in the transition state and the spreading of the developing charge over the three oxygen atoms of the sulfonate group and over the solvent, through hydrogen bonding. Methods B, C, and D in Table V are probably the most valid treatments. The calculated interaction energies for these methods are essentially equivalent, so subsequent calculations have been carried out for only method B, which is based on Tanford spheres centered at the center of the substituted ring.

The calculated interaction for these compounds are listed for a range of charge separations in Table VI. The calculated rates relative to the unsubstituted decalin methanesulfonates are listed in Table VII.

Table VI

Electrostatic Activation Energies[a]

Compd[b]	X[c] 1.0	0.85	0.70	0.50
4b	4.04	3.36	2.68	1.78
6b	4.95	4.11	3.26	2.14
5b	4.34	3.66	2.98	1.98
7b	5.11	4.27	3.42	2.30

[a] Energies in kilocalories. [b] Compounds as listed in Table I. [c] Fractional charge separation in transition state.

Table VII

Calculated k_{CN}/k_H[a] at 90°

Compd[b]	X[c] 1.0	0.85	0.70	0.50
4b	0.0037	0.0095	0.0244	0.0849
6b	0.0011	0.0034	0.0192	0.0512
5b	0.0008	0.0063	0.0161	0.0643
7b	0.0008	0.0027	0.0088	0.0413

[a] Calculated acetolysis rates of 4-cyano-1-decalin methanesulfonates relative to the unsubstituted 1-decalin methanesulfonates. [b] These compounds are depicted in Scheme I. [c] X is the fraction of charge separation in the transition state.

Using the rates for *trans*-1β-decalyl methanesulfonate and *trans*-1α-decalyl methanesulfonate mentioned earlier (*vide supra*), directly calculated rates of acetolysis may be derived from the information in Table VII. The most satisfactory agreement is achieved using a charge separation of 0.70 in the transition state; this leads to the comparison in Table VIII.

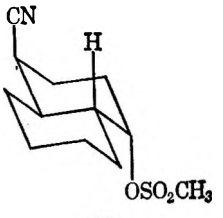
Table VIII

Comparison of Calculated and Experimental Rate Constants

Compd[a]	Calculated rate[b] × 10^7	Experimental rate[c] × 10^7
4b	19.3	26.4
6b	8.63	8.13
5b	522	517
7b	284	642

[a] The compounds are depicted in Scheme I. [b] Calculated acetolysis rates at 90° assuming 70% charge separation in the transition states. [c] Experimental acetolysis rates at 90°.

The agreement between the calculated and experimental rate constants in Table VIII is quite good except for *trans*-4β-cyano-1α-decalyl methanesulfonate (**7b**). A possible reason for the disagreement in this case may be related to the possibility of participation by the tertiary axial hydrogen atom, which has been discussed above. In particular, for **7b**, the cyano group has a direct steric interaction with this axial hydrogen atom. The presence of an axial leaving group creates an ideal geometrical relationship for participation of the axial hydrogen atom, and subsequent relief of the strain between the cyano group and hydrogen atom. The



7b

"*A* value" for the cyano group in cyclohexyl system is relatively small (approximately 0.2 kcal),[5,17] but with the increased steric crowding of a decalin system this interaction may become sufficient to produce a significant rate acceleration.

(17) F. R. Jensen and B. Rickborn, *J. Org. Chem.*, **27**, 4606 (1962).

Experimental Section[18]

1-Acetoxy-4-cyano-$\Delta^{1,10}$-octalin.—A fresh sample of 1-(1-acetoxyvinyl)cyclohexene (60.7 g), prepared from acetylcyclohexene by the method of Ansell and Brooks,[19] was placed in a steel autoclave with acrylonitrile (24.2 g), hydroquinone (0.2 g), and 120 ml of dry toluene. The autoclave was heated to 145 ± 5° and then shaken for 16 hr. After cooling, the dark liquid was distilled under vacuum. After removal of the solvent and excess reagent, 45.3 g (57%) of a mixture of adducts was collected, bp 130–145° (1.5 mm). This mixture solidified on cooling to form a solid, mp 50–68°. Analysis on a 5 ft × 0.25 in. SE-30 on 80/100 mesh Chromosorb W column indicated that the solid was a mixture of two compounds in the ratio of 68:32. These compounds were assigned the structures 1-acetoxy-4α-cyano-$\Delta^{1,10}$-octalin and 1-acetoxy-4β-cyano-$\Delta^{1,10}$-octalin, respectively: ir (CCl_4) 2220, 1710, 1650 cm^{-1}; nmr (CCl_4) δ 1.0–2.8 (m), 2.22 (s).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.81; N, 6.39. Found: C, 71.36; H, 7.66; N, 6.10.

***trans*-4α- and *trans*-4β-Cyano-1-decalones.**—A portion of the mixed 1-acetoxy-4-cyano-$\Delta^{1,10}$-octalins was stirred at 25° for 64 hr with a solution of 0.3 *N* sodium hydroxide (485 ml). The oil and water mixture was extracted three times with 120-ml portions of ether and the ether extracts were dried ($MgSO_4$). The ether was removed by distillation leaving a viscous oil (22.6 g, 88%) which crystallized slowly on standing. Vpc analyses indicated that this solid was a mixture of two major components and two minor components. The two minor components, about 2% of the total, were easily removed by recrystallization from ethanol–water, leaving an oily solid, mp 30–65°, containing the two major components. The minor components are the *cis*-decalone isomers (see below). The two major components, present in a ratio of about 2:1, were more difficult to separate. Samples enriched in one of the two compounds were obtained by distillation using a spinning-band column or by elution chromatography on Woelm grade III aluminum oxide. Enriched samples were fractionally recrystallized from ethanol–water to obtain the pure isomers.

The chief component, mp 69.5–70.0°, was assigned the structure of *trans*-4α-cyano-1-decalone (**1**) on the basis of the following spectral information: ir (CCl_4) 2257 (C≡N), 1720 cm^{-1} (C=O); nmr (CCl_4) δ 1.0–2.9 (m).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.83; H, 8.26; N, 7.87.

The other component, mp 71.0–71.5°, was assigned the structure of *trans*-4β-cyano-1-decalone (**2**) on the basis of the following spectral information: ir (CCl_4) 2237 (C≡N), 1718 cm^{-1} (C=O); nmr (CCl_4) δ 1.1–2.9 (m), 2.94 (broad, 7 cps width at half-height).

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.80; H, 8.48; N, 8.04.

Partial Equilibration of *trans*-4α-Cyano-1-decalone.—Pure ketone **1** (20 mg) was stirred for 64 hr in 7 ml of a 0.30 *N* sodium hydroxide solution. The mixture was then extracted with ethyl ether. The ether extracts were dried over anhydrous magnesium sulfate and analyzed by vpc. About 15% of the material had been converted into *trans*-4β-cyano-1-decalone, and about 2% had been converted into one of the minor components of the enol acetate hydrolysis.

Partial Equilibration of *trans*-4β-Cyano-1-decalone.—Pure ketone **2** (20 mg) was stirred for 40 hr in 7 ml of a 0.30 *N* sodium hydroxide solution. The mixture was then extracted with ethyl ether. The ether extracts were dried over anhydrous magnesium sulfate and analyzed by vpc. About 30% of the material had been converted into *trans*-4α-cyano-1-decalone (**1**) and about 4% had been converted into the same minor component which was obtained from the partial equilibration of the *trans*-4α-cyano-1-decalone.

Partial Equilibration of Mixture Enriched in *cis*-4α- and *cis*-4β-Cyano-1-decalones.—A mixture of the 4-cyano-1-decalones (20 mg), enriched in the *cis* isomers (50%), was obtained from the mother liquors of the original crystallization. This mixture was stirred for 40 hr in 7 ml of a 0.30 *N* sodium hydroxide solution. The ether extracts were dried over anhydrous magnesium sulfate and analyzed (vpc) showing that about 80% of the ketone mixture was now the *trans*-4β- and *trans*-4α-cyano-1-decalones.

***trans*-4α-Cyano-1α-decalol (5a) and *trans*-4α-Cyano-1β-decalol (4a).**—*trans*-4α-Cyano-1-decalone (20.6 g) and aluminum isopropoxide (143 g) were mixed with 500 ml of anhydrous ethyl ether. The mixture was refluxed with vigorous stirring for 24 hr. The mixture was shaken with 10% hydrochloric acid to decompose aluminum salts, and the organic layer then dried over anhydrous magnesium sulfate. The ether and isopropyl alcohol were removed on a rotary evaporator, leaving 20.5 g (98%) of a mixture of two compounds in a ratio of approximately 52:48 as determined by vpc analysis.

A portion of this mixture (9.6 g) was chromatographed on 741 g of grade III Woelm neutral aluminum oxide. The column was eluted, first with *n*-pentane and then with *n*-pentane and ethyl ether mixtures. The 48% component, *trans*-4α-cyano-1α-decalol (**5a**, 4.00 g), was collected in the fractions eluted with 2:1 ether–pentane. This was followed by incompletely separate mixtures (1.21 g) eluted with the same solvent. The solvent was changed to 3:1 ether–*n*-pentane, and *trans*-4α-cyano-1β-decalol (**4a**, 2.47 g) was collected.

The 1α isomer (**5a**) crystallized immediately, forming colorless needles, mp 101–102°. Recrystallization from ethanol–water afforded a pure sample of **5a**: mp 101.5–102.5°; ir ($CHCl_3$) 3509 (OH), 2247 (C≡N) 1040, 1021, 943 cm^{-1}; nmr ($CHCl_3$) δ 0.6–2.4 (m) 3.73 (broad, 7 cps width at half-height).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.71; H, 9.61; N, 8.03.

The 1β isomer (**4a**) was obtained as a clear viscous oil, which crystallized very slowly. Recrystallization was successful with seeding to give a pure sample of **4a**: mp 74–75°; ir ($CHCl_3$) 3509 (OH), 2247 (C≡N), 1064, 1042, 1026 cm^{-1}; nmr ($CHCl_3$) δ 0.2–2.4 (m), 3.21 (broad, 15 cps width at half-height).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.88; H, 9.70; N, 8.02.

***trans*-4β-Cyano-1α-decalol (7a) and *trans*-4β-Cyano-1β-decalol (6a).**—*trans*-4β-Cyano-1-decalone (20.3 g) and aluminum isopropoxide (142.5 g, 0.70 mol) were mixed with 494 ml of anhydrous ethyl ether. The mixture was refluxed while stirring for 30 hr. The mixture was shaken with 700 ml of 10% hydrochloric acid to decompose the excess aluminum isopropoxide and then dried over anhydrous magnesium sulfate. The ether and isopropyl alcohol were removed on a rotary evaporator, leaving 21.3 g (93%) of a mixture of two compounds in a ratio of approximately 70:30, as determined by vpc analysis.

A portion of this product mixture (10.1 g) was chromatographed on grade III Woelm neutral aluminum oxide. The column was eluted, first with *n*-pentane and then with ether–pentane mixtures. The 70% component, *trans*-4β-cyano-1α-decalol (7.07 g, **7a**), was collected in the fractions eluted with a 60:40 ethyl ether–*n*-pentane. This was followed by mixtures of both components (0.28 g) eluted with the same solvent mixture. The solvent was changed to pure ethyl ether and *trans*-4β-cyano-1β-decalol (**6a**, 2.64 g) was collected.

The 1α isomer (**7a**) formed white crystals: mp 90.5–91.5°; ir ($CHCl_3$) 3534 (OH) 2247 (C≡N), 1064, 1006, 971 cm^{-1}; nmr ($CHCl_3$) δ 1.0–2.2 (m) 2.95 (broad, 7 cps width at half-height), 3.78 (broad, 7 cps width at half-height).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.98; H, 9.38; N, 7.65.

The 1β isomer (**6a**) crystallized slowly: mp 89–90°; ir ($CHCl_3$) 3472 (OH), 2242 (C≡N), 1136, 1064, 1032, 961 cm^{-1}; nmr ($CHCl_3$) δ 0.5–2.4 (m), 2.73 (broad, 7 cps width at half-height), 3.17 (broad, 15 cps width at half-height).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.86; H, 9.39; N, 9.58.

***trans*-4α-Cyano-1β-decalyl methanesulfonate (4b)** was prepared in the same manner in 52% yield: mp 162.5–163.5°; ir ($CHCl_3$) 2252 (C≡N), 953, 932, 914 cm^{-1}; nmr ($CHCl_3$) δ 0.6–2.6 (m), 3.02 (s, 3, CH_3SO_2), 4.29 (broad, 15 cps width at half-height, 1, CHO).

Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.00; H, 7.44; N, 5.44; S, 12.46. Found: C, 56.17; H, 7.22; N, 5.20; S, 12.33.

***trans*-4α-Cyano-1α-decalyl Methanesulfonate (5b).**—Methanesulfonyl chloride (1.13 g) and *trans*-4α-cyano-1α-decalol (2.00 g) were mixed with 30 ml of dry ethyl ether. The solution was stirred at 25° while a solution of triethylamine (1.02 g) in 20 ml of ethyl ether was added over 30 min. The stirring was continued

(18) All melting points and boiling points are uncorrected. Melting points were determined on a Fischer-Johns melting point apparatus. Infrared spectra were determined on a Perkin-Elmer Model 237 Infracord spectrophotometer. The nmr spectra were recorded on a Varian Associates Model A-60 or HA-100 spectrometer. Elemental analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of California.

(19) M. F. Ansell and G. T. Brooks, *J. Chem. Soc.*, 4518 (1956).

for 15 min. A white solid precipitated and was collected. The solid was shaken with water to remove the triethylamine hydrochloride and with cold ethyl ether to remove any occluded organic impurities [unreacted alcohol (0.8 g, 40%) was recovered from these ether washings] leaving 1.6 g (56%) of *trans*-4α-cyano-1α-decalyl methanesulfonate (**5b**): mp 141.5–142.5°; ir ($CHCl_3$) 2242, 970, 917 cm^{-1}; nmr ($CHCl_3$) δ 0.6–2.5 (m, 15), 3.00 (s, 3, CH_3SO_2), 4.70 (broad, 7 cps width at half-height, 1, CHO).

Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.00; H, 7.44; N, 5.44; S, 12.46. Found: C, 55.68; H, 7.28; N, 5.26; S, 12.36.

trans-4β-Cyano-1β-decalyl methanesulfonate (**6b**) was prepared similarly from 3.4 g of **6a** in 76% yield, mp 152–153°. Spectral characteristics of **6b** are ir ($CHCl_3$) 2232 (C≡N), 969, 934, 897 cm^{-1}; nmr ($CHCl_3$) δ 0.8–2.4 (m), 2.77 (7 cps width at half-height, 1, CHCN), 3.02 (s, 3, CH_3SO_2), 4.28 (broad, 16 cps width at half-height, 1, CHO).

Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.00; H, 7.44; N, 5.44; S, 12.46. Found: C, 56.28; H, 7.28; N, 5.42; S, 12.40.

trans-4β-Cyano-1α-decalyl Methanesulfonate (**7b**).—From 2.5 g of **7a** there was obtained 2.0 g (**7b**) of *trans*-4β-cyano-1α-decalyl methanesulfonate, mp 138–139°. Spectral properties of **7b** are ir ($CHCl_3$) 2237 (C≡N), 968, 924 cm^{-1}; nmr ($CHCl_3$) δ 1.0–2.3 (m), 2.83 (7 cps width at half-height, 1, CHCN), 3.02 (s, 3, CH_3SO_2) 4.73 (7 cps width at half-height, 1, CHO).

Anal. Calcd for $C_{12}H_{19}NO_3S$: C, 56.00; H, 7.44; N, 5.44; S, 12.46. Found: C, 55.75; H, 7.26; N, 5.28; S, 12.33.

trans-1β-Decalol was prepared by sodium and alcohol reduction of *trans*-1-decalone[20] and crystallization of the crude product from hexane: mp 61.5–62.0° (lit.[20,21] mp 58–59.5°, 63°); nmr ($CHCl_3$) δ 0.6–2.4 (m), 3.13 (15 cps width at half-height, 1, CHO). From this alcohol, *trans*-1β-decalyl methanesulfonate was prepared and purified by crystallization from hexane: mp 44.5–45.0°; nmr ($CHCl_3$) δ 0.5–2.5 (m), 2.90 (s, 3, CH_3SO_2), 4.17 (16 cps width at half-height, 1, CHO).

Anal. Calcd for $C_{11}H_{20}O_3S$: C, 56.85; H, 8.68; S, 13.80. Found: C, 56.98; H, 8.62; S, 13.66.

Kinetic Measurements.—The usual sealed ampoule technique was used. The concentration of the sulfonate ester was 0.012 *M* in anhydrous acetic acid containing sodium acetate (0.025 *M*) and acetic anhydride (0.022 *M*). At appropriate time intervals 5-ml samples were titrated with perchloric acid in acetic acid using a Metrohm Model 336 recording Potentiograph equipped with a 5-ml automatic delivery buret.

Rate constants were calculated using a nonlinear least-squares program.[22] Precision was generally better than ±1%, always better than ±3%.

Registry No.—**1**, 19556-82-2; **2**, 19556-83-3; **4a**, 19556-84-4; **4b**, 19556-85-5; **5a**, 19556-86-6; **5b**, 19556-87-7; **6a**, 19556-88-8; **6b**, 19556-89-9; **7a**, 19556-90-2; **7b**, 19556-91-3; *trans*-1β-decalol, 6549-76-4; 1-acetoxy-4α-cyano-$\Delta^{1,10}$-octalin, 19556-93-5; 1-acetoxy-4β-cyano-$\Delta^{1,10}$-octalin, 19556-94-6; *trans*-1β-decalyl methanesulfonate, 19556-95-7.

(20) W. Hückel, *Ann.*, **441**, 1 (1925).

(21) W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Amer. Chem. Soc.*, **76**, 4420 (1954).

(22) LSKIN2, written by C. E. DeTar and D. F. DeTar, Florida State University, as modified by Dr. H. A. Hammond.

Resin Acids. XV. Oxidative Transformations of the Levopimaric Acid–Acetylenedicarboxylic Ester Adduct[1,2]

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The oxidation of certain Diels–Alder adducts of levopimaric acid was investigated with a view to preparing intermediates suitable for the synthesis of polycyclic molecules. Oxidation proceeded satisfactorily only in the presence of a 1a–4a double bond. Because of its accessibility the adduct of levopimaric acid and acetylenedicarboxylic ester was used as model for studying the oxidative transformations of such compounds and was found to undergo a number of unusual reactions.

Diels–Alder adducts of levopimaric acid such as **1**[4] are potential starting materials for the synthesis of naturally occurring polycyclic systems if a way can be found to degrade the five-carbon bridge across ring C. Unfortunately the *endo* configuration of the most useful adducts appears to render the double bond inaccessible to the common oxidizing agents,[5-11] ozonolysis and permanganate oxidation proceeding normally only in the case of those adducts where R_1 and R_2 are *trans*, as in **3**,[1,12,13] or where R_1 = H.[1,12] In the present paper we describe our work on the oxidative transformations of some derivatives of **1** and of **4**,[14] which was undertaken with a view toward overcoming this difficulty (Chart I).

Our first efforts were directed at **5**,[4] **6**,[4] and **7**.[4,15] None of these substances was attacked by ozone or by potassium permanganate under conditions which effected smooth oxidation of compounds of type **3**; more drastic conditions led to intractable mixtures. More-

(1) Previous paper: W. Herz, R. N. Mirrington, H. Young, and Y. Lin, *J. Org. Chem.*, **33**, 4210 (1968).

(2) Supported in part by a grant from the National Science Foundation (GP-6362).

(3) U. S. Public Health Service Fellow, 1962–1965; Ethyl Corp. Fellow, 1964–1965.

(4) W. Herz, R. C. Blackstone, and M. G. Nair, *J. Org. Chem.*, **32**, 2992 (1967). The numbering of **1** and its transformation products is discussed in ref 15 of this reference. Compounds of type **4** are numbered as shown according to the usual convention. The *Chemical Abstracts* name for **4** is 5a,8-dimethyl-12-isopropyl-1,2,8-tricarboxymethyl-4,4a,5,5a,6,7,8,8a,-9,10-decahydro-3,10a,-ethenophenanthrene.

(5) The only compounds of this type which have been studied are maleopimaric acid (**2**) and some of its derivatives.[6-11]

(6) L. Ruzicka and St. Kaufmann, *Helv. Chim. Acta*, **23**, 1346 (1940); **24**, 939 (1941).

(7) L. Ruzicka and W. A. Lalande, *ibid.*, **23**, 1357 (1940).

(8) L. H. Zalkow, R. A. Ford, and J. P. Kutney, *J. Org. Chem.*, **27**, 3535 (1962).

(9) L. H. Zalkow and N. Girotra, *ibid.*, **28**, 2033 (1963).

(10) Le-Van-Thoi and C. P. Ngoc-Son, *C.R. Acad. Sci., Paris*, **257**, 2495 (1963).

(11) L. H. Zalkow, M. V. Kulkarni, and N. Girotra, *J. Org. Chem.*, **30**, 1679 (1965).

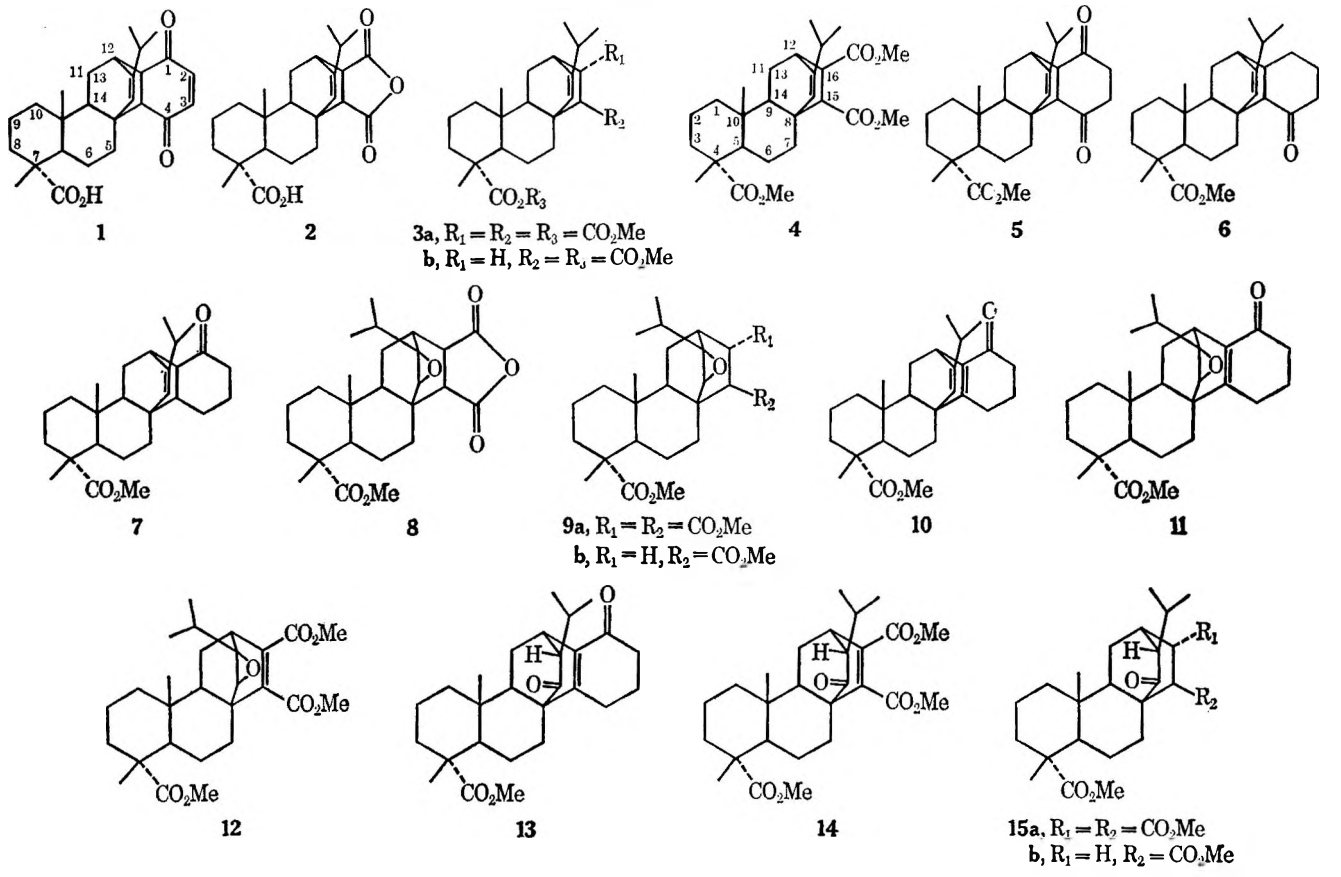
(12) N. Halbrook, R. V. Lawrence, R. L. Dressler, R. C. Blackstone, and W. Herz, *ibid.*, **29**, 1017 (1964). This paper contains an unfortunate misprint. On p 1019, in column 1, lines 45 and 47, and in column 2, line 4, XV should be replaced by XVI. The numbering of adducts of type **3** and **4** is given in this reference.

(13) L. H. Zalkow and D. R. Brannon, *ibid.*, **29**, 1296 (1964).

(14) W. Herz, R. C. Blackstone, and M. G. Nair, *ibid.*, **31**, 1800 (1966).

(15) The preparation of **7** from **1** is relatively tedious and proceeds in poor over-all yield.[4] Several attempts to prepare **6** and/or **7** more directly by inducing a diene condensation between methyl levopimarate and cyclohexenone failed. This provides another example of the sluggishness of cyclohexenone as a dienophile since the lower homolog cyclopentenone affords a mixture of adducts, albeit in only mediocre yield (W. Herz, R. C. Blackstone, and M. G. Nair, to be published).

CHART I



over, as has been reported previously,[4] treatment of **5** with excess *m*-chloroperbenzoic acid resulted only in Baeyer–Villiger oxidation of the less hindered carbonyl group and did not affect the double bond.[16,17] If the lack of reactivity of **5**, **6**, and **7** toward oxidizing agents were indeed due to steric hindrance around the double bond as indicated by Dreiding models, introduction of a 1a–4a double bond as shown in **10**[4] should restore normal accessibility. This proved to be the case. Epoxidation of **10** occurred rapidly and preferentially at the bridge double bond as shown by the spectral properties of product **11** which retained the α,β-unsaturated ketone chromophore of **10** but exhibited the expected upfield shift of H-14 from 5.45 to 3.08 ppm. Similarly, epoxidation of **4** with *m*-chloroperbenzoic acid proceeded smoothly to **12** which displayed its H-14 resonance at 2.97 instead of at 5.45 ppm for **4** and had the ultraviolet absorption characteristic of an α,β-unsaturated ester. Other indications for the location of the epoxide ring on the bridge were the downfield shift of the angular methyl group signal[18–20] and the pronounced nonequivalence of the signals of the methyls of the isopropyl group.[21]

The stereochemistry depicted for **11** and **12** (and that of the other epoxides **8**, **9a**, and **9b**) is based on the severe interference, apparent from models, with approach of oxidizing agent from the side of ring A and on the chemical shift of the angular methyl group which would be expected to exhibit a considerable degree of shielding in the alternative formula.

Attempts to convert epoxides **11** and **12** into glycols by exposure to acidic reagents for the purpose of eventual further degradation encountered the same difficulties as experienced earlier[1] in the case of **9b**. The only compounds formed and obtained in optimum yield by brief treatment with boron trifluoride etherate in benzene were ketones **13** and **14**. In the case of **14**, the ultraviolet spectrum [λ_{max} 233 and 306 nm (ϵ 6800 and 550)] showed the strongly enhanced n–π^* transition characteristic of β,γ-unsaturated ketones as well as the chromophore of the unsaturated ester. The ORD curve exhibited a strong negative Cotton effect which is in accordance with the octant rule if the double bond were in the lower right rear octant as is apparent from the model, but does not permit a decision between the two possible orientations of the isopropyl group. However, an assignment is possible on other grounds.

Undoubtedly the severe hindrance to displacement of the epoxide function, after its coordination with acidic reagents, is responsible for the preference of pinacol rearrangement over rearside attack by an ex-

(16) For this reason the action of stronger oxidizing agents on **6** and **7** was not investigated in the present work. Reaction of **2** with *m*-chloroperbenzoic acid was said to be ineffective[11] but use of pertrifluoroacetic acid[11] or *p*-nitroperbenzoic acid[17] resulted in formation of epoxide **8**. By contrast, epoxidation of **3a** and **3b** to **9a** (see Experimental Section) and **9b** proceeded smoothly with *m*-chloroperbenzoic acid.

(17) N. Langlois and B. Gastambide, *Bull. Soc. Chim. Fr.*, 2966 (1965).

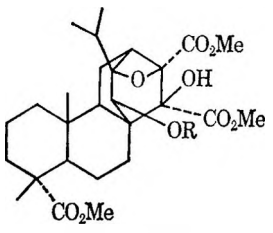
(18) Diels–Alder adducts of levopimaric acid and other compounds containing unsaturation in the bridge display this signal at 0.6–0.7 ppm because of strong shielding by the double bond.[12,19,20] In epoxides **8**,[11,17] **9a**, **9b**,[1] **11**, and **12** it is found 12–15 cycles farther downfield.

(19) W. L. Meyer and R. W. Hoffman, *Tetrahedron Lett.*, 691 (1962).

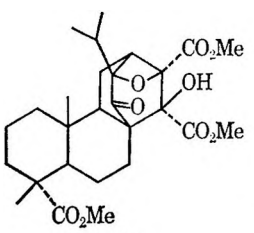
(20) W. A. Ayer, C. E. MacDonald, and J. B. Stothers, *Can. J. Chem.*, **41**, 1113 (1963).

(21) In the nmr spectra of all Diels–Alder adducts and of compounds such as **10**, the isopropyl group is represented by a set of two superimposed or narrowly split methyl doublets near 1 ppm.[4,12,14,20] In epoxides **8**,[11,17] **9a**, **9b**,[1] **11**, and **12**, there are two widely separated doublets near 1.05 and 0.7 ppm, the latter representing the methyl being shielded more effectively by the epoxide ring.

CHART II



16a, R = H
b, R = Ac
c, R = Ms



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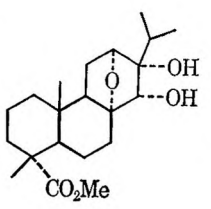
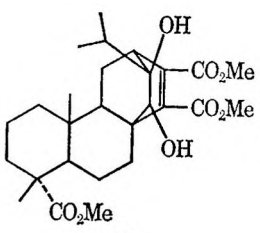
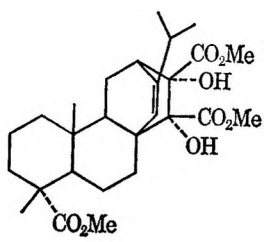


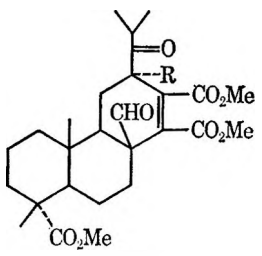
18



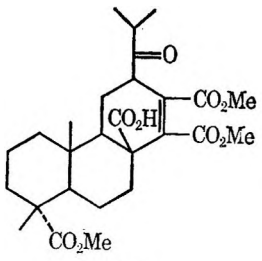
19



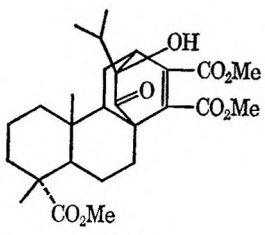
20



21a, R = H
b, R = Br



23



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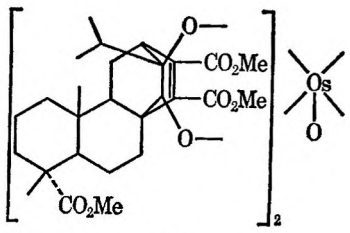


22

ternal nucleophile. Intramolecular rearside attack by hydride ion requires inversion at C-13 and formulation of the ketones as **13** and **14**, an arrangement which from inspection of the models should also be favored thermodynamically and seems to be reflected in the nmr spectra. Comparison of the signals of the isopropyl group in the nmr spectra of the ketones with the corresponding signals in the nmr spectra of precursors **11** and **12** shows that the methyl doublet at lower field (at 1.07 and 1.04 ppm) has not been affected significantly by the pinacol rearrangement, whereas the more shielded methyl doublet, formerly at 0.80 and 0.76 ppm, has experienced a further upfield shift to 0.67 and 0.63 ppm, respectively. This is consistent with that orientation, *i.e.*, **13** and **14**, in which one of the methyl groups experiences greater shielding by the conjugated double bond and perhaps the carbonyl and which, from inspection of the models, should interpose a very considerable amount of steric hindrance to the potential reactions of the carbonyl group.[22] This is actually the case and interferes with the projected utilization of these compounds. **14**, **15a**, and **15b** were not only unreactive toward the usual carbonyl reagents and toward sodium borohydride, but did not undergo the Baeyer–Villiger oxidation. Attempts to effect bromination of **14** or to prepare an enol acetate[23] with a view toward carrying out eventual cleavage reactions were unsuccessful as well.[24]

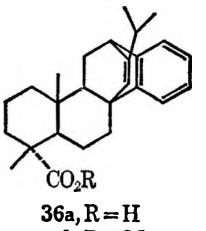
(22) Epoxide **9a** prepared in the course of this study for comparison purposes was noncrystalline and had spectroscopic properties which while clearly in harmony with the postulated structure (see Experimental Section) differed considerably from the properties of a substance of presumably the same structure, mp 179–181°, which was prepared[11] from trimethyl fumaropimarate with pertrifluoroacetic acid. Rearrangement of noncrystalline **9a** with boron trifluoride afforded ketone **15a** (weak positive Cotton effect as predicted superimposed on plain negative background curve), mp 183–185°, whose nmr spectrum exhibited the same signals as reported for the presumed epoxide. Comparison of **15a** with a slightly impure sample of the "epoxide" furnished by Professor Zalkow established identity. A possible reason for the misidentification[11] of the "epoxide" is an nmr peak at 3.13 ppm which was erroneously assigned to an epoxidic proton (H-14), but which is actually due to H-15 or H-16. This could be demonstrated by comparing the nmr spectrum of **30** which has an nmr signal at 3.30 ppm due to allylic H-12 with that of its dihydro derivative **31** which exhibits a two-proton signal at 3.10 due to H-15 and H-16 and a one-proton signal at 2.70 due to H-12.

Because of the relative inaccessibility[4] of **10** further studies on the degradation of the bridge in the presence of a 1a–4a double bond were therefore carried out on **4** as a model. These will now be discussed.

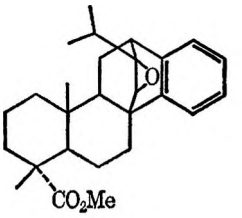
Reaction of **4** with potassium permanganate in acetone proceeded in an unexpected manner and resulted in a noncrystalline diol $C_{27}H_{40}O_9$ (**16a**) (Chart II) which contained an extra oxygen atom and was characterized by conversion into a crystalline monoacetate (**16b**) and monomesylate (**16c**). That a secondary hydroxyl group had been esterified during these conversions and that a tertiary hydroxyl group was also present was shown by the nmr spectra. The ultraviolet spectrum of **16a** indicated the disappearance of the conjugated double bond; the extra oxygen was therefore presumably present in the form of an ether function.

(23) This cannot be due to instability of the enol since a C-13–C-14 double bond is quite stable.

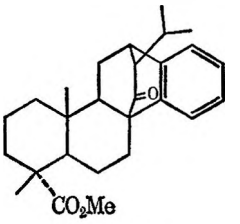
(24) The Experimental Section also contains a description of the conversion of **36a**[4] into **37** and **38** by a sequence analogous to the one applied to **4**, **9a**, **9b**, and **10**. The stereochemical assignments are particularly clear in the present instance since one of the methyl signals of the isopropyl group exhibits the expected large diamagnetic shift (0.35 ppm) in going from **37** to **38**. Osmylation of **36a** gave **39a**.



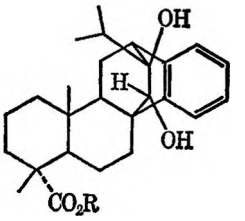
36a, R = H
b, R = Me



37



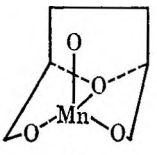
38



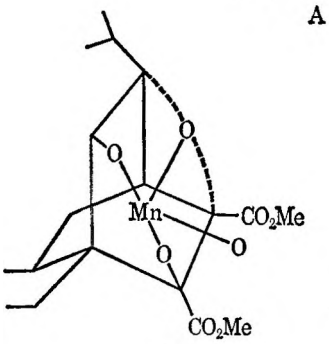
39a, R = H
b, R = Me

That the secondary hydroxyl group was attached to C-14 was shown by oxidation of **16a** to **17** which exhibited a new infrared frequency at 1755 cm^{-1} characteristic of a strained ketone. Attempts to dehydrate **16a** or its derivatives were unsuccessful; this excluded C-13 as the locus of the tertiary hydroxyl group. Treatment with strong acid did not affect **16b**, a result which made the presence of an epoxide linkage unlikely.

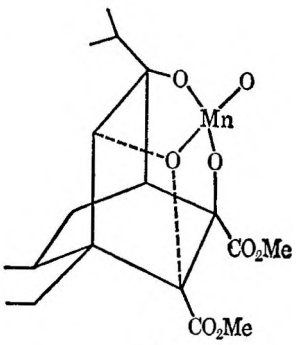
Now ether linkages are occasionally formed in the course of permanganate oxidations of dienes when the double bonds occupy certain spatial relationships. The formation of tetrahydrofurans from 1,5-dienes, more specifically the formation of *cis*-2,5-bishydroxymethyltetrahydrofuran from 1,5-pentadiene,[25] can be explained in terms of the intermediate permanganate ion complex A. Such a complex is also possible for



A

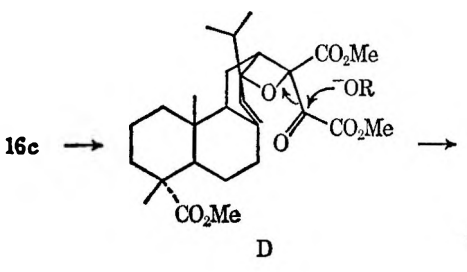


B

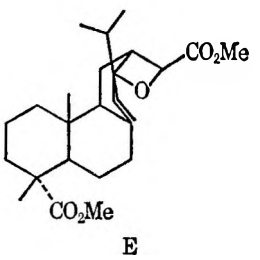


C

levopimaric acid which would lead to the diol of postulated formula **18**,[26] and for **4** which would lead to **16a** through an intermediate complex B.[27] Further evidence for the structure assigned to **16a** was the fragmentation of **16c** with potassium *t*-butoxide to a substance $C_{23}H_{34}O_5$ whose nmr spectrum exhibited signals characteristic of one vinyl proton and two methoxyl groups. This observation could be rationalized by the process **16c** → D → E.



D



E

(25) E. Klein and W. Rojahn, *Tetrahedron*, **21**, 2353 (1965).

(26) J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge University Press, Cambridge, England, 1952, p 439.

(27) Inspection of models suggests that the isomeric complex C is equally probable, although only the product corresponding to B was isolated.

The conversion of **4** into **16a** did not augur well for the use of potassium permanganate on other potentially more useful substrates containing a 1a–4a double bond. Hence other oxidation methods were investigated. Treatment of **4** with osmium tetroxide in benzene proceeded somewhat sluggishly, but gave the hoped-for though difficultly crystallizable **19** (stereochemistry based on relative ease of approach of reagent and on the normal chemical shift of the C-10 methyl signal). Osmylation in pyridine which increases the reactivity of the reagent toward olefins resulted in a diminished yield of **19** and the formation of an isomeric diol **20** whose structure was apparent from the spectra (absence of conjugation in ir and uv spectra, presence of vinyl proton and characteristically shielded C-10 methyl resonances). The effect of ruthenium tetroxide and other oxidizing agents is described in the Experimental Section, as is the osmylation of **10** which could not be carried out selectively, but affected both double bonds and gave a tetrol.

Periodic acid cleavage of **19** to the noncrystalline ketoaldehyde **21a** proceeded very sluggishly, the structure of the product being evident from the uv (λ_{max} 235 nm), ir (aldehyde stretching frequency of 2700 cm^{-1}), and nmr spectra (aldehyde resonance at 9.3, H-12 resonance at 2.86 ppm). The ketoaldehyde was characterized by preparation of the crystalline bromo derivative **21b**.[28] Catalytic oxidation methods with the aim of effecting the conversion of **4** into **21a** in one step proved abortive. Attempted oxidation of **4b** with periodic acid or sodium metaperiodate in the presence of catalytic amounts of osmium tetroxide led to recovery of starting material. Use of larger amounts of osmium tetroxide resulted in the isolation of an osmate(VI) ester **22**[29] whose formation explains the failure of the various catalytic oxidation procedures. Finally it was discovered that **21a** could be prepared conveniently by ozonolysis of **4** in ethyl acetate at −70° in the presence of tetracyanoethylene.[30–32]

The successful cleavage of **4** to **21a**, with the incidental bonus of generating an aldehyde function of C-8 capable of eventual conversion into a methyl group, represented a partial realization of our goal. It was also hoped to effect the cleavage in such a way so as to generate a carboxyl group at C-8 which, being part of an β,γ-unsaturated acid function, might be subject to facile decarboxylation.

Attempts to accomplish this aim by oxidizing the aldehyde group of **21a** or **21b** to **23** were unsuccessful.[33] Consequently we returned to glycol **19**. Oxida-

(28) The assignment of bromine to C-12 is based on the absence of the usual H-12 resonance near 2.9 ppm.

(29) For a previous report on the formation of such an ester, see R. Criegee, B. Marchand, and H. Wannowius, *Ann.*, **550**, 99 (1942).

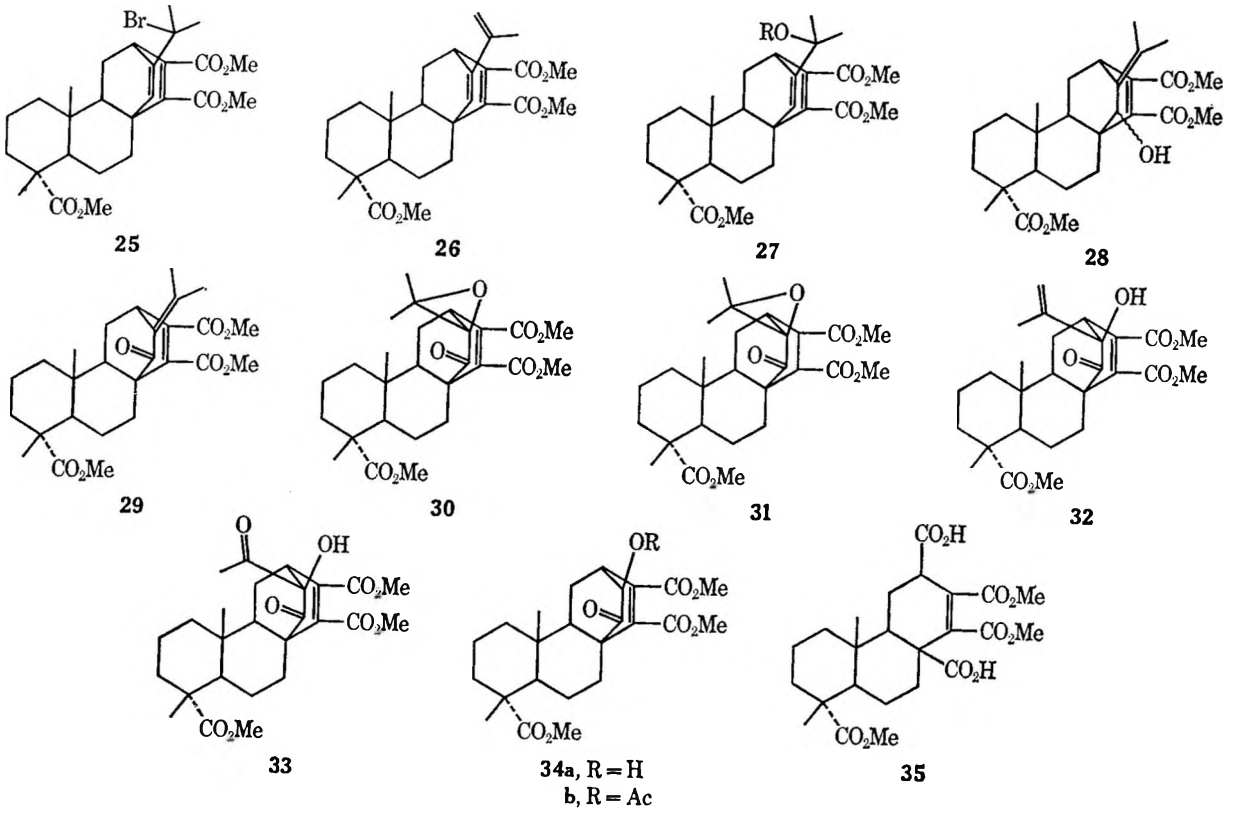
(30) These conditions were modelled on the experience of Munavalli and Ourisson,[31] who observed that addition of tetracyanoethylene altered the course of longifolene ozonolysis from production of an epoxide by abnormal attack of ozone to production of the norketone, after it had been found that ozonolysis of **4** in methanol gave a complex mixture containing epoxide **12** and that addition of pyridine[32] resulted in **12** and recovery of starting material.

(31) S. Munavalli and G. Ourisson, *Bull. Soc. Chim. Fr.*, 729 (1964).

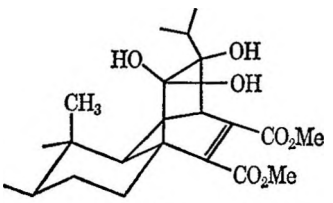
(32) G. Slomp, Jr., and J. L. Johnson, *J. Amer. Chem. Soc.*, **80**, 915 (1958).

(33) Use of silver and other oxidizing agents in basic solution resulted in a mixture of neutral substances, possibly the result of intramolecular aldol condensation as demonstrated in a related series by V. Baburao of this laboratory (unpublished results). Neutral or acidic oxidizing agents were without effect. For similar difficulties in oxidizing a tertiary aldehyde, see E. Caspi, W. Schmid, and B. T. Khan, *Tetrahedron*, **18**, 767 (1962).

CHART III



tion with Jones reagent[34] gave ketol **24**, whose spectral properties were similar to those of **14** and characteristic of a β,γ-unsaturated bicyclic ketone. Unfortunately **24** was not attacked by periodic acid, presumably because formation of *gem*-diol F, thought to be the necessary precursor for the formation of a cyclic iodate ester as a prelude to oxidation, would be inhibited by the C-10 methyl group.



F

As an alternative approach we studied the effect on **4** of various agents known to attack allylic positions because we hoped to obtain a product containing an oxygen function at C-13a. Such a function was expected to facilitate removal of the isopropyl group following ozonolysis. N-Bromosuccinimide afforded an unstable bromide **25** which underwent dehydrohalogenation with diazabicyclononene[35] to diene **26** (Chart III) whose nmr spectrum (see Experimental Section) was in conformity with the postulated structure. Attempted hydrolysis of **25** afforded mainly **26** which, though it appeared to be an ideal candidate for oxidative cleavage, could not be converted into a useful product by ozonolysis.

Oxidation of **4** with *t*-butyl chromate gave in 40% yield a substance containing two additional oxygen atoms. The ir spectrum showed the absence of hydroxyl groups, the uv spectrum the presence of a β,γ-unsaturated ketone, and the ORD curve a Cotton effect indistinguishable from that of **14**, thus locating a ketone group on C-14. The conjugated ester system was still present, but the nmr spectrum showed no signal characteristic of the isopropyl group. Instead, two additional methyl singlets at 1.53 and 1.47 ppm suggested that the second oxygen atom was attached to C-13a. Catalytic hydrogenation of **30** to **31** reduced the unsaturated ester system (uv spectrum) without affecting the oxygen functions.

That the second oxygen atom was that of an epoxide became evident on treatment of **30** with strong acid. This resulted in formation of an isomer which had a tertiary hydroxyl (ir, nmr spectrum), two new vinyl protons apparently part of a methylene group (nmr spectrum), and a vinyl methyl group resonating at 1.94 ppm. The methyl signals near 1.5 ppm had disappeared. These changes are consistent with the transformation of α-epoxy ketone **30** into **32**. The formation of **30** from **4** probably proceeds through the initial allylic oxidation product **27**, or its equivalent which could rearrange to **28** or its equivalent. Oxidation of the latter to **29** followed by epoxidation of the double bond would complete the necessary series of reactions. Epoxidations of double bonds in the course of chromate oxidations have been observed.[36,37]

Ozonolysis of **32** in the presence of tetracyanoethylene furnished additional proof for the assigned structures by yielding the methyl ketone **33** (nmr signal at 2.4 ppm). Treatment of the latter with base resulted

(34) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 142.

(35) E. Truscheit and K. Eiter, *Ann.*, **658**, 65 (1962).

(36) W. A. Mosher, F. W. Steffgen, and P. T. Lansbury, *J. Org. Chem.*, **26**, 670 (1961).

(37) For steric reasons we assume that the configuration at C-13 is as depicted in **32** and hence the same in all compounds derived therefrom (**33-36**).

in cleavage of the β-diketone system and afforded gummy **34a** (loss of methyl ketone signal) which was characterized as the crystalline acetate **34b**. Although **33** did not react with periodic acid, it was cleaved slowly and in poor yield by lead tetraacetate in benzene[38] to **35** which underwent decarboxylation on heating. Treatment of **33** with excess peracetic acid effected conversion into **35** in somewhat improved yield, presumably through a series of Baeyer–Villiger reactions. This constituted realization of our original objective in relatively few steps (**4** → **30** → **32** → **33** → **35**) although the over-all yield was low.

Experimental Section[39]

Epoxidation of 10.—To a solution of 3 g of **10** in 15 ml of chloroform was added with stirring 1.5 g of *m*-chloroperbenzoic acid (85% assay). Stirring was continued for 1 hr during which time the solution warmed up noticeably. The reaction mixture was diluted with 50 ml of ether and extracted with 5% sodium bicarbonate solution, washed with water, and evaporated to give a colorless product (**11**) which was recrystallized from ethyl acetate and had mp 155–158°; yield 1.9 g; $[\alpha]_D$ 100°; ir 1725 (ester), 1658 (conjugated ketone), and 1630 cm^{-1} (conjugated double bond); nmr 3.67 (methoxyl), 3.48 br (H-12), 3.08 (H-14 on epoxide), 1.20 (C-7 methyl), 1.07 d and 0.80 d (J = 7, isopropyl), and 0.93 ppm (C-10a methyl).

Anal. Calcd for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98; O, 15.00. Found: C, 75.91; H, 8.95; O, 15.27.

Preparation of 13.—To a solution of 3 g of **11** dissolved in 50 ml of benzene was added 0.5 ml of boron trifluoride etherate. The solution was allowed to stand for 10 min, extracted with sodium bicarbonate solution, washed with water, and evaporated to dryness. The residue was chromatographed on 100 g of alumina to yield 1.2 g of **13** which after recrystallization from methanol had mp 205–208°; $[\alpha]_D$ −140°; ir 1725 (ester), 1710 (ketone), 1678 (conjugated ketone), and 1630 cm^{-1} (conjugated double bond); nmr 3.63 (methoxyl), 3.55 br (H-12), 1.17 (C-7 methyl), 1.02 d and 0.67 d (J = 7, isopropyl), and 0.80 ppm (C-10a methyl).

Anal. Calcd for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98; O, 15.00. Found: C, 76.10; H, 9.05; O, 14.82.

Attempts to hydrolyze **11** to a glycol using aqueous perchloric acid in acetone were not successful; compound **13** was the major product.

Epoxidation of 4.—To a solution of 30 g of **4** in 125 ml of chloroform was added with stirring 13.8 g of *m*-chloroperbenzoic acid. Stirring was continued overnight, after which *m*-chlorobenzoic acid was removed by filtration, the filtrate was evaporated to dryness in a rotary evaporator, and the residue was dissolved in ether. The ether solution was extracted twice with 5% sodium bicarbonate solution, washed with water, dried with anhydrous sodium sulfate, and evaporated to dryness to give a colorless syrup (**12**) which began to crystallize after standing for 2 weeks. Using seed crystals, the epoxide was recrystallized several times from chloroform–hexane. The yield was 21 g; the product had mp 135–137°, $[\alpha]_D$ 65°; ir 1730 (ester), 1715 (conjugated esters), 1601 cm^{-1} (weak, conjugated double bond); nmr 3.67, 3.63, and 3.69 (methoxyls), 3.28 (allylic H-12), 2.96 H-14 on epoxide), 1.10 (C-4 methyl), 1.04 d and 0.76 d (J = 7, isopropyl), and 0.86 (C-10 methyl); λ_{max} 237 nm (ϵ 4610).

Anal. Calcd for $C_{27}H_{38}O_7 \cdot H_2O$: C, 65.83; H, 8.19. Found: C, 65.86; H, 7.90.

Preparation of 14.—Rearrangement of 10 g of **12** in 50 ml of dry benzene with 1 ml of boron trifluoride etherate was carried out in the usual fashion. The product was crystallized from ethanol to yield 6 g of **14** which had mp 190–191°; ir 1730–1705 (carbonyls not resolved) and 1630 cm^{-1} (double bond); nmr 3.77 (double intensity) and 3.66 (methoxyls), 3.50 (allylic H-12), 1.15 (C-4 methyl), 1.05 d and 0.63 d (J = 7, isopropyl), and 0.78 ppm (C-10 methyl); λ_{max} 312 (ϵ 520, enhanced n–π* absorption), and 239 nm (5200, conjugated esters); ORD curve $[\alpha]_{400}$ −1270°, $[\alpha]_{350}$ −4180°, $[\alpha]_{325}$ −10,300°, $[\alpha]_{308}$ 0°, $[\alpha]_{285}$ 10,100°, $[\alpha]_{234}$ 0°.

Anal. Calcd for $C_{27}H_{38}O_7$: C, 68.33: H, 8.07; O, 23.60. Found: C, 68.55; H, 7.98; O, 23.68.

The same substance was produced in 35% yield by heating a sample of **12** to 250° in a nitrogen atmosphere for 10 min, dissolving the glassy residue in methanol, and chilling.

Attempted Baeyer–Villiger oxidation of **14** with *m*-chloroperbenzoic acid in chloroform for 1 month resulted in recovery of starting material. Oxidation with pertrifluoroacetic acid yielded a complex mixture in which the uv absorptions of 312 and 239 nm were considerably reduced. Attempted reduction with sodium borohydride gave a quantitative recovery of starting material as did attempts to carry out brominations with bromine–acetic acid, N-bromosuccinimide, and pyridinium bromide perbromide. Treatment with isopropenyl acetate–*p*-toluenesulfonic acid or acetic anhydride resulted in recovery of starting material as did exposure to aqueous perchloric acid–acetone.

Epoxidation of 3a.—A solution of 2.5 g of fumaropimaric acid in ether was mixed with excess ethereal diazomethane. Removal of ether yielded 2.7 g of the noncrystalline trimethyl ester **3a**. It was dissolved in 10 ml of chloroform and 1.2 g of *m*-chloroperbenzoic acid was added with stirring. The reaction mixture was stored in the dark for 4 days. The solvent was removed and the residue dissolved in ether, washed with sodium carbonate, dried, and evaporated to yield 3 g of noncrystalline **9a**: ir 1740 and 1722 cm^{-1} (esters); nmr at 3.56, 3.50, 3.44 (methoxyls), 2.99 (H-14 on epoxide), 1.11 (C-4 methyl), 1.04 d and 0.60 d (J = 7, isopropyl), and 0.75 ppm (C-10-methyl). Since **9a** could not be purified satisfactorily for analysis it was used directly for the next experiment.

Preparation of 15a.—Rearrangement of 3 g of **9a** in 30 ml of benzene with 0.5 ml of boron trifluoride etherate was carried out as described for the preparation of **13**. The crude product crystallized after standing for 1 week to give 2.1 g of **15a**. The analytical sample was prepared by recrystallization from methanol and had mp 183–185°; $[\alpha]_D$ +46°; ir 1742, 1722 (esters), and 1710 cm^{-1} (sh, ketone); nmr 3.72, 3.62, 3.58 (methoxyls), 1.28 d and 0.97 d (J = 7, isopropyl), 1.11 (C-4 methyl), and 0.70 ppm (C-10 methyl); ORD curve $[\alpha]_{400}$ −68°, $[\alpha]_{338}$ −110°, $[\alpha]_{324}$ −46°, $[\alpha]_{284}$ −290°, $[\alpha]_{274}$ −280°, $[\alpha]_{245}$ −390°. This material was identical (tlc, ir, and nmr spectrum) with a somewhat impure sample of Zalkow's[22] "epoxide IV".

Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46; O, 23.50. Found: C, 67.90; H, 8.69; O, 23.53.

Attempts to oxidize this compound with *m*-chloroperbenzoic acid were unsuccessful as were attempts to hydrolyze it to a glycol.

Epoxidation of 36b (by M. G. Nair).—Methylation of 0.5 g of **36a**[4] with ethereal diazomethane gave a gum which was homogeneous by nmr and tlc criteria and was oxidized with 1.5 g of *m*-chloroperbenzoic acid in 25 ml of chloroform. After 18 hr at room temperature the mixture was heated on the steam bath for 1 min, allowed to cool, and mixed with 2 g of potassium iodide in 15 ml of water. The iodine was destroyed with a saturated solution of sodium thiosulfate, and the chloroform layer washed with water, dried, and evaporated. The residual gum was chromatographed over 3 g of silicic acid. Benzene eluted 0.4 g of **37** which was recrystallized from petroleum ether and had mp 155–157°; ir 1745 (ester); nmr 7.35 (four aromatic protons), 3.70 (methoxyl), 3.25 (H-14), 1.25 (7-methyl), 0.95 d and 0.85 d (J = 7, isopropyl), and 0.90 ppm (C-10a methyl).

Anal. Calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88; O, 11.75. Found: C, 79.15; H, 81.73; O, 12.16.

(38) The reaction was considerably more rapid in pyridine but very little acidic material could be isolated, probably because of oxidative decarboxylation of **35** in pyridine solution.

(39) Melting points are uncorrected. Analyses were carried out by Dr. F. Pascher, Bonn, Germany. Nmr spectra were run on a Varian A-60 instrument with deuteriochloroform as solvent and tetramethylsilane as the internal standard unless otherwise noted. Values for all line positions are expressed in parts per million (ppm) from tetramethylsilane. Signals are characterized in the usual way: d, doublet; t, triplet; br, broad singlet or unresolved multiplet; c, complex band whose center is given. Coupling constants are expressed in cycles per second. Infrared spectra were determined on a Perkin-Elmer Model 257 spectrophotometer or a Perkin-Elmer Infracord instrument in chloroform solution unless otherwise noted. Infrared wavelengths are reported in cm^{-1}. Ultraviolet spectra were determined on a Carey 14 recording spectrophotometer in 95% ethanol solution unless otherwise noted. Optical rotatory dispersion curves were run on a Jasco Model ORD-5 instrument in 95% ethanol. All petroleum ether used was low boiling (30–60°). All alumina used in chromatography was Alcoa F-20, all silicic acid used was Mallinckrodt 100 mesh, all silica gel used was Baker 3405, and all Florisil used was Floridin Co. 100/200 mesh product activated at 1200°F.

Preparation of 38 (by M. G. Nair).—Rearrangement of 0.1 g of **37** in 20 ml of anhydrous ether with 0.5 ml of boron trifluoride etherate was carried out as described for the preparation of **13**. The product was recrystallized from methanol: yield 0.085 g; mp 152°; $[\alpha]^{25}D$ −25° ($CHCl_3$, *c* 0.03); λ_{max} 307 nm [enhanced n,π^* transition of β,γ-unsaturated ketone; *cf.* λ_{max} of 5-norbornenone 305 nm (ϵ 290[40])]; ir 1750 and 1745 cm^{-1} (esters); nmr 7.25 (four aromatic protons), 3.70 (methoxyl), 1.20 (C-7 methyl), 0.95 d and 0.40 d (J = 6, isopropyl), and 0.90 ppm (C-10a methyl).

Anal. Calcd for $C_{27}H_{36}O_3$: C, 79.37; H, 8.88; O, 11.75. Found: C, 78.94; H, 8.98; O, 12.09.

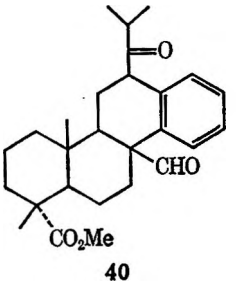
Preparation of 39a (by M. G. Nair).—Solutions of 0.5 g of **36a** in 5 ml of pyridine and 0.6 g of osmium tetroxide in 21 ml of benzene were mixed and kept for 3 days. The solution was saturated with hydrogen sulfide and filtered. The precipitate was washed with hot chloroform and the combined filtrate and washings were combined, dried, and evaporated. The residue was recrystallized from benzene: yield 0.3 g; mp 176–177°; ir 3550–3500 (hydroxyls) and 1720 cm^{-1} (carboxyl). Analysis and nmr spectrum indicated that this material was a benzene solvate. The solvent was removed by heating at 180° under high vacuum, but the melting point remained unchanged.

Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80; O, 15.51. Found: C, 75.56; H, 8.71; O, 15.92.

Methyl ester **39b** melted at 191° and had $[\alpha]^{25}D$ 41.7° ($CHCl_3$, C 0.012); ir 3450 (two hydroxyls) and 1725 cm^{-1} (ester); nmr 7.35 (four aromatic protons), 4.0 (H-14), 3.70 (methoxyl), 3.20 dd (H-12), 1.25 (C-7 methyl), 1.15 (C-10a methyl), 1.05 d and 0.95 d (J = 6, isopropyl). The chemical shift of the isopropyl group indicated that it is not shielded by the aromatic ring and that the stereochemistry is that depicted by formula **39**.

Anal. Calcd for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 75.63; H, 9.01.

Oxidation of **39b** with periodic acid gave the expected but unstable product **40**. Rapid work-up permitted isolation of the substance in relatively low yield. In a typical experiment 0.1 g of **39b** in 75 ml of methanol was mixed with 0.5 g of periodic acid in 15 ml of water. After 8 hr at room temperature with stirring, the solution was concentrated *in vacuo*, diluted with water, and extracted with ether. The washed and dried ether extracts were chromatographed over silicic acid. Benzene eluted 10 mg of a yellow gum. The more polar fraction constituted 25 mg of **40** which showed a single spot in tlc. Recrystallization from petroleum ether afforded material which melted at 70–71° and decomposed on standing: ir 2800 (1745, 1720, and 1715 cm^{-1}); nmr 10.1 (aldehyde), 7.4 (four aromatic protons), 3.70 (methoxyl), 1.30 d and 1.10 d (J = 6, isopropyl), 1.20 (C-7 methyl), and 0.96 ppm (C-10a methyl).



40

Oxidation of 4 with Potassium Permanganate.—To a solution of 20 g of **4** in 300 ml of acetone was added with stirring 5 g of potassium permanganate. The permanganate was rapidly consumed and the solution assumed a clear brown color. Upon addition of 100 ml of water, a heavy precipitate of manganese dioxide formed which was removed by suction filtration. The solution was evaporated to dryness. Thin layer chromatography showed the presence of only two substances, one of which was starting material. Chromatography on Florisil yielded 11 g of a colorless gum (**16a**) which was homogeneous according to spectral and tlc criteria, but could not be crystallized. The compound displayed ir 3540 br (bonded OH), 1740, and 1722 cm^{-1} (esters), but no double-bond absorption; nmr 3.92 (H-14), 3.76, 3.73, and 3.55 (methoxyls), 1.03 (C-4 methyl), 0.92 d and 0.85 d (J = 7, isopropyl), and 0.96 ppm (C-10 methyl); nmr (benzene) 4.16 (H-14), 3.74 (H-12), 3.37 (all methoxyls), 1.16 (C-4 methyl), 1.08 d and 0.95 d (J = 7, isopropyl), and 0.75 ppm (C-10 methyl); uv end absorption only.

Monoacetate **16b** was prepared by heating 1 g of **16a** with acetic anhydride for 4 hr. Excess acetic anhydride was removed under vacuum, and the residue was crystallized from methanol. It had mp 171–172°; $[\alpha]D$ −36.2°; ir 3540 (hydroxyl), 1745 and 1725 cm^{-1} (esters), no double-bond absorption; nmr 5.72 (H-14), 3.77, 3.71, and 3.62 (methoxyls), 3.60 (OH), 2.12 (acetate), 1.15 (C-4 methyl), 1.12 (C-10 methyl), 1.02 d and 0.87 d ppm (J = 7, isopropyl); nmr (benzene) at 5.92 (H-14), 3.85 (OH), 3.42 and 3.38 (methoxyls), 1.66 (acetate), 1.19 (C-4 methyl), 1.04 (C-10 methyl), 1.03 d and 0.87 d ppm (J = 7, isopropyl).

Anal. Calcd for $C_{29}H_{42}O_{10}$: C, 63.25; H, 7.69; O, 29.06. Found: C, 63.24; H, 7.58; O, 29.19.

Monomesylate **16c** was prepared by treating 1 g of **16a** in pyridine with excess methanesulfonyl chloride at 0° for 2 hr. The solution was poured into ice water and all organic material was extracted into ether. The ether layer was washed with water, acid, water, and dried. Evaporation yielded 0.9 g of **16c** which had mp 167–169°; $[\alpha]D$ −42.0°; ir 3540 (hydroxyl), 1740–1720 cm^{-1} (esters); nmr 5.41 (H-14), 3.73, 3.66 and 3.58 (methoxyls), 3.04 (mesylate), 1.14 (C-4 methyl), 1.03 (C-10 methyl), 1.09 d and 0.96 d ppm (J = 7, isopropyl).

Anal. Calcd for $C_{28}H_{42}O_{11}S$: C, 57.32; H, 7.22; O, 30.00; S, 5.46. Found: C, 57.30; H, 7.55; O, 30.13; S, 5.06.

Fragmentation of 16c.—To a solution of potassium *t*-butoxide prepared from 1 g of potassium and 50 ml of anhydrous *t*-butyl alcohol was added with stirring 2 g of **16c**. The mixture was allowed to stand at room temperature for 4 days. At the end of this period tlc analysis indicated that starting material had disappeared and that only one product, much less polar than **16c**, was present. The solution was carefully neutralized with dilute hydrochloric acid and evaporated at reduced pressure. The residue was taken up in ether, washed thoroughly, dried, and evaporated. The residue (E, 1.1 g), could not be induced to crystallize. It had ir bands at 1747, 1722 (ester), and 1640 cm^{-1} (double bond), and no hydroxyl absorption; nmr signals at 5.55 (vinyl proton), 3.79 br (hydrogen under epoxide) 3.66 (two methoxyls), 1.16 (C-4 methyl), 0.96 d (J = 7, six protons, isopropyl), and 0.90 ppm (C-10 methyl).

Anal. Calcd for $C_{23}H_{36}O_6$: C, 70.74; H, 8.78; O, 20.49. Found: C, 70.99; H, 8.60; O, 20.40.

Preparation of 17.—To a solution of 3 g of **16a** in 40 ml of acetone was added dropwise with stirring Jones reagent[34] until an excess of the reagent was present. The solution was allowed to stand for 1 hr, then diluted with 200 ml of water and extracted with ether. The ether layer was washed with dilute sodium bicarbonate solution, and water, dried, and evaporated. The residue was recrystallized several times from acetone–hexane to give 3.1 g of the ketol which had mp 129–131°; ir 3540 (bonded hydroxyl), 1755 (strained-ring ketone), 1740, and 1728 cm^{-1} (esters), no double-bond absorption; nmr (benzene) at 4.12 br t (H-12), 3.72 (D_2O exchangeable, hydroxyl), 3.46 (six protons) and 3.43 (methoxyls), 1.23 (C-4 methyl), 1.17 d and 1.04 d (J = 7, isopropyl), and 0.68 ppm (C-10 methyl).

Anal. Calcd for $C_{27}H_{38}O_9$: C, 64.01; H, 7.56; O, 28.43. Found: C, 64.12; H, 7.59; O, 28.46.

Osmium Tetroxide Oxidation of 4.—To a solution of 2 g of **4** in 75 ml of benzene was added with stirring 500 mg of osmium tetroxide. The solution began to darken slowly. After standing 70 hr, the solution was saturated with hydrogen sulfide, allowed to stand overnight, and the precipitate was removed by filtration. Thin layer chromatography of the filtrate revealed two main components, one of which was starting material. The filtrate was evaporated to dryness, and the residue was chromatographed on 40 g of Florisil. Elution with benzene–chloroform (1:1) removed all starting material from the column. Elution with chloroform and chloroform–ether (1:1) yielded 700 mg of a gum which was homogeneous by nmr spectral and tlc criteria. Seed crystals were obtained only after the gum was allowed to stand for 4 months. Using the seed crystals, the remainder was crystallized twice from methanol. The yield of **19** was 510 mg. It had mp 162–165°; $[\alpha]D$ +85.5°; ir 3540 br (–OH), 1740–1720 (carbonyls not resolved), 1601 (conjugated double bond), 1435 and 1387 cm^{-1} (isopropyl doublet); nmr 3.84, 3.80, and 3.7 (methoxyls), 3.42 t (H-12 allylic to double bond), 2.73 d and 2.57 (D_2O exchangeable, hydroxyl protons), 1.20 (C-4 methyl), 1.07 (C-10 methyl), 0.96 d and 1.04 d ppm (isopropyl, J = 7).

(40) H. Labhart and B. Wagniere, *Helv. Chim. Acta*, **42**, 2219 (1959).

Anal. Calcd for $C_{27}H_{40}O_8$: C, 65.83; H, 8.19; O, 25.99. Found: C, 65.67; H, 8.19; O, 25.98.

The nmr spectrum run in benzene revealed the presence of H-14 (under the secondary hydroxyl) at 3.83 d (J = 8) which collapsed to a singlet upon addition of D_2O.

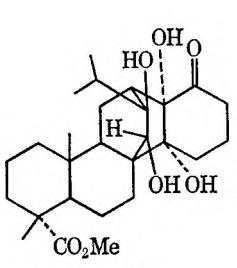
Oxidation of 4 with Osmium Tetroxide–Pyridine.—To a solution of 2 g of **4** in 75 ml of benzene–pyridine (1:1) was added with stirring 500 mg of osmium tetroxide. The solution darkened rapidly, and after 48 hr, the reaction mixture was worked up with hydrogen sulfide as described in the preceding section. Preparative tlc afforded after crystallization 300 mg of **19** and 180 mg of **20** which had mp 135–136°; $[\alpha]D$ 20°; nmr 5.30 t (J = 1.5, H-14), 4.17, and 4.03 (D_2O exchangeable, protons on OH), 3.82, 3.68, and 3.66 (methoxyls), 1.14 (C-4 methyl), 1.10 d and 1.07 d (J = 7, isopropyl), and 0.64 ppm (C-10 methyl); ir 3500 (OH), 1740–1720 (ester carbonyls not resolved), and 1640 cm^{-1} (isolated double bond); uv end absorption only.

Anal. Calcd for $C_{27}H_{40}O_8$: C, 65.83; H, 8.19; O, 25.99. Found: C, 66.05; H, 8.07; O, 25.74.

Oxidation of **4** with ruthenium tetroxide gave a 10% yield of **19** and a complex mixture of other products, presumably due to further cleavage of the two isomeric diols. Reaction of **4** with perosmic acid in *t*-butyl alcohol resulted in recovery of 85% of starting material after 6 months; similar results were obtained with pervanadic and perchromic acid.

Osmium Tetroxide Oxidation of 10 (by M. G. Nair).—To a solution of 0.78 g of **10** in 20 ml of benzene was added dropwise a solution of 0.5 g of osmium tetroxide in 30 ml of benzene and 5 ml of pyridine. After 3 days, the solution was saturated with hydrogen sulfide and filtered. Evaporation of the filtrate and recrystallization from methanol afforded 0.34 g of tetrol **41** which had mp 249–250° ir; 3500–3300 (hydroxyls), 1740 (ester), and 1718 cm^{-1} (ketone); nmr 4.12 (H-14), 3.61 (methoxyl), 0.98 d and 0.96 d (J = 6, isopropyl), 1.20 (C-7 methyl), and 1.01 ppm (C-10a methyl).

Anal. Calcd for $C_{27}H_{44}O_7$: C, 67.47; H, 9.23; O, 23.30. Found: C, 67.64; H, 8.91; O, 23.27.



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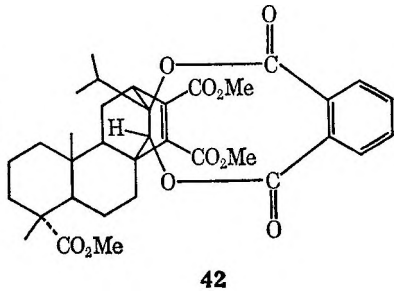

42

Reaction of 4 with Phthaloyl Peroxide.—A solution of 1.00 g of monomeric phthaloyl peroxide (peroxide content 95%)[41] and 2.25 g of **4** in 200 ml of carbon tetrachloride was refluxed for 16 hr and evaporated to dryness *in vacuo*. The residue was taken up in ether, washed with dilute base, water dried, and evaporated. Tlc showed three components the least polar of which appeared to be starting material. Preparative tlc on 120 g of silica gel PF gave **4** as the least polar fraction. The most polar fraction appeared to be a mixture arising from oxidation of both double bonds and was not studied further. The remaining fraction, *ca.* 1 g, was homogeneous. Two recrystallizations from methanol–water yielded 610 mg of fluffy needles which had mp 185–186°; $[\alpha]D$ −132°; ir 1737 (sh), 1725, 1710 (sh, phthalate ester), 1648 (aryl double bond), 1604 (double bond), 1436, and 1390 cm^{-1} (isopropyl doublet); nmr 7.54 (four aromatic protons), 5.30 (H-14 under ester), 3.80, 3.67, 3.60 (methoxyls) 1.25 (C-4 methyl), 1.12 (C-10 methyl), 1.09 d (J = 7, isopropyl methyl), 0.98 d ppm (J = 7, isopropyl methyl). The analysis and spectral properties identified this compound as phthalate **42**. The reaction could be scaled up easily by substituting column chromatography for tlc.

Anal. Calcd for $C_{35}H_{42}O_{10}$: C, 67.51; H, 6.80; O, 25.69; Found: C, 67.28; H, 7.02; O, 25.30.

Hydrolysis of 0.6 g of **42** with methanolic sodium hydroxide followed by neutralization with phosphoric acid, reesterification of the hydrolysate with ethereal diazomethane, and recrystallization from methanol gave 0.39 g (80%) of **19**, identical in all respects with the material from the osmylation reaction.

Reaction of 4 with Osmium Tetroxide–Potassium Metaperiodate.—A solution of 3 g of **4**, 2 g of potassium metaperiodate, and 15 mg of osmium tetroxide in 200 ml of 30% aqueous dioxane was stirred for 3 weeks. At the end of this period, tlc showed that no reaction had taken place. After addition of 100 mg of osmium tetroxide, the mixture gradually turned green. Tlc showed that a small amount of green product had formed, but that most of the starting material was still present. After 2 months, the solution was evaporated *in vacuo* and the residue dissolved in benzene and chromatographed over Florisil. Chloroform eluted **4** and ether eluted 0.38 g of osmate **22** which had mp 310–312°; ir 1730 and 1722 (esters), 1645 (double bond), 1440 and 1395 cm^{-1} (isopropyl doublet); nmr 5.02 (H-14), 4.82, 4.80, and 4.76 (methoxyls), 1.23 (C-4 methyl), 1.10 (C-10 methyl), 1.16 and 0.46 br d (J = 7, isopropyl).

Anal. Calcd for $C_{54}H_{76}O_{17}Os$: C, 54.62; H, 6.46; O, 22.91. Found: C, 54.61; H, 6.35; O, 22.29.

Periodic Acid Cleavage of 19.—To a solution of 500 mg of **19** in 25 ml of methanol was added 500 mg of periodic acid with stirring. The progress of the reaction was followed by tlc. After 12 days nearly all of the glycol had reacted. The solution was evaporated to dryness and the residue taken up in ether. The ether solution was washed with water, very dilute sodium bisulfite to remove traces of iodine, and again with water. Evaporation yielded about 500 mg of ketoaldehyde **21a** as a colorless gum which could not be induced to crystallize. The compound exhibited ir absorption at 2710 (aldehyde CH), 1725 (carbonyls not resolved), and 1601 cm^{-1} (conjugated double bond); nmr 8.84 (aldehyde proton), 3.60 (six protons) and 3.56 (methoxyls), 2.73 q (J = 7, H-12 allylic and α to ketone), 1.03 d and 0.95 d (J = 7, isopropyl), 0.97 (C-4 methyl), and 0.68 ppm (C-10 methyl). The analytical sample was prepared by preparative thin layer chromatography.

Anal. Calcd for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81; O, 26.09. Found: C, 66.28; H, 7.70; O, 26.41.

Ozonolysis of 4.—A solution of 5.0 g of **4** and 1.4 g of freshly recrystallized tetracyanoethylene in 100 ml of ethyl acetate was ozonized at −70° until the blue color of excess ozone was present. The solution was then purged with pure oxygen at −70° to remove all excess ozone. (If the solution is warmed to room temperature while it still contains excess ozone, extensive decomposition takes place.) The solution was allowed to warm to room temperature and the ethyl acetate was removed in a rotary evaporator. Tlc of the residue revealed only two spots, one whose R_f was identical with that of an authentic sample of ketoaldehyde **21a**, the other near the origin being due to tetracyanoethylene oxide. The residue was taken up in chloroform and chromatographed on a silica gel column. The tetracyanoethylene oxide decomposed on the column to a brown polymer which could not be eluted; elution with chloroform gave an almost quantitative yield of ketoaldehyde **21a**. The reaction was easily scaled up to quantities as large as 20 g.

Ozonolysis in methanol at −70° and oxidative work-up with sodium hypochlorite in the manner described for the ozonolysis of fumaropimaric acid[12] gave no acidic material. The neutral fraction consisted of at least seven components (tlc), one of which was epoxide **12**. Ozonolysis of 3 g of **4** in 100 ml ether and 2 ml of pyridine at −70° until the blue color of excess ozone was present, removal of pyridine by washing with dilute acid, evaporation, and chromatography gave 2.1 g of starting material and 0.78 g of **12**.

Bromination of 21a.—To a solution of 10 g of **21a** and 3 g of sodium acetate in 500 ml of 60% aqueous acetic acid was added 4 g of bromine. The solution was allowed to stand at room temperature. Within 24 hr, crystals began to appear and after 4 days the bromine color had largely faded. The solid material was recrystallized from methanol to yield 4 g of **21b** which gave a positive Beilstein test, and had mp 175–176°; $[\alpha]D$ −71°; ir 2730 (aldehyde CH stretch), 1735, 730–1705 (carbonyls only partly resolved), 1640 (medium, conjugated double bond), 1437 and 1391 cm^{-1} (isopropyl doublet); nmr 8.80 (aldehyde proton), 3.70, 3.68, and 3.66 (methoxyls), 1.26 d and 1.18 d (J = 7, isopropyl), 1.15 (C-4 methyl), and 0.76 ppm (C-10 methyl).

Anal. Calcd for $C_{27}H_{37}O_8Br$: C, 56.94; H, 6.55; Br, 14.03. Found: C, 57.33; H, 6.57; Br, 14.14.

Oxidation of **21a** or **21b** with silver oxide gave no acidic fraction. The ir spectrum of the neutral fraction indicated the

(41) K. E. Russell, *J. Amer. Chem. Soc.*, **77**, 4814 (1955).

presence of hydroxyl groups. At least three components were present which were not separable by preparative tlc. Similar results were obtained with Tollens reagent and Fehlings solution. Jones reagent did not attack 21a and chromic acid in acetic acid led to extensive decomposition.

Preparation of 24.—To a solution of 200 mg of 19 in 20 ml of acetone, Jones reagent was added dropwise until an excess was present. After standing for 0.5 hr, the reaction mixture was poured into 100 ml of ether and washed with water. The ether layer was separated, dried, and evaporated, and the residue was subjected to preparative tlc. There was isolated 110 mg of 24 which had mp 174–176°; $[\alpha]_D$ −132°; ir 3500 br (OH), 1725 br (carbonyls not resolved), and 1601 cm^{-1} (conjugated double bond); nmr 3.78, 3.75, and 3.66 (methoxyls), 3.57 b (allylic H-12), 1.17 (C-4 methyl), 1.09 d and 1.02 d (J = 7, isopropyl), and 0.82 ppm (C-10 methyl).

Anal. Calcd for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81. Found: C, 66.23; H, 7.95.

This compound was not attacked by periodic acid.

Bromination of 4 with N-Bromosuccinimide.—To a solution of 20 g of 4 in 400 ml of carbon tetrachloride was added 7.7 g of freshly recrystallized N-bromosuccinimide. The suspension was refluxed with illumination. After a brief induction period, the initial light orange faded, and a rapid reaction ensued. When all N-bromosuccinimide had reacted, the solution was cooled and filtered. The filtrate was evaporated to dryness, and the residue (crude 25) was dissolved in either benzene or ether and treated with 5 g of diazabicyclononene. After 0.5 hr the solution was extracted with dilute hydrochloric acid and washed with water. Evaporation of the solvent yielded 19 g of crude 26. Recrystallization from benzene–hexane yielded 14 g of pure 26 which had mp 104–106°; $[\alpha]_D$ +91°; ir 1730, 1722 (esters), 1645, 1620, and 1602 cm^{-1} (double bonds); nmr 5.90, 5.70, 4.90 (vinyl protons), 4.42 (doubly allylic H-12), 3.77, 3.70, 3.65 (methoxyls), 1.85 (vinyl methyl), 1.15 (C-4 methyl), and 0.68 ppm (C-10 methyl).

Anal. Calcd for $C_{27}H_{36}O_6$: C, 71.02; H, 7.95; O, 21.03. Found: C, 70.99; H, 8.07; O, 21.01.

Treatment of the intermediate allylic bromide 25 with sodium acetate in acetic acid or sodium carbonate in aqueous acetone also resulted in almost quantitative conversion into 26. Chromatography of 10 g of freshly prepared 25 over silicic acid containing 10% by weight of water and elution with benzene resulted in isolation of 7.5 g of 26. Elution with more polar solvents yielded 700 mg of a mixture of polar products. Tlc showed the presence of two main components which were separated by preparative tlc. These substances were identified as the epimeric allylic alcohols 28 on the basis of their nmr spectra, but could not be purified sufficiently to give good analyses. One epimer had nmr signals at 4.10 (H-14), 3.80, 3.74, 3.67 (methoxyls), 3.60, (H-12), 2.20, 1.50 (vinyl methyls), 1.19 (C-4 methyl), and 0.73 ppm (C-10 methyl); the other had signals at 4.46 (H-14), 4.14 (H-12), 3.84, 3.76, 3.70 (methoxyls), 2.16, 1.98 (vinyl methyls), 1.21 (C-4 methyl), and 0.87 ppm (C-10 methyl). The ir spectra of both compounds showed bands at 3540 (hydroxyl), 1730–1720 (esters), 1640, and 1601 cm^{-1} (double bonds).

Oxidation of 4 with *t*-Butyl Chromate. Preparation of 30.—A solution of 25 g of 4 dissolved in 400 ml of carbon tetrachloride was added to 700 ml of *t*-butyl chromate solution (prepared from 68 g of chromium trioxide, 600 ml of carbon tetrachloride, 200 ml of *t*-butyl alchol, 100 ml of acetic acid, and 30 ml of acetic anhydride). The mixture was refluxed for 28 hr, a heavy green precipitate forming during this time. Cold water was added and the layers were separated with the help of added chloroform. The aqueous layer was extracted once with chloroform, and the combined solvent layers were filtered, washed with water, base, and again with water, dried, and concentrated. The residual brown mixture (tlc) was chromatographed over 1 kg of Florisil using chloroform as the eluent. An initial impure fraction was followed by approximately 15 g of nearly pure 30 which was crystallized several times from acetone–*n*-hexane to give 12 g of 30 which had mp 165–166°; $[\alpha]_D$ −136°; ir 1735, 1722 (esters) 1710 cm^{-1} (ketone); nmr 3.78, 3.74, 3.67 (methoxyls), 3.30 (H-12), 1.53, 1.47 (methyls on epoxide), 1.13 (C-4 methyl), and 0.70 ppm (C-10 methyl); uv λ_{max} 316 nm (ϵ 565) and 234 (4650); ORD curve $[\alpha]_{400}$ −2970°, $[\alpha]_{339}$ −9900°, $[\alpha]_{315}$ 0°, $[\alpha]_{291}$ +6100°.

Anal. Calcd for $C_{27}H_{38}O_8$: C, 66.37; H, 7.43; O, 26.20. Found: C, 66.52; H, 7.34; O, 26.39.

Hydrogenation of 30.—A solution of 3 g of 30 in 100 ml of acetic acid was shaken overnight with 100 mg of platinum oxide at 40-lb hydrogen pressure. The catalyst was removed by filtration and the solvent was removed *in vacuo*. The residue was dissolved in ether, washed, and dried. Evaporation yielded a colorless oil which was chilled and scratched to induce crystallization of 31 in almost quantitative yield. The analytical sample was recrystallized from methanol and had mp 176–178°; $[\alpha]_D$ +23°; ir 1740, 1722, (esters), 1714 cm^{-1} sh (ketone); nmr 3.62, 3.57, 3.54 (methoxyls), 2.70 (H-12), 1.52 (six protons, methyls on epoxide), 1.12 (C-4 methyl), 0.64 ppm (C-10 methyl); uv spectrum λ_{max} 308 nm (ϵ 80) and end absorption; ORD curve $[\alpha]_{356}$ 0°, $[\alpha]_{330}$ −408°, $[\alpha]_{314}$ 0°, $[\alpha]_{288}$ 735°, $[\alpha]_{252}$ 0°, $[\alpha]_{230}$ −980°.

Anal. Calcd for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81; O, 26.09. Found: C, 66.38; H, 7.87; O, 25.98.

Preparation of 32.—To a solution of 3 g of 30 in 25 ml of 90% formic acid was added 1 ml of concentrated sulfuric acid. After standing at room temperature for 72 hr the solution was poured into 200 ml of ice water. The precipitate was extracted with ether, washed, dried, and evaporated to dryness. The residue was crystallized from methanol to give 1.7 g of 32 which had mp 180–181°; $[\alpha]_D$ −143°; ir (Nujol) 3460 br (hydroxyl), 1740, 1723 (esters), and 1643 cm^{-1} (double bond); nmr 5.23, 5.17 (vinyl protons), 3.80, 3.76, 3.67 (methoxyls), 1.94 (vinyl methyl), 1.13 (C-4 methyl), and 0.68 ppm (C-10 methyl).

Anal. Calcd for $C_{27}H_{36}O_8$: C, 66.37; H, 7.43; O, 26.20. Found: C, 66.65; H, 7.38; O, 26.36.

Preparation of 33.—A solution of 1 g of 32 in methanol was ozonized at −70° until the blue color of excess ozone was present. The solution was purged with nitrogen at −70° until all excess ozone was removed and then allowed to come to room temperature. The solvent was removed *in vacuo* and the residue crystallized from acetone–hexane to give 600 mg of 33 which had mp 183°; $[\alpha]_D$ −131°; ir 3440 (hydroxyl), 1730–1705 cm^{-1} (carbonyls not resolved); nmr 3.78, 3.74, 3.64 (methoxyls), 2.35 (acetyl), 1.14 (C-4 methyl), and 0.67 ppm (C-10 methyl).

Anal. Calcd for $C_{26}H_{34}O_9$: C, 63.66; H, 6.99; O, 29.36. Found: C, 63.78; H, 6.96; O, 29.49.

Preparation of 34b.—A solution of 200 mg of 33 in 20 ml of ethanol containing 500 mg of sodium hydroxide was refluxed for 5 hr and then neutralized with dilute hydrochloric acid. The solvent was removed by evaporation and the residue was extracted with ether. The organic product 34a could not be crystallized. It was therefore converted with acetic anhydride into acetate 34b which had mp 201°; ir 1730–1710 cm^{-1} (carbonyls not resolved); nmr 4.93 d (J = 3.5, H-13) 3.81, 3.79, 3.67 (methoxyls), 2.14 (acetate), 1.16 (C-1 methyl), and 0.84 ppm (C-10 methyl); λ_{max} 236 nm (ϵ 4620).

Anal. Calcd for $C_{26}H_{34}O_9$: C, 63.66; H, 6.99; O, 29.36. Found: C, 63.50; H, 6.82; O, 28.96.

Preparation of 35. A.—A solution of 100 mg of 33 and 200 mg of lead tetraacetate in 25 ml of benzene was allowed to stand for 4 weeks. Ethylene glycol was added to destroy excess lead tetraacetate. The solution was filtered and extracted several times with 5% sodium carbonate solution. The combined extracts were carefully neutralized with dilute hydrochloric acid. This resulted in a precipitate of 11 mg of 35 which was recrystallized from methanol and had mp 210–214° dec; ir 3200–2500 acid hydroxyl, 1730–1700 cm^{-1} (carbonyls not resolved); nmr 3.80, 3.76, 3.65 (methoxyls), 1.17 (C-4 methyl), and 0.87 ppm (C-10 methyl); λ_{max} 238 nm (ϵ 4730).

Anal. Calcd for $C_{24}H_{32}O_{10}$: C, 59.99; H, 6.71; O, 33.30. Found: C, 60.15; H, 6.39; O, 33.59.

B.—A solution of 0.7 g of 33 and 0.1 g of sodium acetate in 5 ml of 90% peracetic acid was allowed to stand, progress of the oxidation being monitored by tlc. After 2 weeks, excess peracetic acid was destroyed by adding acetone and the mixture was evaporated *in vacuo*. The residue was taken up in ether and the acid fraction was isolated by extraction of the ether layer with sodium carbonate solution and subsequent acidification. This gave 0.17 g of crude and after recrystallization 0.11 g of pure 35.

The substance underwent decarboxylation on being heated above the melting point.

Registry No.—11, 19543-00-1; 12, 19543-01-2; 13, 19581-56-7; 14, 19543-02-3; 15a, 19543-03-4; 16a,

19543-04-5; **16b**, 19613-62-8; **16c**, 19543-05-6; residue E, 19543-06-7; **17**, 19543-07-8; **19**, 19543-08-9; **20**, 19543-09-0; **21a**, 19543-10-3; **21b**, 19543-11-4; **22**, 19624-50-1; **24**, 19543-12-5; **26**, 19543-13-6; **28**, 19543-14-7; **30**, 19614-21-2; **31**, 19614-22-3; **32**, 19581-57-8; **33**, 19553-07-2; **34b**, 19581-58-9; **35**, 19614-23-4; **37**, 19581-59-0; **38**, 19553-08-3; **39a**, 19553-09-4; **39b**, 19553-10-7; **40**, 19553-11-8; **41**, 19553-12-9.

Studies on the Mechanism of Decomposition of Alkyl Diphenylphosphinates[1]

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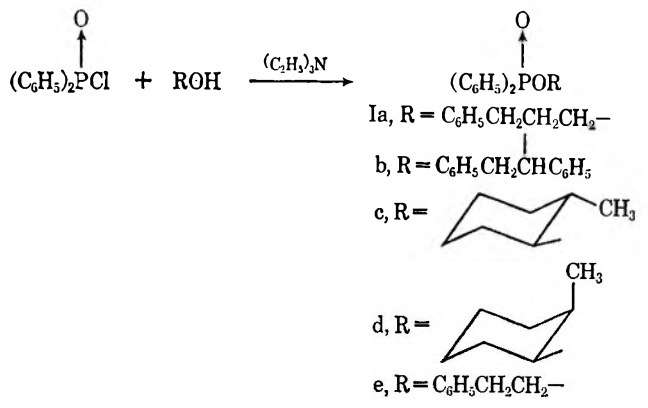
The following esters of diphenylphosphinic acid have been prepared and pyrolyzed: 3-phenylpropyl (Ia), 1,2-diphenylethyl (Ib), *trans*-2-methylcyclohexyl (Ic), *cis*-2-methylcyclohexyl (Id), 2-phenylethyl (Ie), menthyl (If), and bornyl (Ig). Pyrolysis was conducted in a static system under N_2 at atmospheric pressure or in a boiling solvent [dimethyl sulfoxide (DMSO) or diphenyl ether]. Although a concerted mechanism is used to explain most of the thermal pyrolyses, decomposition of Ia, If, and particularly Ig gives pyrolysates containing several alkenes which suggests an ionic process perhaps involving ion pairs. In boiling DMSO, Ic and Id appear to decompose by an E2 mechanism.

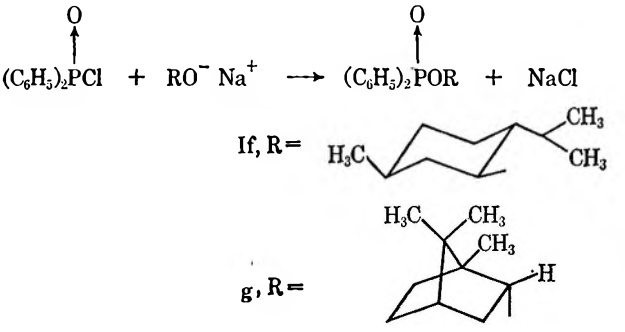
A recent report indicated the usefulness of the pyrolytic decomposition of alkyl diphenylphosphinates I in the preparation of olefins.[5] A mechanism was postulated to involve a cyclic transition state. Several new esters (see Table I) have been prepared and pyrolyzed with the intent of further elucidating this reaction mechanism. From the new results herein, it is apparent that a concerted cyclic mechanism cannot account for the product distribution.

The selected esters used in this study were prepared by the reaction of the appropriate alcohol with diphenylphosphinic chloride in the presence of triethylamine[6] (method I), or by the reaction of diphenylphosphinic chloride with the sodium salt of the alcohol in toluene (method II). Pyrolysis was effected in a static system under a nitrogen atmosphere at atmospheric pressure or in the presence of a boiling solvent [dimethyl sulfoxide (DMSO) or diphenyl ether]. Once the pyrolysis temperatures (Table II) were reached, the reactions were, in all cases, apparently complete within 15 min.

Method I

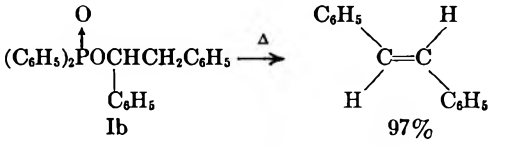


Method II



When 3-phenylpropyl diphenylphosphinate (Ia) was pyrolyzed (Table II) at 185°, a mixture containing 78% allylbenzene and 22% 1-phenyl-1-propene was obtained. When the terminal alkene was heated to 200° (15° above the pyrolysis temperature) for 45 min in a sealed tube, both neat and in the presence of diphenylphosphinic acid, no detectable isomerization occurred. It appears then that the isomeric alkenes must arise directly as a consequence of the mechanism of the decomposition. However, one might anticipate formation of a greater amount of the more conjugated 1-phenyl-1-propene in the event of a carbonium ion involvement. Allylbenzene has been prepared in 76% yield by the pyrolysis of 3-phenyl-1-propyl acetate.[7]

Pyrolysis of 1,2-diphenylethyl diphenylphosphinate (Ib) resulted in essentially complete conversion into



trans-stilbene. In both a static pyrolysis (220–240°) and in DMSO (190°) the *trans* isomer was obtained in high yield. Examination of Newman projection formulas of the transition states leading to the two stilbenes

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(4) NSF College Teacher Research Participant, summer 1965.

(5) K. D. Berlin and T. H. Austin, *J. Org. Chem.*, **30**, 2745 (1965).

(6) K. D. Berlin, T. H. Austin, and M. Nagabhushanam, *ibid.*, **30**, 1267 (1965).

(7) A. W. Fort and J. D. Roberts, *J. Amer. Chem. Soc.*, **78**, 587 (1956).

TABLE I

PHOSPHINIC ESTERS, $(C_6H_5)_2P(O)OR$

Ester	Yield, %	Mp, °C	Ir, μ		Calcd, %			Found, %		
			P→O	P—O—C	C	H	P	C	H	P
Ia	91.0	69.5–70	8.22	9.95	74.99	6.29	9.51	74.82	6.31	9.35
Ib	82.5	142–143	8.22	10.0	78.38	5.82	7.77	78.73	5.94	7.29
Ic	68.0	73–74	8.13	9.90	72.59	7.38	9.85	72.63	7.40	10.04
Id	78.0	84–85	8.15	9.95	72.59	7.38	9.85	72.59	7.27	9.97
If[a]	51.2	72–73	8.17	9.87	74.13	8.20	8.69	74.17	8.15	8.69
Ig[b]	53.8	74–75	8.13	9.78	74.55	7.68	8.74	74.61	7.66	9.01

[a] $[\alpha]^{25.5}D$ −73.0° (8.280 g/100 ml of $CHCl_3$). [b] $[\alpha]^{25.5}D$ −14.3° (5.892 g/100 ml of $CHCl_3$).

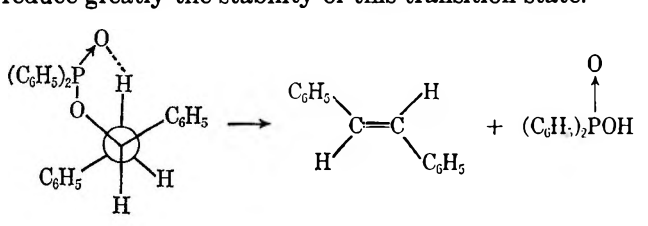
TABLE II

PYROLYSIS DATA OF PHOSPHINIC ESTERS[a]

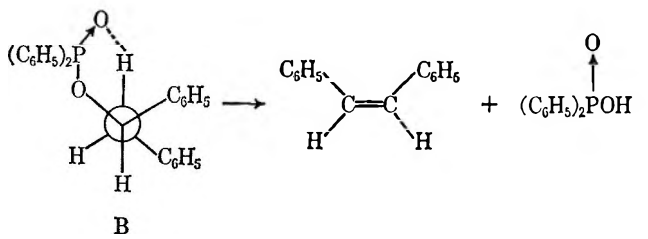
Ester	Solvent	Pyrolysis temp,[b] °C	Yield,[c] %	Product distribution	
				Products	%
Ia	Neat	185	Quant.	Allylbenzene	78.1
				1-Phenyl-1-propene	
				trans-	18.70
				cis-	2.91
Ib	Neat	210–240	88	*trans*-Stilbene	96.9
				cis-Stilbene	3.1
Ib	DMSO	184–190	65	*trans*-Stilbene	97.6
				cis-Stilbene	2.4
				Cyclohexenes, %	
				1-Methyl-	3-Methyl-
Ic[d]	Neat	200–220	93	60.25	39.75
Ic	DMSO	185–192	48	1.0	99.0
Ic	$(C_6H_5)_2O$	210–235	90	54.6	45.4
Ic	$(C_6H_5)_2O$ + hydroquinone	210–234	86	53.8	46.2
Id[d]	Neat	190–210	75	91.80	9.20
Id	DMSO	184–186	56	43.87	56.1
Id	$(C_6H_5)_2O$	200–235	90	88.16	11.84
				Products	%
If	Neat	220–260	88	*p*-Menth-2-ene (100% optically pure)	42
				p-Menth-3-ene (71% optically pure)	54
				Isomeric menthenes	4
Ig	Neat	220–260	96	Bornylene	1.4
				Tricyclene	21.2
				Camphene (38% optically pure)	77.6

[a] A minimum of two pyrolyses was examined with each ester. [b] After the indicated temperature is reached, completion of pyrolysis takes approximately 15 min or less. [c] Percentage yields were determined by glpc using standard solutions. [d] Only the 1- and 3-methyl cyclohexenes were observed in the pyrolysates.

reveals that steric interactions are at a minimum in conformation A, thus favoring the formation of the *trans* isomer. In transition state B *gauche* interactions between the bulky phenyl groups would be expected to reduce greatly the stability of this transition state.



A



B

The isomerization of *cis*- to *trans*-stilbene under reaction conditions is catalyzed by heat and acid (Table III). When *cis*-stilbene was heated (neat) under N_2 for 40 min (220–240°), glpc analysis of the mixture revealed a 75:25 ratio of *cis*- to *trans*-alkene. When an equivalent amount of diphenylphosphinic acid was added to *cis*-stilbene under identical conditions, the amount of *trans*-stilbene was markedly increased (55% *cis*, 45% *trans* isomer). Thus it is probable that not much *cis*-stilbene is formed in the pyrolysis of Ib.

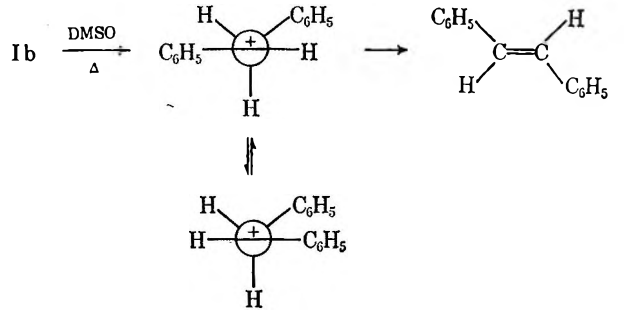


TABLE III

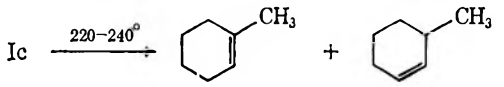
PRODUCT EQUILIBRATION STUDIES

Compd	Catalyst and solvent	Temp, °C	Time, hr	Products, %		
				Allylbenzene	*cis*-1-phenyl-1-propene	*trans*-1-Phenyl-1-propene
Allylbenzene[a]	$(C_6H_5)_2P(O)OH$	200	0.75	100	0	0
Cyclohexene derivative				1-Methylcyclohexene		3-Methylcyclohexene
3-Methyl	$(C_6H_5)_2P(O)OH$	102–120	1.0			100
1- and 3-[b] methyl	$(C_6H_5)_2P(O)OH$ in diphenyl ether	90–105	3.0	46.5		54.4
1-Methyl	$(C_6H_5)_2P(O)OH$ in DMSO	160–177	3.0	84.84		15.16
1-Methyl[c]	$(C_6H_5)_2P(O)OH$ in DMSO, 0.5% water added	135	2.0	58.66		41.34
				cis-Stilbene		*trans*-Stilbene
cis-Stilbene	Heat	220–245	1.0	75.3		24.7
	Heat + acid	220–245	0.8	55.4		46.5
trans-Stilbene	Heat + acid	210–240	1.0	2.2		97.8
				Bornylene	Camphene	Tricyclene
Bornylene[a]	$(C_6H_5)_2P(O)OH$	220–260	0.75	4.7	64.1	31.2
Bornylene[a]	Neat	220–260	0.75	94.0	4.2	1.8

[a] Sealed tube. [b] The initial ratio of 1-:3-methylcyclohexene was 46.5:54.4. [c] Water was added to the above sample after 1 hr heating period. The mixture was then heated for an additional 2-hr period.

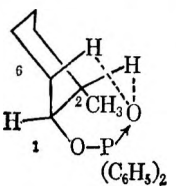
That an ionic E1 type of mechanism might be operative in DMSO with Ib must be considered in light of work reported by Nace.[8] DMSO was found to be effective in promoting the decomposition of sulfonic esters by an ionic pathway.[8] However, since pyrolysis of Ib proceeding through either an E1 or concerted elimination process would be expected to lead to a predominance of *trans*-stilbene, it is not possible to distinguish between the two processes in DMSO.

Pyrolysis of neat *trans*-2-methylcyclohexyl diphenylphosphinate (Ic) at 220–240° gave a mixture of 1- and 3-methylcyclohexene in a ratio of 60.25:39.75. The possibility does exist that after formation of the 3 isomer an isomerization (acid catalyzed) to the 1-alkene could occur. However, attempts to isomerize 3-methylcyclo-



hexene under these conditions (Table III) were unsuccessful.[9] Had an equilibrium been established, one would expect to find evidence of the 4 isomer as well as methylenecyclohexane; neither isomer was detected in any of the isomerization studies.

The nearly statistical ratio of 1- and 3-methylcyclohexene obtained from Ic suggests a *cis*-concerted process but does not rule out a mechanism involving ion pairs. Both the *cis* protons at C-2 and C-6 are readily accessible to the phosphoryl oxygen in a cyclic transition state. The predominance of the 1-methylcyclohexene is reminiscent of the higher ratio of Saytzeff to Hoffmann alkene in the pyrolysate of such esters as menthyl[10] and *trans*-2-phenylcyclohexyl xanthate.[11]



The *cis*-2-methylcyclohexyl ester Id, when pyrolyzed, led to a 91.80:8.20 ratio of 1-:3-methylcyclohexene. This result is clearly inconsistent with a *cis*-concerted mechanism since no simple conformation of Id can be imagined from examination of models in which the tertiary proton at C-2 alone is available for abstraction. Indeed, there is some evidence from nmr data that the ground state of Id may be that conformer in which the ester function is axial, in which case only the secondary hydrogens are available to form a pseudoheterocyclic transition state. The hydroxy function in *cis*-2-methylcyclohexanol is assigned the axial position due to the apparent deshielding of the proton geminal to the hydroxy group in the *trans* (equatorial) isomer, relative to the proton geminal to the hydroxy group of the *cis* isomer.[12] The resonances of the counterpart protons in the *cis*- and *trans*-diphenylphosphinic esters bear the same relative relationship (in $DCCl_3$) as in the case of the alcohols;[13] this suggests the axial position for the ester function of the *cis* isomer. There is, of course, no requirement that the actual transition state resemble the ground-state configuration. The predominance of the 1-alkene product contrasts markedly with the re-

(8) H. R. Nace, *J. Amer. Chem. Soc.*, **81**, 5428 (1959).

(9) A. C. Cope, D. Ambros, E. Ciganek, C. F. Howell, and Z. Jacura [*J. Amer. Chem. Soc.*, **82**, 1750 (1960)] equilibrated 1-methylcyclohexene and methylenecyclohexene in the presence of *p*-toluenesulfonic acid in acetic acid. Only the *exo* and *endo* isomers were found; no other methylcyclohexenes were detected. The implication is that under the mildly acidic conditions employed in our pyrolysis no isomerization to the 3 isomer occurs. The low solubility of diphenylphosphinic acid in the 3- and 1-methylcyclohexene may be the reason that no isomerization of the 3 isomer was observed.

(10) For a review of these pyrolyses, see C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431, 438 (1960).

(11) W. J. Bailey and C. N. Bird, abstracts of papers presented at the 131st National Meeting of the American Chemical Society, Miami Beach, Fla., April 1957, p 44–O.

(12) E. L. Eliel, M. H. Gianni, and Th. D. Williams, *Tetrahedron Lett.*, 741 (1962).

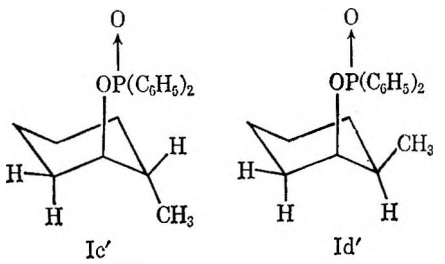
(13) 3.05 ppm for *trans*-2-methylcyclohexanol, 3.77 ppm for *cis*-2-methylcyclohexanol, 4.07 ppm for *trans*-2-methylcyclohexyl diphenylphosphinate, 4.53 ppm for *cis*-2-methylcyclohexyl diphenylphosphinate.

sults of the pyrolysis of the acetic ester in which the 3-alkene is reported to be the sole product.[14] Loss of the diphenylphosphinate anion to give the secondary carbonium ion followed by loss of the acidic proton from C-1 could yield the product, 1-methylcyclohexene, observed in our work.

Botteron and Shulman[15] have found essentially the same ratio of 1-:3-methylcyclohexene (56:44) when the corresponding *trans*-2-methylcyelohexyl methylxanthate was pyrolyzed. An observed increase in the ratio of 1:3 isomer on addition of benzoyl peroxide was suggested to imply a free-radical mechanism. Several observations do not offer support for a free-radical mechanism during pyrolysis of the phosphinates. Pyrolysis of Ic in diphenyl ether in the presence of added hydroquinone, a known radical scavenger, produced no change in the ratio of methylcyclohexenes. When 2-phenylethyl diphenylphosphinate (Ie) was pyrolyzed, no polymerization of styrene was found.[5] Examination of the pyrolysate from benzyl diphenylphosphinate revealed toluene and diphenylmethane (possible radical products).[16] However, in this case absence of β hydrogen precludes operation of a concerted *cis*-elimination pathway.

The results (99% 3-methylcyclohexene) obtained when *trans* ester Ic was pyrolyzed in DMSO precludes the possibility of a *cis*-concerted process in this case. Although the *trans*-diaxial conformation in Ic is certainly not the expected ground-state conformation, it is conceivable that under conditions of the pyrolysis elimination may occur in this conformation by an E2-type pathway. The observed ratio (56.13:43.87) of 3-:1-methylcyclohexene obtained from the *cis* ester Id also is explicable by this pathway. Heating 1-methylcyclohexene to 170° in DMSO in the presence of diphenylphosphinic acid for 3 hr causes isomerization to an 85:15 mixture of 1- and 3-methylcyclohexene. Addition of 0.5% water to DMSO causes a considerable increase in the rate of isomerization. At 135° for 2 hr under the latter condition converts 1-methylcyclohexene into a 59:41 1:3 isomer mixture. Nevertheless, the times for these isomerizations to occur are considerably longer (2–3 hr) than the time that it takes the pyrolyses themselves to occur (approximately 0.25 hr at maximum). Thus only a small part of the 3-methylcyclohexene from either Ic or Id could have formed by isomerization.

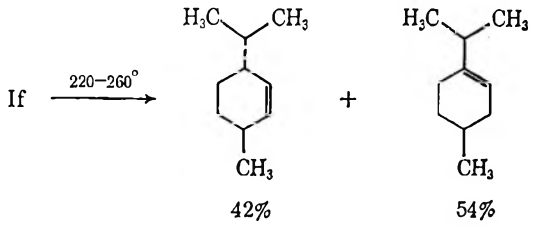
The difference in observed ratios of the products obtained by pyrolysis of Ic or Id neat and in diphenyl ether compared with those in DMSO could possibly be attributed in part to the greater ease of formation of the conformers Ic′ and Id″ in DMSO, respectively. Also



Ic′ Id′

the ability of DMSO to abstract a proton may be important. It is noteworthy that the *cis*- and *trans*-2-methylcyclohexyl *p*-toluenesulfonates were found to give essentially the same product ratio of alkenes (as we observed) when treated with potassium *t*-butoxide in DMSO at 55°.[17] We cannot rule out the possibility that a subtle mechanism is operative in pyrolyses of Ic or Id in DMSO.[18]

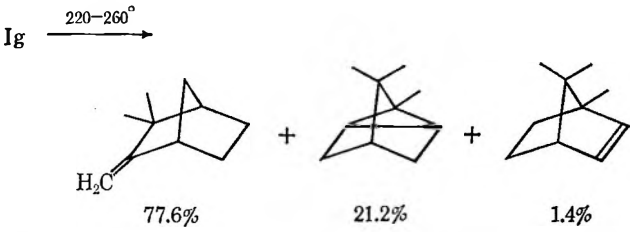
Pyrolysis of menthyl diphenylphosphinate (If) produces (88% conversion) *p*-menth-3-ene (54%), *trans*-*p*-menth-2-ene (42%), and other isomers (4%). This compares with a 75:25 ratio for the 3 *vs.* the 2 isomer for the menthenes from methylmenthyl xanthate with no other menthene isomers produced.[19]



42% 54%

Optical rotation values for the menthenes (from pyrolysis of If) in diethyl ether were measured using a micropolarimeter tube for preparatively chromatographed samples. The rotations are $[\alpha]^{22}D$ +77.3° for the 3 isomer and $[\alpha]^{22}D$ +162° for the 2 isomer. These compare with literature values of $[\alpha]^{16}D$ +109° and $[\alpha]^{16}D$ +132.5° (homogeneous), respectively.[20] From the percentage composition and the measured optical rotations, a rotation of 109.6° was calculated for the mixture compared with the $[\alpha]^{21}D$ 107.5° value measured directly on the original sample. The disparity of the product ratios, the presence of traces of extraneous menthene isomers, and the inferior value for the optical rotation of the *p*-menth-3-ene again cast doubt as to whether the mechanism could be considered strictly *cis* concerted.

Pyrolysis of bornyl diphenylphosphinate (Ig) gave principally camphene and tricyclene (77.6 and 21.2%)



77.6% 21.2% 1.4%

(14) W. Hückel and D. Rücker, *Ann.*, **666**, 43, (1963).

(15) D. G. Botteron and G. P. Shulman, *J. Org. Chem.*, **27**, 2007 (1962).

(16) Unpublished results of K. D. Berlin and W. C. Pivonka, Oklahoma State University, 1965.

(17) D. H. Froemsdorf and M. E. McCain, *J. Amer. Chem. Soc.*, **87**, 3983 (1965).

(18) Rutherford and Fung have suggested *some* carbonium ion character in the transition state in the pyrolyses of the hydrogen phthalate of *trans*-1,2-dimethylcyclohexanol. All three expected isomers were obtained, however, in the ratio of 19:46:35; see K. G. Rutherford and D. P. C. Fung, *Can. J. Chem.*, **42**, 2657 (1964). A referee has suggested a *trans*-concerted elimination (1,2) with Ic and Id but we feel that the following arguments are valid. Assuming that the six atoms, HCCOP→O, are not required to approach coplanarity in the transition state, surely for a *trans*-concerted elimination the activation energy arising from torsional effects between one departing group and a residual group on the vicinal carbon atom as the double bond is developing is higher than for *cis*-concerted elimination.

(19) The menthene isomer ratios were determined by quantitative gas chromatography on samples prepared in this laboratory. The literature values for the 3:2 isomer ratio is 70:30, this result being obtained by selective racemization of the *p*-menth-3-ene by *p*-toluenesulfonic acid: see W. Hückel and W. Tappe, *Ann.*, **537**, 113 (1939).

(20) N. McNiven and J. Read, *J. Chem. Soc.*, 153 (1952). This reference contains the highest value for the rotations of the menthene isomers. Nothing was found in the literature to indicate that pure (+)-*p*-menth-3-ene has ever been isolated and measurements taken on it directly. Likewise, if the previous samples of *trans*-*p*-menth-2-ene were less than homogeneous, the discrepancy between the literature value for its rotation and that obtained in this laboratory would be explained.

and a trace of bornylene (1.4%). The camphene formed is approximately 38% optically pure. The results contrast with the yields of bornylene (70, 61, and 24.5%) obtained from the methyl xanthate,[21] acetate,[22] and benzoate,[21] respectively. Heating 95% bornylene (the balance is camphene plus a trace of tricyclene) to 220–260° for 45 min in the presence of diphenylphosphinic acid (sealed tube) causes isomerization to camphene and tricyclene leaving only 4.6% bornylene unchanged (Table III). This amount of bornylene, however, is in excess of that formed in the pyrolysis of Ig where the contact time at the elevated temperature is considerably shorter (15-min maximum). Heating the bornylene to 220–260° in the absence of the acid causes no isomerization. These results are probably best explained by some charge formation in the transition state from Ig to products.

In conclusion, the experimental results from the pyrolysis of a number of alkyl diphenylphosphinates are not entirely in accord with the proposition of a simple *cis*-concerted mechanism. However, the low pyrolysis temperatures, the high conversion, and the relatively simple compositions of many of the product mixtures argue against a wholly ionic transition state. The diphenylphosphinyl function might be viewed as capable of forming the hydrogen-bridged pseudoheterocyclic transition state, albeit with a certain degree of charge separation therein. When for steric or other reasons the concerted transition state has difficulty in forming, the mechanism passes over into an ionic mode, perhaps involving an associated ion pair. In the case of highly reactive carbonium ion species, hydride migration or skeletal rearrangements may occur competitively with proton abstraction by the anion, such as in the case of Ia, If, and Ig.

As a method of alkene preparation, pyrolysis of diphenylphosphinic esters is still attractive since the esters are crystalline solids which are easily prepared and purified. Moreover, conversions are excellent and, unlike the case of other commonly pyrolyzed esters, the product needs little purification. With alkenes extremely sensitive to skeletal rearrangement in the presence of even weak acids or where small amounts of isomeric products are undesirable, xanthate or acetate pyrolysis may still be of equivalent value or superior.

Experimental Section

Materials.—The following chemicals were obtained from commercial sources: *cis*-stilbene, *trans*-stilbene, 3-methylcyclohexene, 1,2-diphenylethanol, *trans*-2-methylcyclohexanol (ir maxima 9.40, 9.50, and 9.63 μ)[23] *cis*-2-methylcyclohexanol (ir maxima 9.82, 10.23, and 10.58 μ),[23] borneol ($[\alpha]^{23}D$ −20.8°) and menthol ($[\alpha]^{23}D$ −44.7°). Samples of methylcyclohexene, 3-phenyl-1-propene, and *cis*- and *trans*-1-phenyl-1-propene were generously supplied by Dr. E. J. Eisenbraun. We also express our thanks to Dr. Don H. Burpo who helped in the preparation of If and Ig.

Preparation of Diphenylphosphinic Chloride.—Dried (H_2SO_4) oxygen was bubbled through diphenylphosphinous chloride (neat) at 135–140° for 28 hr.[24] Oxidation was monitored by observing the decrease in refractive index to a constant value of $n^{23.4}D$ 1.6080. The resulting dark yellow-orange liquid distilled *in vacuo* at 137–138° (0.03–0.06 mm) [lit.[24] 140° (0.1 mm) to give 86% yield of diphenylphosphinic chloride, $n^{24.8}D$ 1.6083 (lit.[25] $n^{26}D$ 1.6095).

Preparation of 1,2-Diphenylethyl Diphenylphosphinate (Ib). Method I.—A solution of 11.8 g (0.05 mol) of diphenylphosphinic chloride in 50 ml of anhydrous ether was added dropwise with stirring over 0.5 hr to a solution of 9.9 g (0.05 mol) of 1,2-diphenylethanol and 10.1 g (0.1 mol) of triethylamine in 75 ml of anhydrous ether. During addition, the temperature rose so as to cause gentle refluxing. After addition of ether (150 ml) to facilitate stirring of the heavy slurry, the mixture was heated under reflux for 1.5 hr. The precipitate was collected by filtration, washed with water to remove triethylamine hydrochloride, and recrystallized from benzene–hexane to yield 14.4 g (72.7%) of 1,2-diphenylethyl diphenylphosphinate. The compound was identified by elemental and spectral analysis (Table I).

The work-up in the above procedure was modified slightly for the 2-methylcyclohexyl esters. After removal of the amine hydrochloride and the solvent, the residual oil crystallized on standing. The solid was then recrystallized twice from hexane (Table I).

Preparation of Menthyl Diphenylphosphinate (If). Method II.—Sodium (2.76 g, 0.12 g-atom), menthol (15.63 g, 0.10 mol, $[\alpha]^{23}D$ −44.7°), and 50 ml of toluene (dried over sodium) were stirred vigorously for 7 hr at 100–105°. After the mixture had cooled to room temperature, the excess sodium was mechanically removed. Diphenylphosphinic chloride (26.0 g, 0.11 mol) in 50 ml of toluene was added dropwise to the sodium menthoxide with ice bath cooling to keep the reaction temperature below 40°. After the addition of the diphenylphosphinic chloride was complete, the reaction mixture was heated to 85° for 4 hr, then cooled and extracted with 5% sodium bicarbonate and with water. To remove unreacted menthol, the organic layer was steam distilled until 1.5 l. of distillate was collected. The nonvolatile residue was extracted with ether, and the ether layer was dried ($MgSO_4$) and evaporated. Crystallization of the resulting oil from *n*-hexane yielded 18.25 g (51.2% If, mp 72–73°). The compound was identified by elemental and spectral analysis (Table I).

Pyrolysis of *trans*-2-Methylcyclohexyl Diphenylphosphinate (Ic).—The procedure employed for pyrolysis during this study is essentially the same as that reported by Berlin and Austin[5] with some modifications. The method employed for *trans*-2-methylcyclohexyl diphenylphosphinate will be described.

The reaction was carried out in a 10-ml pear-shaped flask equipped with a thermometer, magnetic stirrer, and nitrogen inlet which was connected to a pyrolysis train. The train consisted of three traps connected in series, the first being air cooled and the latter two immersed in Dry Ice–acetone traps. Each of the traps was filled with ether to approximately 1 in. above the lower end of the inlet tube. The system was protected with a drying tube ($CaCl_2$) and was swept with dried N_2. The reaction vessel was charged with 1.200 g (0.0038 mol) of ester Ic, and heat was applied slowly until the ester had melted (75°). The temperature was raised to 200° at which point liquid droplets were observed in the connecting tube. The temperature was held between 200 and 220° for 0.75 hr. After 15 min no further condensation was observed. The system was allowed to cool to room temperature. The slightly discolored solid in the flask was dissolved in 10% NaOH and the yellow alkaline solution was extracted several times with ether. Contents of the three traps were combined with the ether extract, condensed, and diluted to 25.0 ml with ether for glpc analysis.

The aqueous solution, when acidified with 6 *N* HCl, gave a white solid which, after drying at 25° *in vacuo* for 24 hr, melted at 193–194° (lit.[26] mp 192–193.5°). The infrared spectrum was identical with that of an authentic sample of diphenylphosphinic acid.

Preparation of Menthene Standards.—Carbon disulfide and then methyl iodide were added, in order, to an ice-cooled solution of sodium menthoxide (prepared from sodium and menthol in toluene) in anhydrous ether. The ether solution was boiled 1 hr between respective additions. The ether was removed by distillation and the resulting residual oil was crystallized from ethanol to give methyl menthyl xanthate (86%).[27] The xanthate

(21) C. A. Bunton, K. Khaleeluddin, and D. Whitaker, *Nature*, **190**, 715 (1961).

(22) E. U. Emovon, *J. Chem. Soc., B*, 588 (1966).

(23) Reported values: *trans*-2-methylcyclohexanol 9.39, 9.50, and 9.63 μ; *cis*-2-methyleyclohexanol 9.83, 10.23, and 10.60 μ [E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, **79**, 5986 (1957)].

(24) R. A. Baldwin and R. M. Washburn, *J. Org. Chem.*, **30**, 3864 (1965).

(25) T. H. Austin, Ph.D. Thesis, Oklahoma State University, 1965.

(26) G. M. Kosolapoff and R. F. Struck, *J. Chem. Soc.*, 3950 (1959).

(27) D. Malcolm and J. Read, *ibid.*, 1037 (1939).

(10.0 g, 0.042 mol) was distilled through a water-cooled condenser from a sand bath heated to 200°. The resulting liquid was heated over 2 g of sodium for 11 hr and then distilled at 65–72° (aspirator vacuum). The produced menthene (3.1 g, 55%) had a standard rotation of $[\alpha]^{23}D$ 113.7° (ether) [lit.[27] $[\alpha]^{14}D$ +114.1° (alcohol)] and contained (by glpc) *p*-menth-3-ene (70.0%), *trans*-*p*-menth-2-ene (23.2%), and unidentified components (6.8%). *trans*-*p*-Menth-2-ene was identified by mixed injection on glpc with an authentic sample of *trans*-*p*-menth-2-ene prepared by base-catalyzed elimination on menthyl *p*-toluenesulfonate.[28,29]

Gas Chromatography of Alkenes.—A 6 ft × 1/8 in. 5% SE-30 on 60/80 mesh, acid-washed, DMCS treated Chromosorb G column served to separate all alkene mixtures with the exception of the menthenes. A 1 m × 0.25 in. column packed with 30% silver nitrate in ethylene glycol (25%) on 60–80 mesh, acid-washed firebrick performed well in separating 2- and 3-*p*-menthenes. (Retention volumes for the 2- and 3-menthenes are 1.21 and 3.17, respectively, relative to toluene.)[30] The column was operated at room temperature with a helium flow rate of 60–90 ml/min. A 0.5-in.-o.d. version of this column was used to chromatograph the isomers preparatively.

Optical Purity of Camphene from Bornyl Diphenylphosphinate.—Ig was pyrolyzed by the standard method and the alkene products were taken up in ether. The ether solution was analyzed quantitatively by glpc and the concentration found to be 1.11 g of alkene/10.0 ml. The rotation due to the 1.4% bornylene (lit.[31] $[\alpha]^{18}D$ −21.69°) was assumed to be negligible. Thus from the observed rotation, $\alpha^{23}D$ −3.41°, of the alkene mixture, assuming all rotation due to the 78.2% camphene, a specific rotation, $[\alpha]^{23}D$ −39.4°, was calculated. Taking $[\alpha]^{17}D$ −104.7° (ether) for pure (−)-camphene,[32] an optical purity of 38% is calculated for the camphene.

Registry No.—Ia, 19639-45-3; Ib, 19639-46-4; Ic, 19639-93-1; Id, 19669-14-8; If, 19639-94-2; Ig, 19639-95-3.

(28) N. Mori, *Nippon Kagaku Zasshi*, **78**, 36 (1957); *Chem. Abstr.*, **53**, 5320 (1959).
(29) A. K. MacBeth and W. G. P. Robertson, *J. Chem. Soc.*, 895 (1953).
(30) J. Herling, J. Shabtai, and E. Gil-Av, *J. Chromatogr.*, **8**, 349 (1962).
(31) J. Bredt and H. Sandkuhl, *Ann.*, **366**, 1 (1909).
(32) J. L. Simonsen, "The Terpenes," Vol. II, 2nd ed, University Press, Cambridge, 1949, p 289.

Bis(polyfluoroalkyl)acetylenes. VI. Thermal and Photochemical Additions of Perfluoro-2-butyne to Aromatic Compounds

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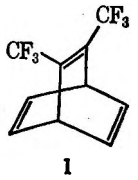
Received October 3, 1968

1,4 adducts have been isolated from thermal addition of perfluoro-2-butyne to benzene, toluene, and *o*-, *m*-, and *p*-xylenes. These thermal adducts are unstable at elevated temperatures. The photochemical addition of perfluorobutyne to aromatic compounds and the photosensitized rearrangement of the thermal adducts have also been investigated.

The high reactivity of bis(perfluoroalkyl)acetylenes as dienophiles was demonstrated in their addition to aromatic compounds to form 1,4 adducts.[2a] The addition to simple benzenoid compounds to form isolable 1,4 adducts was, however, limited to durene.[2a] We wish to report here the generality of the reaction as demonstrated by isolation of adducts from reactions of perfluoro-2-butyne (PFB) with benzene and other simple benzenoid compounds. The photochemical addition of PFB to several aromatic compounds and the photorearrangements of the thermal 1,4 adducts have also been investigated.[2b]

Results and Discussion

Thermal Addition Reactions.—The earlier investigation[2a] of the reaction of PFB with benzene at 250° under pressure did not result in detection of the 1,4 adduct **1**. However, the isolation of 1,2-bis(trifluoromethyl)benzene strongly suggested the transient existence of **1**. Compound **1** has now been isolated when the reaction is run under autogeneous pressure and at slightly lower temperatures (180–200°). Even at these temperatures, thermolysis of **1** and further reaction of **1** with PFB competes with formation of **1**. Therefore, even under optimum conditions, **1** could be isolated in only 7–10% yield. The structural assignment of **1** was based on the chemical transformations shown in Scheme I. Elemental analyses and spectroscopic data agree with the assignment. Further, the assignment is supported by the excellent agreement between the observed and calculated 100-Mc proton magnetic resonance (pmr) spectra.[2b]



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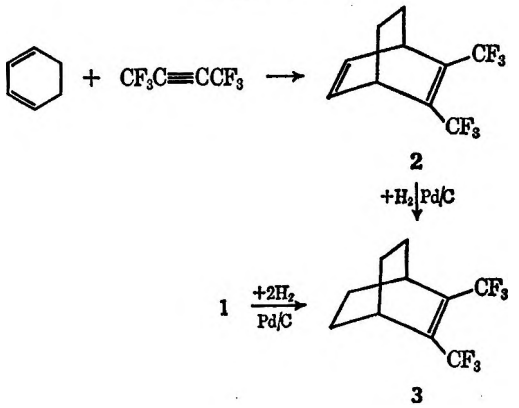
SCHEME I



(1) To whom inquiries should be addressed: Department of Chemistry, University of Hawaii, Honolulu, Hawaii 96822.
(2) (a) C. G. Krespan, B. C. McKusick, and T. L. Cairns, *J. Amer. Chem. Soc.*, **83**, 3428 (1961). (b) Part of this work was described previously in a preliminary report: R. S. H. Liu, *ibid.*, **90**, 215 (1968).

TABLE I

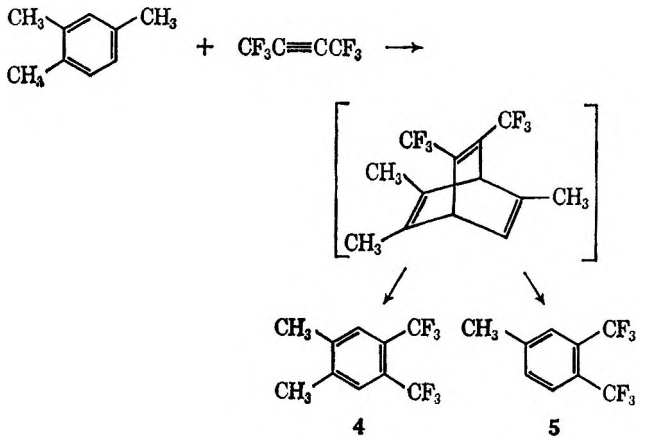
REACTIONS OF PERFLUORO-2-BUTYNE WITH BENZENOID COMPOUNDS

Reactant	Reaction conditions,[a] temp in °C, time in hr	1,4 adduct (% yield)	Other products
Benzene	180, 20	2,3-Bis(trifluoromethyl)-bicyclo[2.2.2]octatriene (8)	*cis*-Hexafluoro-2-butene, 1,2-bis(trifluoromethyl)benzene, 1,2,4,5-tetrakis(trifluoromethyl)benzene, and 2,3,6,7-tetrakis(trifluoromethyl)naphthalene
	250, 12[b]		Above products plus 1,2,4-tris(trifluoromethyl)benzene and 1,4,6,7-tetrakis(trifluoromethyl)naphthalene
Toluene	180, 12	5-Methyl- (21)	Other products not identified
o-Xylene	200, 8	5,6-Dimethyl- (8)	1,2-Bis(trifluoromethyl)benzene plus other unidentified products
	250, 13		Same as above
m-Xylene	180, 10	5,8-Dimethyl- (6.7) 1,5-Dimethyl- (2.2)	Other products not identified
p-Xylene	200, 10	5,7-Dimethyl- (57) only	Other products not identified
1,2,4-Trimethylbenzene	220, 13	None isolated	1-Methyl-3,4-bis(trifluoromethyl)benzene, 1,2-dimethyl-4,5-bis(trifluoromethyl)benzene, and other unidentified products
Mesitylene	225, 10		Mixture of high-boiling materials
Durene[b]	200, 10	5,6,7,8-Tetramethyl- (41) only	

[a] Aromatic compound in excess. [b] Reference 2a.

1,4 adducts have also been isolated from reactions of PFB with benzene homologs. In general, better yields are obtained in these cases. The results are summarized in Table I. Structural assignments of these adducts were mainly based on the results of analyses of their pmr spectra. The spectra, together with data on several related compounds for comparison, are described in Table II. The major side reactions in these cases are again fragmentation of adducts and their further reaction with PFB. Thus, reactions at higher temperatures gave no 1,4 adducts (Table I). However, some of the identified products [*e.g.*, 1-methyl-3,4-bis(trifluoromethyl)benzene, **4**, and 1,2-dimethyl-4,5-bis(trifluoromethyl)benzene, **5**, from addition to 1,2,4-trimethylbenzene, Scheme II] again clearly indicate the intermediacy of such 1,4 adducts.

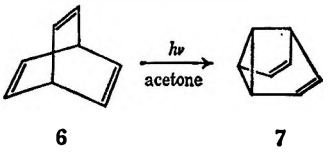
SCHEME II



Because of these secondary reactions, no attempt was made to obtain quantitative data related to factors controlling the direction and efficiency of these addition reactions.

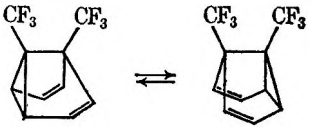
Photosensitized Reactions of the 1,4 Adducts.—All of the 1,4 adducts are photochemically labile and rearrange efficiently (quantum yield, 1)[3] in the presence of a high energy sensitizer (>60 kcal/mol). The product mixtures are generally complex and difficult to separate. However, in the case of **1**, the benzophenone-sensitized reaction produces a mixture of three products, as detected by glpc, in the approximate ratio of 4:2:1. The second major product has a much longer retention time and can be easily isolated by preparative glpc, while the remaining two products can be isolated only after repeated glpc separation.

All three compounds are colorless liquids. Their structures can be deduced from their nmr spectra and also by analogy with the known rearrangement of the parent bicyclo[2.2.2]octa-2,5-7-triene, **6**.[4] The pmr spectrum of the second major product (Figure 1a), having the longest retention time, consists of two peaks with some fine structures in a ratio of 2:1. The chemical shift of the major signal (4.72 ppm) has a value between those for tertiary and vinylic hydrogens normally observed for these compounds. This feature is reminiscent of that shown by compound **7**. The



6 **7**

product is therefore assigned the symmetrical structure **8**, existing as a rapidly fluctuating system. The sym-



8

metrical feature is also noted in the ^{19}F nmr spectrum,[5] which shows only a singlet at 3545 Hz (from $CFCl_3$).

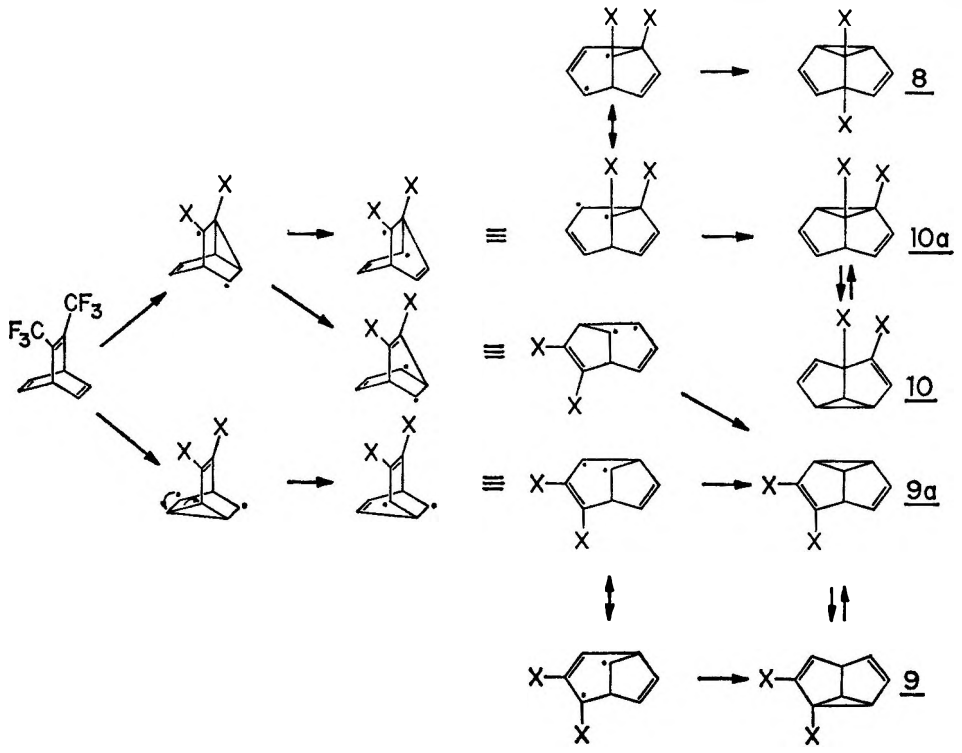
The pmr spectra of the two other products (Figure 1b and 1c) indicate their unsymmetrical structure.

(3) R. S. H. Liu and J. R. Edman, *J. Amer. Chem. Soc.*, **90**, 213 (1968).

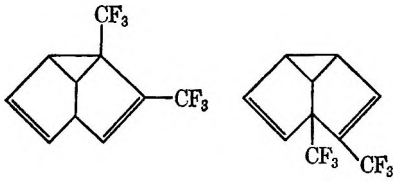
(4) H. E. Zimmerman and G. L. Grunewald, *ibid.*, **88**, 183 (1966).

(5) Attempts to retard the dynamic equilibrium by scanning the sample at low temperature (−100°) failed. In our most extreme experiment a frozen propane solution of **8** was placed in the nmr probe. On warming, the ^{19}F spectrum, observable as soon as the sample began to thaw, was identical with the room temperature signal.

SCHEME III
COMPLETE SCHEME OF REARRANGEMENT OF BIS(TRIFLUOROMETHYL)BICYCLO[2.2.2]OCTA-2,5,7-TRIENE (1).



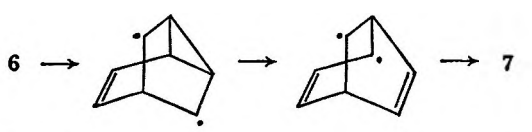
They have been assigned structures **9** and **10** for the following reasons. The spectrum of **9** (1b) shows three saturated protons appearing as an A_2M structure with the A_2 part further split into doublets. There are three vinyl protons with two strongly coupled. The coupling constant (J = 5.7 Hz) suggests that they are both in a five-membered ring.[6] The ^{19}F spectrum shows two overlapping quartets centered at 3639 Hz. These features agree with the structure **9**. Compound **10** is the one formed in the least amount, thus most



9 **10**

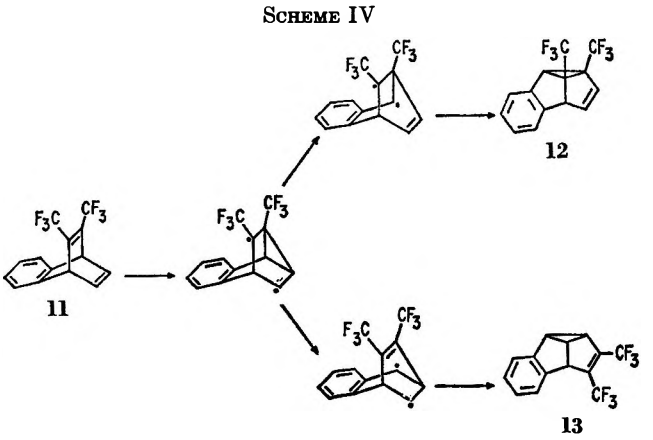
difficult to isolate. Its pmr spectrum (1c) again indicates the presence of three saturated hydrogen and three different vinyl protons. The ^{19}F spectrum shows two quartets at 3432 and 3954 Hz. Its structure is tentatively assigned as shown.

The mechanism of photosensitized rearrangement of bicyclo[2.2.2]octatriene, **6**, has been studied in detail by Zimmerman, *et al.*[7] Through labeling experiments, they showed that the pathway of rearrangement is that shown below. Following this mechanism, products **8**–**10** are indeed predicted from rearrangement of **1** (see Scheme III).[8] The absence of other products, *e.g.*, **9a** and **10a**, is probably due to their unfavorable energy content in comparison with their counter partners, compounds **9** and **10**, in the corresponding dynamic fluctuating equilibrium.



Other substituted 1,4 adducts were also found to undergo facile photosensitized rearrangements. The product mixtures were generally complex. In no case was isolation of product followed by definitive structural assignment possible. However, irradiation of the closely related compound **11** in the presence of acetophenone yielded two products, **12** and **13**, in a ratio of 9:1 (Scheme IV). The products, **12**, a colorless liquid,

SCHEME IV



and **13**, a low-melting solid, were isolated by preparative glpc. The pmr spectrum of the major product shows five groups of signals. Two high-field protons

(6) O. L. Chapman, *J. Amer. Chem. Soc.*, **85**, 2014 (1963); G. V. Smith and H. Kriloff, *ibid.*, **85**, 2017 (1963); P. Laszlo and P. von R. Schleyer, *ibid.*, **85**, 2018 (1963).

(7) H. E. Zimmerman, R. W. Binkley, R. S. Givens, and M. A. Sherwin, *ibid.*, **89**, 3932 (1967).

(8) We are grateful to Professor Howard Zimmerman for first pointing this out, and also communicating the results of his group to us prior to publication.

TABLE II

ASSIGNMENTS OF NMR SPECTRA OF 1,4 ADDUCTS[a]

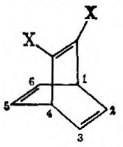
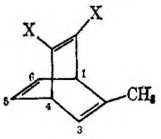
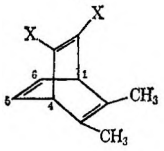
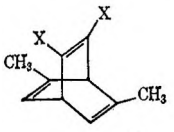
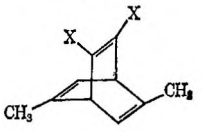
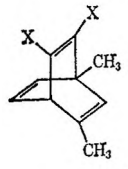
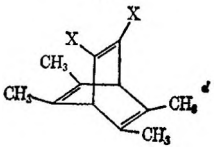
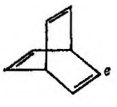
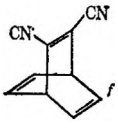
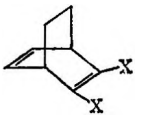
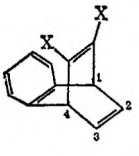
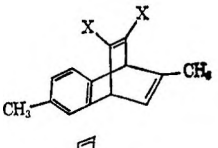
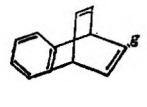
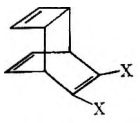
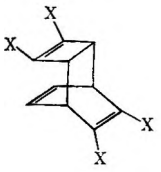
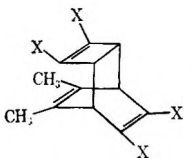
Compound (X = CF_3)	No.	Proton signal, structure (number of H)[b]			Fluorine signal,[c] $-CF_3$, Hz
		Methyl and methylene	Bridgehead	Olefinic and aromatic	
	1		5.08 m (2 H_1)	6.89 m (4 H_2)	3545
	19	1.90 d (3) (J = 1.8)	4.68 m (H_1) 4.90 m (H_4)	6.26 m (H_3) 6.85 sx (H_5, H_6)	3533
	20	1.77 s (6)	4.63 sx (2H_1)	6.80 sx (2 H_5)	3522
	21	1.93 d (6) (J = 1.8)	4.34 t (H_1) (J = 1.8) 4.73 t (H_4) (J = 5.8)	6.28 m (2 H_3)	3516
	22	1.90 d (6) (J = 1.6)	4.52 d,d (2 H_1) (J = 5.7, 1.7)	6.27 m (2 H_3)	3521
	23	1.91 s (3) 1.91 d (3) (J = 1.8)	4.67 m (H_4)	5.97 m (H_2) 6.52 d,d (H_6) (J = 6.5, 1.8) 6.82 t (H_5) (J = 6.2)	3349 (J = 11) 3398
		1.79 s (12)	4.23 s (2 H_1)		
			4.69 (2)	6.64 (6)	
			5.1 (2)	6.9 (4)	
	2	1.46 t (4) (J = 0.9)	4.05 broad (2)	6.38 sx (2)	3496
	11		5.17 sx (2 H_1)	7.23 sx (2 H_2) 6.8–7.1 m (4 H)	3516
	24	1.99 d (3) (J = 1.7) 2.21 s (3)	4.77 m (1 H_1) 4.97 d (1 H_4) (J = 5.8)	6.34 m (1 H_3)	
			4.62 m (2)	6.80 sx (4)	

TABLE II
(*Continued*)

Compound (X = CF_3)	No.	Proton signal structure (number of H)[b] Methyl and methylene	Bridgehead	Olefinic and aromatic	Fluorine signal[c] $-CF_3$, Hz
	17		2.69 m (2) 3.85 m (2)	6.06 s (2) 6.11 sx (2)	3489
	16		2.92 m (2) 4.10 m (2)	6.30 sx (2)	3491 3504
	18	1.79 s (6)	2.88 broad (2) 3.73 broad (2)		3504 3685

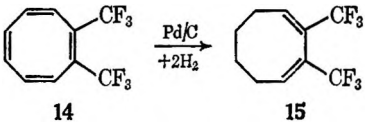
[a] All taken in CCl_4 unless specified, on A-60. [b] Tetramethylsilane as internal standard; chemical shift reported in parts per million (J = Hz): s, singlet; d, doublet; t, triplet; sx, sextet; m, multiplet; coupling constant in hertz. [c] $CFCl_3$ as internal standard; fluorine chemical shift reported in hertz upfield; taken on A-56. [d] Reference 2a. [e] Reference 4. [f] In $CDCl_3$: E. Ciganek, *Tetrahedron Lett.*, 3321 (1967). [g] R. G. Miller and M. Stiles, *J. Amer. Chem. Soc.*, **85**, 1798 (1963).

appear as a singlet at 4.07 and a doublet (J = 2.3 Hz) at 4.35 ppm. Two coupled vinyl protons (J = 5.5 Hz) appear at 5.27 and 5.84 ppm, with the lower field one further splitting into doublets (J = 2.4 Hz), and four aromatic protons appear as a complex multiplet between 7.0 and 7.5 ppm. The coupling constant of the vinyl protons and the presence of one unique proton at 5.27 ppm agree with the structure 12. The ^{19}F spectrum shows two coupled quartets (J = 8 Hz) centered at 3568 and 3725 Hz. The pmr spectrum of the minor compound shows a complex group of signals between 2.8 and 3.7 ppm (3 H), a doublet (J = 6 Hz) at 4.23 ppm, and signals for four aromatic protons between 7.1 and 7.5 ppm. The lack of signals in the regions for vinyl protons is most indicative of the structure. The ^{19}F spectrum shows two quartets (J = 8 Hz) at 3186 and 3501 Hz, the higher field quartet further splitting into doublets (J = 0.9 Hz). Based on this evidence, we have assigned the structure of **13** as shown.

The photosensitized rearrangement of compounds analogous to **11** has recently been reported.[9,10] It is interesting to note that products **12** and **13** are again predicted by the mechanism suggested by Zimmerman, *et al.*, in their study of the labeled parent hydrocarbon of **11**.[8,10]

Photoaddition of Perfluorobutyne to Aromatic Compounds in the Vapor Phase.—When a mixture of benzene and PFB vapor is irradiated in a Vycor tube with 2537-Å light, slow formation of at least eight compounds could be detected by glpc. Although the relative amounts of the minor products appear to vary from run to run and depend upon the irradiation period, the two major products usually comprise approximately 40 and 25%, respectively, of the product mixture. They have been isolated by preparative glpc.

The major product is a colorless liquid. Molecular weight measurement and elemental analysis indicate that it is a 1:1 adduct. Its pmr spectrum shows two singlets at 6.73 and 6.0 ppm with relative intensity 2:4, and it exhibits uv absorption with λ_{max} at 265 mμ (ϵ 700). These data agree with the structure 1,2-bis(trifluoromethyl)cyclooctatetraene, **14**. On hydrogenation over palladium/charcoal, **14** readily absorbs 2 mol of H_2 to give a compound of which the spectroscopic data agree with the structure of 2,3-bis(trifluoromethyl)-1,3-cyclooctadiene, **15**. This hydrogenation result is surprising, though not without precedent. Bryce-Smith, *et al.*, observed that cyclooctatetraene-1,2-dicarboxylic acid on hydrogenation absorbs 2 mol of H_2 to give a product[11] analogous to **15**. The second major product (25%) was shown to be identical with **9**, obtained from rearrangement of **1**. Among the minor products, compounds **8** and **10** have also been detected in relative yields of approximately 12 and 5%.



14 **15**

It is interesting to note that **1**, the 1,4 adduct, was as expected[12] not present in the product mixture. Further, that the relative amounts of **8**, **9**, and **10** obtained in this experiment are different from those from rearrangement of **1** clearly indicates that their formation does not involve the intermediacy of **1**.

(9) J. P. N. Brewer and H. Henry, *Chem. Commun.*, 811 (1967).
(10) H. E. Zimmerman, R. S. Givens, and R. M. Pagni, *J. Amer. Chem. Soc.*, **90**, 4191 (1968).
(11) D. Bryce-Smith and J. E. Lodge, *J. Chem. Soc.*, 695 (1963).
(12) A symmetry forbidden product: R. Hoffman and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 2046 (1965).

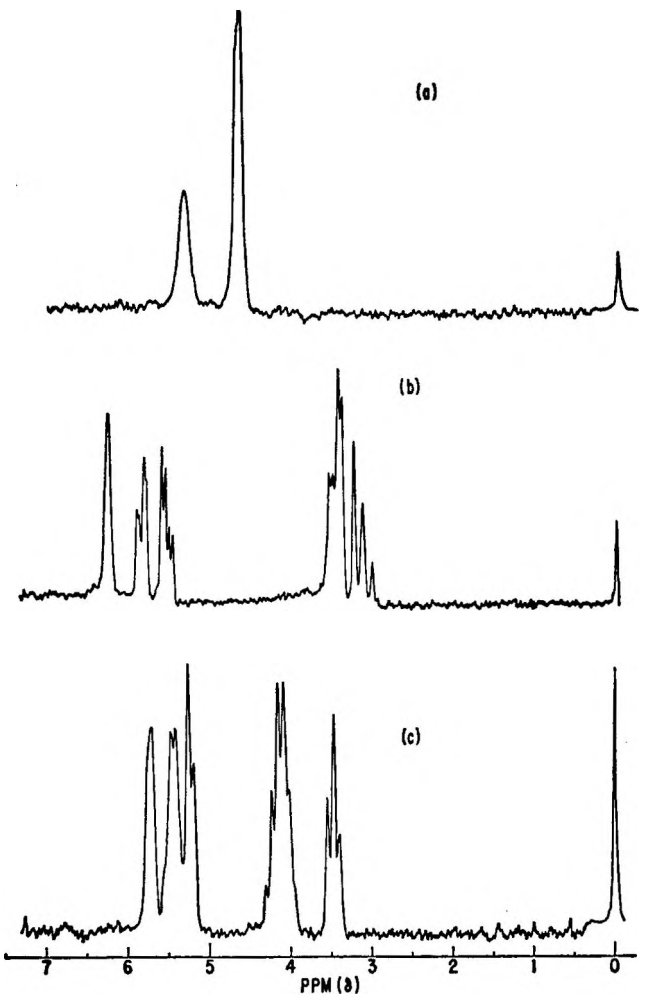
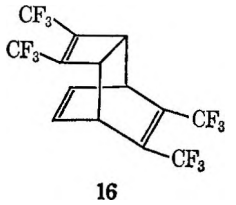


Figure 1.—60-MHz pmr spectra of compounds **8** (upper), **9** (middle), and **10** (lower).

When benzene analogs were irradiated with PFB in the vapor phase, very complex reaction mixtures were obtained. The addition reactions were probably complicated by side reactions involving loss of hydrogen atom from the aromatic compounds. No attempts were made to identify products.

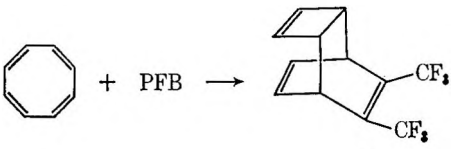
In Solution.—Adducts can also be obtained in low conversion on prolonged irradiation of a solution of benzene and PFB. The major product (73% relative yield) is a white solid, mp 110–111°. Elemental analysis and molecular weight suggest the molecular formula, $C_{14}H_6F_{12}$, a 2:1 adduct containing 2 mol of PFB. The mass spectrum has, besides the parent peak, a characteristic peak at 188, corresponding to $C_6H_2F_6$, possibly a bis(trifluoromethyl)cyclobutadiene fragment. The compound is therefore assigned the structure **16**. Nmr



16

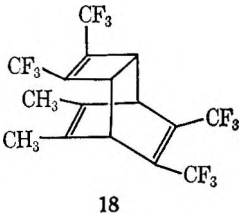
and ir data agree with the assignment. Among the minor products are **8** and **14** in relative amounts of 9 and 14%.

The formation of the 2:1 adduct is analogous to photochemical addition of benzene to maleic anhydride[13] and maleimide,[14] but differs from the addition of benzene to other acetylene compounds, where 1:1 adducts, the corresponding cyclooctatetraenes, were the only products.[15] However, based on the results of addition of PFB to cyclooctatetraene, it is likely that product **16** results from thermal addition of PFB to bis(trifluoromethyl)cyclooctatetraene.



17

Irradiation of PFB with other benzenoid compounds gave complex mixtures. No extensive effort was made to identify most products. However, in the case of *o*-xylene, a white solid was also obtained. Its spectroscopic properties show that it is an analogous 2:1 adduct, **18**.



18

Experimental Section

Thermal Addition of Benzene to Perfluorobutyne (PFB).—To a 400-ml high-pressure shaker tube was added 220 ml of benzene. After being cooled (−78°) and evacuated, the tube was charged with 25 g (0.15 mol) of PFB (Peninsular Chemical). The tube was heated under autogenous pressure at 180° for 20 hr. The net decrease of pressure inside the tube was 20 psi. The yellowish product was distilled under atmospheric pressure. The fraction boiling at 32–39° (0.85 g) contained mostly *cis*-1,1,1,4,4,4-hexafluoro-2-butene, identified by its nmr spectrum. The next fraction contained only unreacted benzene. The pot residue, after concentration to approximately 40 ml, was distilled under vacuum. The fraction (5.6 g) boiling at 98–99° (210 mm) was collected. Analysis by glpc (silicon nitrile column) showed that it was a mixture of three components in an approximate ratio of 1:2:5. These were separated by preparative glpc. The minor product, mp 71.5–73°, was 1,2,4,5-tetrakis(trifluoromethyl)-benzene (0.45 g, 1.7% yield), identified by melting point and nmr[16] and ir spectra. The major product, **1** (2.3 g, 6.6% isolated yield), a colorless liquid, was eluted next: uv (cyclohexane) λ_{max} 262 mμ (ε 144), shoulder at 220 (278).

Anal. Calcd for $C_{10}H_6F_6$: C, 50.01; F, 47.48; H, 2.52; mol wt, 240. Found: C, 49.58; F, 46.98; H, 2.65; mol wt, 240.[17]

The last product eluted was 1,2-bis(trifluoromethyl)benzene.

The pot residue solidified on standing. Recrystallization from methanol gave 7.8 g (23% yield) of 2,3,6,7-tetrakis(trifluoromethyl)naphthalene, mp 172.5–173.5°.

Reaction of 1,3-Cyclohexadiene with PFB.—A mixture of 1,3-cyclohexadiene (12 g) and PFB (26 g, 0.15 mol) was heated at 100° for 6 hr in a sealed tube in the presence of 0.15 g of hydroquinone. The yellowish product was distilled, and the fraction

(13) H. J. F. Angus and D. Bryce-Smith, *Proc. Chem. Soc.*, 326 (1959); G. O. Schenck and R. Steinmetz, *Tetrahedron Lett.*, 1 (1960); E. Grovenstein, D. V. Rao, and J. W. Taylor, *J. Amer. Chem. Soc.*, **83**, 1705 (1961).

(14) D. Bryce-Smith and M. A. Hems, *Tetrahedron Lett.*, 1895 (1966); J. S. Bradshaw, *ibid.*, 2039 (1966).

(15) See, *e.g.*, G. Schröder, "Cyclooctatetraene," Verlag Chemie, Weinheim, Germany, 1965, p 6.

(16) The nmr spectra of the cycloadducts are described in Table II.

(17) All molecular weights were determined by mass spectrometry.

boiling at 53–55° (20 mm), 16.7 g, 58%, contained the expected bicyclooctadiene, **2**.

Anal. Calcd for $C_{10}H_8F_6$: C, 49.59; H, 3.33; F, 47.08. Found: C, 49.43; H, 3.28; F, 47.48.

Hydrogenation of 2.—A solution of 2.0 g of the bicyclooctadiene in methanol (50 ml) containing a catalytic amount of palladium/charcoal was shaken under H_2 until the uptake stopped (~1 hr). The solution was filtered and extracted with 50 ml of petroleum ether and 50 ml of water. The organic layer was washed twice with water and dried over sodium sulfate. The solvent was evaporated leaving 1.34 g (66%) of **3**, a colorless liquid. Elemental analysis and nmr data showed that only 1 equiv of H_2 was absorbed.

Anal. Calcd for $C_{10}H_{10}F_6$: C, 49.18; H, 4.13; F, 46.69. Found: C, 49.82; H, 4.17; F, 46.92.

Hydrogenation of 1.—A methanol solution of 2.0 g of a 50:50 mixture of benzene and the bicyclooctatriene was subjected to catalytic (palladium/charcoal) hydrogenation. The product mixture was shaken with petroleum ether/water. Glpc analysis of the petroleum ether layer showed complete disappearance of the triene and the formation of one new product. The product was isolated from the petroleum ether layer by preparative glpc. Ir and nmr spectra of the product are identical with those of **3**, prepared previously.

Thermal Addition of Toluene to PFB.—A mixture of 220 ml of toluene and 16 g (0.1 mol) of PFB was used (Table I). The reaction mixture, after concentration to 25 ml by distillation under atmospheric pressure, was vacuum distilled. The fraction boiling at 66–67° (26 mm), 4.3 g, was found to contain essentially pure 2,3-bis(trifluoromethyl)-5-methylbicyclo[2.2.2]octa-2,5,7-triene, **19**: uv (*n*-hexane) λ_{max} 268 mμ (ε 170), 232 (350).

Anal. Calcd for $C_{11}H_8F_6$: C, 51.98; H, 3.17; F, 44.85. Found: C, 51.96; H, 3.56; F, 45.52.

A second fraction, bp 67–71° (26 mm), 1.9 g, was also obtained which contained (by nmr) approximately 50% bicyclic compound. No attempts were made to identify other products. However, the nmr spectrum of the mixture showed that the isomeric 1-methyl-2,3-bis(trifluoromethyl)bicyclo[2.2.2]octa-2,5,7-triene was not present in significant amounts.

Thermal Addition of *o*-Xylene to PFB.—A mixture of 40 ml of *o*-xylene and 33 g (0.2 mol) of PFB was used. The reaction mixture was distilled under vacuum, and the fraction of bp 52–55° (7 mm) (with major portion at 54–55°) was collected. Gc analysis (6-ft 20% TCEP column, 120°) showed that the mixture contained approximately 37% unreacted xylene, and the desired 1,4 adduct. The adduct (13.3 g, 21%) was isolated by preparative glpc, and its nmr spectrum agrees with the structure **20**: uv (cyclohexane) λ_{max} 275 mμ (ε 91), 230 (shoulder) (350).

Anal. Calcd for $C_{12}H_{10}F_6$: C, 53.74; H, 3.76; F, 42.51; mol wt 268. Found: C, 53.96; 53.74; H, 3.79, 3.74; F, 44.36, 43.45; mol wt, 268.

No extensive effort was made to identify other minor products. However, 1,2-bis(trifluoromethyl)benzene was found to be the second major product.

Thermal Addition of *p*-Xylene to PFB.—A mixture of *p*-xylene (220 ml), and PFB (29 g, 0.18 mol) was used. Glpc analysis (6-ft TCEP column 100°), showed the presence of one new product. The solution was concentrated to ~60 ml by distillation, and the yellow residue was distilled under vacuum. Three fractions [38–46, 46–50.5, and 50.5–52.5° (7.7 mm)] were collected which contained 60, 80, and 98%, respectively, of the 1,4 adduct, giving a total yield of 57% 2,3-bis(trifluoromethyl)-5,7-dimethylbicyclo[2.2.2]octa-2,5,7-triene, **22**: uv (*n*-hexane) λ_{max} 272 mμ (ε 109), 226 (334).

Anal. Calcd for $C_{12}H_{10}F_6$: C, 53.74; H, 3.76; F, 42.51. Found: C, 53.47; H, 3.87; F, 42.66.

Thermal Addition of *m*-Xylene to PFB.—A mixture of *m*-xylene (220 ml) and PFB (29 g, 0.18 mol) was used. Glpc analysis (6-ft TCEP column, 120°) showed two major new products. The reaction mixture was vacuum distilled, and two fractions were collected: one of bp 53–54° (1.6 mm), 4.3 g; and one of bp 54–55° (1.6 mm), 1.9 g. These contained essentially all of the desired 1,4 adducts plus some unreacted xylene. Based on glpc, 2,3-bis(trifluoromethyl)-5,8-dimethylbicyclo[2.2.2]octatriene, **21**, the major product, was formed in 6.7% yield and 2,3-bis(trifluoromethyl)-1,5-dimethylbicyclo[2.2.2]octatriene, **23**, in 2.2% yield. Other minor products were not identified.

Thermal Addition of 1,2,4-Trimethylbenzene to PFB.—1,2,4-Trimethylbenzene (12 g, 0.10 mol) and 24 g (0.15 mol) of PFB was used. From the product mixture was isolated a 10% yield of 1,2-dimethyl-4,5-bis(trifluoromethyl)benzene, mp 39–40°, identified by mixture melting point and ir, and 0.3% methylbis(trifluoromethyl)benzene, probably the 1,3,4 isomer.

Anal. Calcd for $C_9H_6F_6$: C, 47.38; H, 2.65. Found: C, 47.88; H, 2.86.

Thermal Addition of Cyclooctatetraene to PFB.—A mixture of 20 g of cyclooctatetraene, 0.2 g of hydroquinone, and 32 g (0.2 mol) of PFB was heated at 120° in an 80-ml shaker tube for 6 hr. A net pressure drop of 50 psi was noted. The brownish reaction mixture was vacuum distilled. A forerun of 3.1 g of unreacted cyclooctatetraene was recovered. The fraction of bp 56–56.5° (4.8 mm) was the 1:1 adduct **17**, 20.1 g (52% yield).

Anal. Calcd for $C_{12}F_6H_8$: C, 54.15; H, 3.02; F, 42.83. Found: C, 54.42; H, 2.98; F, 42.73.

Photosensitized Rearrangement of 1.—A deoxygenated benzene solution (100 ml) of the bicyclooctatriene (5.0 g) in a Pyrex immersion apparatus with benzophenone (0.2 g) as photosensitizer was irradiated with a Hanovia medium-pressure mercury lamp (200 W). The course of the reaction was followed by glpc analysis (3-ft silicone GE XE-60 column, 100°). Three products were detected almost immediately after irradiation was started. The reaction was complete within 1 hr.

The three products formed in the ratio of 4:1:2 (in the order of retention time) could be separated only by preparative glpc. The first two compounds, **9** and **10**, failed to separate cleanly; thus, the minor compound **10** was difficult to obtain in high purity. Compound **8**, with the longest retention time, was easily isolated. Structure assignments were based on spectroscopic information (see discussion).

The rearrangement can be sensitized efficiently with any sensitizer with energy greater than 60 kcal/mol, *e.g.*, benzophenone, anthraquinone, triphenylene, acetophenone, and xanthone. The relative amounts of the three products were not dependent upon sensitizer.

Photosensitized Reaction of 11.—An ether solution (120 ml) of the benzobicyclooctatriene (10.0 g) and 1.0 g of acetophenone in a Pyrex well was irradiated with a 450-W Hanovia lamp. Reaction was followed by glpc analysis (6-ft 20% silicon column, 150°). After 2 days the reaction was complete. Ether was evaporated and the residue was vacuum distilled at 99–101° (9.2 mm) yielding a mixture of compound **12** and **13** (55%). They were separated by preparative glpc.

Anal. Calcd for $C_{14}H_8F_6$: C, 57.94; H, 2.78; F, 39.28. Found for **12**: C, 58.18; H, 2.79; F, 39.96. Found for **13**: C, 57.61; H, 2.85; F, 40.54.

The relative amounts of **12** and **13** (9:1) do not depend on irradiation period. They can be sensitized only with sensitizers of energy greater than 70 kcal/mol. Benzophenone, therefore, failed to sensitize the reaction. With acetophenone, prolonged irradiation reduced the yield, probably owing to reaction of sensitizer with products.

Photochemical Addition of Benzene to PFB. A. In the Vapor Phase.—A mixture of 20 g of benzene and 15.2 g of PFB was sealed under vacuum (1 mm) in a large Vycor tube (18 × 2.5 in.). The lower portion of the tube was covered with black tape so that light did not reach the solution directly. The tube was placed in the Srinivasan-Griffin reactor and irradiated with low pressure mercury lamps. After 3 days the solution began to turn slightly yellow and small amounts of polymeric material began to coat the tube. Irradiation was continued for a total of 7 days. Unreacted butyne was removed by distillation, and the benzene solution of the product mixture was concentrated by distillation under vacuum to approximately 5 ml, containing 50% benzene.

Preparative gc (Carbowax 20M column) was used for separation of the product mixture. At least eight peaks were detected. The three major components (40, 25, and 12%) were isolated. The major product (40%), **14**, was a colorless liquid: uv (cyclohexane) λ_{max} 265 mμ (ε 700).

Anal. Calcd for $C_{10}H_6F_6$: C, 50.01; H, 2.52; F, 47.47; mol wt, 240. Found: C, 50.22; H, 2.70; mol wt, 240.

The second major product (25%) was also a colorless liquid and identical with **9**, a photorearranged product of **1**: uv (cyclohexane), no absorption maxima, ≥220 mμ.

Anal. Found: C, 49.56, 50.25; H, 2.53, 2.69; F, 46.80; mol wt, 240.

The third major product, a colorless liquid, was identical with **4**, the major photorearranged product from **1**.

Anal. Found: C, 49.37; H, 2.65; F, 47.57; mol wt, 240.

B. In Solution.—A deoxygenated solution of 2 ml of benzene and 8 ml of PFB was irradiated in a sealed quartz tube (15 × 180 mm) for 3 days. The solution turned slightly yellow. Unreacted PFB was removed by distillation and the residual benzene solution was analyzed by gc. A mixture of compounds similar to that obtained in the vapor phase was found, but, in different relative amounts and the conversion was low (~5%). Three products are predominant (73, 14, and 9%). The two minor ones (14 and 9%) have retention times identical with those of **9** and **14**. Evaporation of the solution gave a yellow crystalline residue. After one recrystallization from methanol, 150 mg of a white crystalline solid, **16**, mp 110–111°, was obtained.

Anal. Calcd for $C_{14}H_8F_{12}$: C, 41.81; H, 1.50; F, 56.69; mol wt, 402. Found: C, 42.10, 42.43, 42.50; H, 1.38, 1.88, 1.74; F, 55.49; mol wt, 402.

Hydrogenation of 9.—A sample of 0.1037 g of the cyclooctatetraene in ethanol was hydrogenated over palladium/charcoal. Rapid uptake of H_2 was observed, and the reaction was complete after 14 min; 0.0175 g H_2 was absorbed (2.08 mol equiv).

From a separate preparative hydrogenation run, a pure sample of the hydrogenated product, **3**, was obtained by gc separation (5-ft Carbowax column): ^1H nmr (CCl_4), a triplet centered at 6.67 (J = 8.0 Hz) (2 H) and complex multiplets between 0.9 and 2.6 ppm (8 H); ^{19}F nmr (CCl_4), a singlet at 3656 Hz; uv (methanol), no maxima above 220 mμ, 218 (ε 2.0 × 10⁴), 225 (1.1 × 10⁴).

Anal. Calcd for $C_{10}H_{10}F_6$: C, 49.18; H, 4.13; F, 46.69. Found: C, 49.42; H, 4.04; F, 47.57.

Photochemical Addition of *o*-Xylene to PFB.—A sealed quartz tube containing 8 ml of *o*-xylene and 1 g of PFB was irradiated with 2537-Å light for 5 days. Glpc analysis of the yellowish irradiation solution showed the formation of at least three new products in low yield. One major component isolated by glpc (silicone X-60 column) was a white solid, mp 72–73°, mol wt 430, thus in agreement with the formula $C_{16}H_{10}F_{12}$ (compound **18**).

Registry No.—PFB, 692-50-2; **1**, 781-13-5; **2**, 19640-15-4; **3**, 19640-16-5; **8**, 19640-17-6; **9**, 19640-18-7; **10**, 19640-19-8; **11**, 1580-25-2; **12**, 19640-21-2; **13**, 19640-22-3; **14**, 19640-23-4; **16**, 19640-24-5; **17**, 19640-25-6; **18**, 19640-26-7; **19**, 19669-17-1; **20**, 1554-49-0; **21**, 19640-28-9; **22**, 19640-29-0; **23**, 19640-30-3; **24**, 19640-31-4; 1,2,4,5-tetrakis(trifluoromethyl)benzene, 320-23-0; 2,3,6,7-tetrakis(trifluoromethyl)naphthalene, 2559-74-2.

Fluorinated Cyanates and Isocyanates. A New Type of Rearrangement

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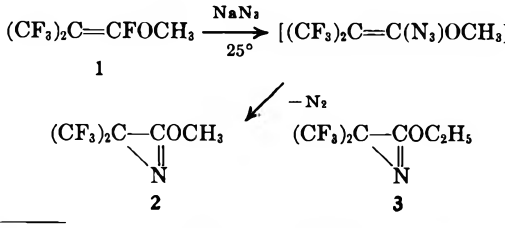
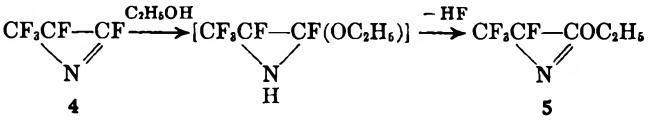
Three isomeric compounds, 2,2-bis(trifluoromethyl)-3-methoxy-2H-azirine (**2**), α-methylhexafluoroisopropyl cyanate (**12**), and α-methylhexafluoroisopropyl isocyanate (**7**), have been prepared. While the normal isomerization of cyanate **12** to isocyanate **7** did not occur, the novel rearrangement of azirine **2** to isocyanate **7** proceeded readily at 95°. α-Phenylhexafluoroisopropyl cyanate did rearrange, but with migration of the isocyanate group to the benzene ring.

Alkoxyfluoroazirines.—Direct syntheses of fluoroazirines starting from fluoro olefins and azide salts were examined earlier with unpromising results.[1] Best results were obtained by isolating the intermediate α,β-unsaturated azide and decomposing it in a separate second step, both in our work with hexafluoropropylene and triethylammonium azide[1] and in other work with sodium azide.[2]

A successful one-step synthesis has now been accomplished starting with a fluoro olefin containing only one readily replaceable halogen and employing diglyme–water as solvent. Reaction of methyl 1,3,3,3-tetrafluoro-2-(trifluoromethyl)propenyl ether (**1**) with sodium azide at 0–25° gave an 11% isolated yield of 2,2-bis(trifluoromethyl)-3-methoxy-2H-azirine (**2**). Azirine **2** is much less reactive than the related perfluoroazirines, particularly in its stability toward polymerization and addition of active hydrogen compounds. This lowered reactivity accounts for the ability of **2** to survive in part the reaction conditions. Azirine **2** does exhibit the expected[1] ir absorption for fluoroazirine C=N at short wavelength (5.48 μ).

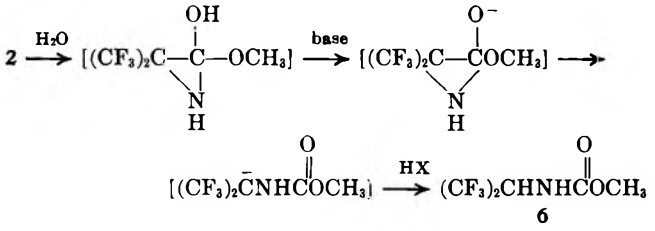


The ethoxy compound **3** corresponding to **2** may have been the product obtained in unspecified yield by Knunyants and Bykhovskaya from sodium azide and octafluoroisobutylene in ethanol solution, although the ir band for C=N is indicated to be at 5.80 μ.[3] Azetene structures have been proposed by these workers for several such compounds, including **3** and **4**, structures which have not been confirmed in separate work.[1,2] Another product, derived by Knunyants and Bykhovskaya from the compound now known to be azirine **4**, can also be assigned one of two isomeric ethoxyazirine structures (probably **5**) rather than an azetene structure. Formation of **5** by addition of ethanol to the C=N bond and elimination of HF is in accord with known additions of other active hydrogen compounds to **4**.[1]



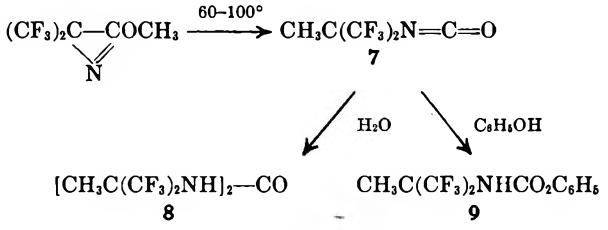
A similar addition of water across the azirine C=N in **2** is indicated in the present work by the isolation of carbamate **6** as a by-product. The actual step of cleavage of the ring occurs at the carbon–carbon bond, and must be facilitated by the ability of the *gem*-trifluoromethyl groups to stabilize a negative charge. This mode of ring scission is abnormal for unfluorinated azirines and is also different from that postulated by

(1) C. S. Cleaver and C. G. Krespan, *J. Amer. Chem. Soc.*, **87**, 3716 (1965).
(2) R. E. Banks and G. J. Moore, *J. Chem. Soc.*, 2304 (1966).
(3) I. L. Knunyants and E. G. Bykhovskaya, *Proc. Acad. Sci. USSR, Chem. Sect.*, **131**, 411 (1960).



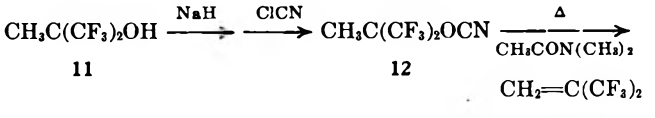
Banks and Moore to occur during hydrolysis of azirine **4**. In the latter case a carbon–nitrogen bond was said to be broken,[2] just as it is with unfluorinated azirines.

Isomerization of Azirine 2.—Synthesis of **2** under aprotic conditions, *i.e.*, in diglyme, to avoid hydrolysis reactions resulted in an increased yield of crude product. However, an attempt to purify this material by careful fractionation resulted in steady generation of a new, lower boiling product, **7**. Prolonged reflux resulted in 20% purified **7**, identified as the isocyanate by chemical and spectral methods. Reaction of **7** with water gave urea **8** and with phenol gave urethan **9**.



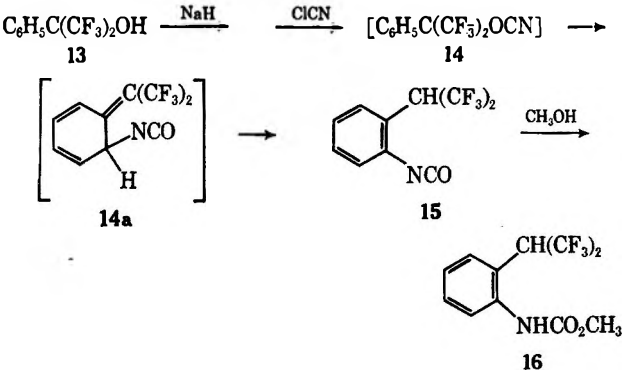
Fluorinated Cyanates.—A more conventional route to isocyanates such as **7** might be through the corresponding cyanates. Alkyl cyanates rearrange and trimerize readily and members of this class have only recently been isolated.[4] However, negative substituents on the alkyl moiety tend to stabilize cyanates, so that Grigat and Pütter[5] were able to prepare 2,2,2-trifluoroethyl cyanate (**10**) directly from 2,2,2-trifluoroethanol and cyanogen chloride in 80% yield. No details were given, but the stability of **10** to heat was apparently good. Alcohols containing two α-trifluoromethyl groups are readily obtained from hexafluoroacetone;[6] reactions of sodium salts of two of these fluoro alcohols with cyanogen chloride were carried out in attempts to prepare the corresponding cyanates.

2-Methylhexafluoro-2-propanol (**11**) was converted into the sodium salt with sodium hydride and treated with cyanogen chloride to give α-methylhexafluoroisopropyl cyanate (**12**) in 80% yield. Cyanate **12** is unchanged after 6 hr at reflux (95°), confirming the stabilizing effect of α-trifluoromethyl groups in an alkyl cyanate.



Isomerization of cyanate to isocyanate is promoted by ionizing conditions;[7] so cyanate **12** was heated in dimethylacetamide. Ionization and recombination to isocyanate were not observed; instead, dissociation to 1,1-bis(trifluoromethyl)ethylene and a solid presumably derived from cyanic acid was promoted by the polar medium. Difficulty in generating from **12** a carbonium ion flanked by negative trifluoromethyl groups may favor the nearly exclusive occurrence of an elimination reaction by the less ionic E2 mechanism. A similar formation of olefin is reported to be the predominant reaction on thermolysis of even simple secondary alkyl cyanates.[8]

In order to forestall the elimination reaction and promote ionization, a benzylic alcohol was used. 2-Phenylhexafluoro-2-propanol (**13**) was converted into its toluene-soluble sodium salt and treated with cyanogen chloride. Although cyanate **14** may have been present as a higher boiling impurity, the major product (41%) obtained by distillation was *o*-(2H-perfluoroisopropyl)-phenyl isocyanate (**15**). The identity of **15** was established by its ir and nmr spectra, and by conversion into carbamate **16**.



The unusual rearrangement **14** → **15** may be another manifestation of the negativity of the trifluoromethyl groups, in that an essentially concerted and hence nonionic rearrangement to **14a** is favored over the normal ionization–recombination mechanism.

Mass Spectral Results.—The rearrangement **2** → **7** appears to be without precedent. Although 1,4 shifts with ring openings have been observed recently with aziridine derivatives,[9] these saturated rings cleaved at the carbon–nitrogen bond. In order to detect any correlation between thermally induced reactions and bond cleavage under electron bombardment, the mass spectra of azirine **2** and its isomers **7** and **12** were taken. At least a rough correlation is evident.

For azirine **2**, the mass spectrum showed major fragments resulting from cleavage of methyl and from loss of two difluoromethylene groups with the loss of methyl. The only major peak not necessarily involving loss of methyl is that for trifluoromethyl cation. The mass spectrum for isocyanate **7**, on the other hand, contained minor peaks for loss of methyl. The predominant fragmentations involved instead cleavage of trifluoromethyl and loss of difluoromethylene with the loss of trifluoromethyl. No peaks for direct loss of NCO were observed. Peaks involving cleavage of NCO dominate the mass spectrum of cyanate **12**, indicating the expected lower stability in the C–OCN bond in **12** compared with the C–NCO bond in **7**. However, loss of trifluoromethyl and to some extent of methyl occurs as well, so that several modes of fragmentation are available.

(4) For a review of this chemistry, see E. Grigat and R. Pütter, *Angew. Chem. Intern. Ed. Engl.*, **6**, 206 (1967).
(5) E. Grigat and R. Pütter, *Chem. Ber.*, **97**, 3012 (1964).
(6) C. G. Krespan and W. J. Middleton, *Fluorine Chem. Rev.*, **1**, 145 (1967).
(7) J. C. Kauer and W. W. Henderson, *J. Amer. Chem. Soc.*, **86**, 4732 (1964).
(8) K. A. Jensen, M. Due, and A. Holm, *Acta Chem. Scand.*, **19**, 438 (1965).
(9) D. A. Tomalia and E. C. Britton, *Tetrahedron Lett.*, 2559 (1967).

Experimental Section[10]

2,2-Bis(trifluoromethyl)-3-methoxy-2H-azirine (2).—A mixture of 42.4 g (0.20 mol) of methyl 1,3,3,3-tetrafluoro-2-(trifluoromethyl)propenyl ether (1)[11] and 100 ml of glyme was stirred magnetically in a 500-ml flask fitted with a side-arm dropping funnel and a condenser with wet-test meter attached. The mixture was held at −5 to 0° in an ice-water–acetone bath while a solution of 19.5 g (0.3 mol) of sodium azide in 75 ml of water was added dropwise over a 40-min period. The mixture was stirred another 1.5 hr at 0°, after which time 1.5 l. of gas had been evolved. Stirring was continued while the mixture was allowed to warm to 25°. After a total of 15 hr, 6.0 l. of gas had been evolved (without correction for expansion due to warming). The reaction mixture was diluted with 500 ml of water, and the lower layer was separated, washed with two 250-ml portions of water, dried, and distilled. A little ether was added to codistill with any hydrazoic acid which might have formed. Azirine 2 was obtained as 4.6 g (11%) of colorless liquid, bp 42–43° (80 mm). A sample was purified for analysis by glpc on a di(2-ethylhexyl) sebacate column at 75°: n^{25}D 1.3058; ir 3.29 and 3.36 (CH), 5.48 (ring C=N), and 6.85 and 6.95 μ (weak, small ring and/or CH_3 bond); nmr (neat), H′ at τ 5.72 (singlet, CH_3); ^{19}F (external reference) at 70.8 ppm (singlet, CF_3); mass spectrum (relative intensity), 207 (0.02), 192 (70), 188 (7), 173 (16), 154 (18), 142 (100), 110 (13), 92 (54), 76 (7), 69 (59), 50 (7), 43 (6), 31 (14), 29 (14), 15 (68).

Anal. Calcd for $C_5H_3F_6NO$: C, 29.00; H, 1.46; F, 55.05; N, 6.77; mol wt, 207. Found: C, 29.60; H, 1.81; F, 55.29; N, 7.18; mol wt, 207 (mass spectrum).

The residue from distillation of 2 was sublimed at 70° (70 mm) and recrystallized from trichlorofluoromethane at −80° to give 2.2 g (5%) of methyl N-(hexafluoro-2H-isopropyl)carbamate (6), mp 85–88° (subl). An analytical sample, mp 88–90° (subl), was obtained by resublimation at 70° (100 mm): ir (KBr) 3.05 (NH), 3.23 and 3.36 (CH), 5.84 (C=O), and 6.39 μ (amide); nmr ($CFCl_3$), H′ at τ 4.3 (broad, 1, NH or CH), 5.0 (broad, 1, NH or CH), and 6.27 (singlet, 3, CH_3); ^{19}F at 74.7 ppm [doublet, J_{FH} = 7 Hz, $(CF_3)_2CH$]; mass spectrum (relative intensity), 225 (3), 206 (8), 205 (13), 194 (12), 186 (11), 174 (34), 166 (8), 156 (100), 154 (26), 124 (22), 113 (8), 112 (16), 92 (15), 74 (20), 69 (34), 59 (87), 51 (5), 50 (5), 44 (9), 42 (15), 32 (16), 31 (50), 29 (13), 28 (35), 15 (83).

Anal. Calcd for $C_5H_3F_6NO_2$: C, 26.68; H, 2.23; F, 50.64; N, 6.22; mol wt, 225. Found: C, 26.95; H, 2.22; F, 50.26; N, 6.13; mol wt, 225 (mass spectrum).

Similar results were obtained from the reaction of sodium azide with the propenyl ether when carried out at 30–50° in methanol–water medium.

α-Methylhexafluoroisopropyl Isocyanate (7).—A mixture of 14.3 g (0.22 mol) of sodium azide, 42.4 g (0.20 mol) of ether 1, and 200 ml of diglyme was stirred at 25° while gas was slowly evolved. After 15 hr, 4.2 l. (89%) of gas (assumed to be nitrogen) had been evolved. Rough distillation of the reaction mixture up to 165° (1 atm) was used to separate the volatile products. Ir analysis of the crude distillate showed major bands at 5.45 (azirine 2) and 5.9 and weak bands at 4.45 (isocyanate 7) and 5.6 μ. Fractionation of the crude product in a spinning-band column, with very slow take-off since prolonged reflux was found to give rise to a low boiler, afforded 14.4 g of colorless liquid, bp 55–67° (a smaller amount of a mixture, bp 88–98°, was also obtained). Redistillation from P_2O_5 gave 8.4 g (20%) of isocyanate 7: bp 61–62°; ir 3.30 and 3.39 (CH), 4.43 μ (NCO); nmr (neat), H′ (external reference) at τ 8.58 (septet, J_{HF} = 1.1 Hz, CH_3); ^{19}F (external reference) at 79.6 ppm (quadruplet, J_{HF} = 1.1 Hz, CF_3); mass spectrum (relative intensity), 207 (0.1), 192 (7), 188 (7), 142 (12), 138 (100), 118 (5), 95 (7), 92 (35), 88 (59), 74 (10), 69 (42), 31 (7), 15 (8).

Anal. Calcd for $C_5H_3F_6NO$: F, 55.05; N, 6.77, mol wt, 207. Found: F, 55.14; N, 6.72; mol wt, 207 (mass spectrum).

A sample of 7 slowly picked up water on standing to form crystalline urea 8, which sublimed rapidly at ~200° without melting: ir (KBr) 3.00 (NH), 3.22 and 3.35 (CH), 5.94 μ (C=O), 6.35 (amide).

Anal. Calcd for $C_9H_8F_{12}N_2O$: F, 58.74; N, 7.22. Found: F, 58.68; N, 6.98.

Isocyanate 7 (1.50 g, 0.0072 mol) and phenol (0.75 g, 0.008 mol) remained immiscible on mixing at 25°. Addition of 5 ml of benzene gave a homogeneous solution, but no spontaneous warming to indicate reaction. Pyridine (3 drops) was added and the mixture was allowed to stand 2 days. Solvent was then evaporated, and the solid residue was recrystallized twice from petroleum ether (bp 30–60°) at 0° to give 1.3 g (60%) of carbamate 9: mp 45–46°; ir (KBr) 3.03 (NH), 3.25 (CH), 5.75 (C=O), 6.45 (amide), 6.27 and 6.69 μ (aromatic ring).

Anal. Calcd for $C_{11}H_9F_6NO_2$: C, 43.86; H, 3.01; F, 37.85; N, 4.65. Found: C, 44.20; H, 3.07; F, 37.87; N, 5.08.

α-Methylhexafluoroisopropyl Cyanate (12).—2-Methylhexafluoro-2-propanol (11) was prepared from an ether solution of 22 g (1.0 mol) of methyllithium (5.2% by weight) stirred at 0° in a flask fitted with a −80° condenser while 166 g (1.0 mol) of hexafluoroacetone was distilled in over 3 hr. Solvent was then distilled off and the residue was evacuated at 100 mm. Sulfuric acid (200 ml) was added dropwise and the product distilled. Redistillation afforded 165 g (91%) of 11, bp 61–62°.[12]

A slurry was prepared under dry N_2 from 9.9 g (0.22 mol) of 53% sodium hydride–mineral oil and 100 ml of *p*-xylene. A solution of 36.4 g (0.20 mol) of 11 in 50 ml of *p*-xylene was added dropwise to the stirred slurry over 1 hr. The mixture was heated and stirred at 90–100° for 30 min, after which time evolution of gas had ceased. The mixture was then cooled to 10° and stirred while 14 g (0.23 mol, 12 ml at 0°) of cyanogen chloride was distilled in. The ensuing exothermic reaction carried the temperature as high as 46° during 1 hr. The reaction mixture was allowed to stand overnight and then distilled to give a 45-g cut, bp 80–125°. Redistillation gave 33.1g (80%) of cyanate 12, bp 93–95°. An analytical sample was prepared: bp 95°; n^{25}D 1.3118; ir 3.30 and 3.37 (CH), 4.42 with shoulder at 4.53 (OCN), 8.75 μ (COC or CF); nmr (neat), H′ at τ 7.99 (septet, J_{HF} = 1.2 Hz, CH_3); ^{19}F at 78.7 ppm (quadruplet, J_{HF} = 1.2 Hz, CF_3); mass spectrum (relative intensity), 207 (0.3), 165 (37), 145 (37), 138 (5), 113 (17), 95 (27), 92 (15), 77 (52), 75 (10), 69 (100), 65 (10), 56 (17), 51 (17), 43 (11), 42 (5), 33 (14), 31 (8), 27 (8), 15 (6).

Anal. Calcd for $C_5H_3F_6NO$: F, 55.05; N, 6.77; mol wt, 207. Found: F, 55.14; N, 6.89; mol wt, 207 (mass spectrum).

A sample of 12 was recovered unchanged after refluxing for 6 hr. When 10 g of 12 was heated in 75 ml of dimethylacetamide, orange color developed rapidly and a low boiler was given off. The gas evolved (6 g, 80%) was identified as pure 1,1-bis(trifluoromethyl)ethylene by comparison of its ir spectrum with that of an authentic sample.

o-(2H-Hexafluoroisopropyl)phenyl Isocyanate (15).—2-Phenylhexafluoro-2-propanol (13) was prepared by a procedure similar to that in the literature,[13] bp 160–161°.

Sodium hydride–mineral oil (11.3 g, 0.25 mol) was placed under nitrogen in a two-way sintered-glass filter funnel and rinsed with three 50-ml portions of dry ether. A 500-ml round-bottom flask was fitted to the top, the filter was inverted, and a solution of 48.8 g (0.20 mol) of 13 in 100 ml of ether was slowly introduced. The filter was rinsed with an additional 100 ml of ether and the mixture was stirred until nitrogen evolution ceased (15 min). The resulting solution was filtered and the solvent was evaporated, finishing at 0.5 mm for 1 hr on the solid residue. Dry toluene (100 ml) was added, the mixture was cooled at 0°, and 14 g (12 ml, 0.23 mol at 0°) of cyanogen chloride was distilled in over 30 min. The mixture was homogeneous after warming to room temperature, at which point a mildly exothermic reaction set in. After standing overnight, the salt was filtered off and rinsed with toluene. Distillation of the combined filtrate and washings gave 22.0 g (41%) of isocyanate 15, bp 46.5–48.5° (2 mm), along with considerable high-boiling residue. An analytical sample purified by glpc had mp 28–29°; ir 3.25 and 3.35 (CH), 4.39 (NCO), 6.21 and 6.27 μ (aromatic C=C); nmr (neat), H′ (external reference) at τ 5.47 [septet, 1, J_{HF} = 8.5

(10) Melting points and boiling points are uncorrected. Proton nmr spectra were obtained with a Varian A-60 spectrometer. Peak center positions for protons are reported as τ 10 − δ_H ppm. Fluorine nmr spectra were obtained with a Varian A56/60 spectrometer using $CFCl_3$ as an internal standard, unless otherwise noted. Mass spectra were taken on a CEC 21-103C instrument at 70 eV; peaks of 5% or greater relative intensity are reported thus, *m/e* (relative intensity).

(11) R. J. Koshar, T. C. Simmons, and F. W. Hoffmann, *J. Amer. Chem. Soc.*, **79**, 1741 (1957).

(12) The nmr spectrum corresponded to that reported for this compound by E. G. Howard, P. B. Sargeant, and C. G. Krespan, *ibid.*, **89**, 1422 (1967), as obtained from a different synthesis.

(13) (a) D. C. England, French Patent 1,325,204 (1963); (b) B. S. Farah, E. E. Gilbert, and J. P. Sibilia, *J. Org. Chem.*, **30**, 998 (1965).

Hz, $CH(CF_3)_2$] and complex grouping at 2.5–3.5 for aryl H of approximate area 4; ^{19}F (external reference) at 84.3 ppm [doublet, J_{HF} = 8.5 Hz, $CH(CF_3)_2$].

Anal. Calcd for $C_{10}H_5F_6NO$: C, 44.62; H, 1.87; N, 5.21; F, 42.35. Found: C, 45.01; H, 2.12; N, 5.27; F, 42.31.

A sample of **15** was treated with excess methanol. After the exothermic reaction had subsided, excess methanol was evaporated and the residue of urethan **16** was recrystallized twice from petroleum ether: mp 74–75°; ir 3.08 (NH), 3.27, 3.32, and 3.36 (CH), 5.93 (C=O), 6.29 and 6.70 (aromatic C=C), 6.54 μ (urethan); nmr (saturated CCl_4) H′ at τ 6.38 (singlet, 3, OCH_3), 5.22 [septet, 1, J_{HF} = 8 Hz, $CH(CF_3)_2$] and complex multiplet at 2.1–2.9 for aryl H and NH (area 5). Addition of CF_3CO_2H moved NH (area 1) to τ 1.81, separate from unsymmetrical aryl H (area 4).

Anal. Calcd for $C_{11}H_9F_6NO_2$: C, 43.86; H, 3.01; N, 4.65; F, 37.85. Found: C, 44.28; H, 3.40; N, 4.76; F, 37.70.

Registry No.—**2**, 19755-54-5; **6**, 19755-55-6; **7**, 19755-56-7; **8**, 19755-57-8; **9**, 19779-34-1; **12**, 19755-58-9; **15**, 19779-35-2; **16**, 19755-59-0.

Structure Assignments in Polysubstituted Ethylenes by Nuclear Magnetic Resonance[1a]

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An nmr technique is described by which structures can be assigned to many di- and trisubstituted ethylenes simply from a knowledge of the vinyl proton resonance positions in the compound under study. The technique depends on the additivity of vinyl substituent shielding effects on the vinyl protons present. Tables of substituent shielding constants (σ values) for several common functional groups are presented, and various methods for obtaining σ values are outlined. Solutions to several structural assignment problems are presented, including cases in which steric and electronic interactions between substituents must be taken into account.

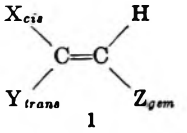
This paper describes a nuclear magnetic resonance technique by which geometric structures can be assigned to a wide variety of di- and trisubstituted ethylenes. The only data required on the compound under study are the resonance positions of its vinyl protons.

The principles underlying this technique were outlined several years ago by Goldstein and coworkers in a series of papers on the origin of nmr shielding effects.[2] The "differential shielding" method of Jackman and Wiley[3] which is also based on these principles provides only the relative vinyl proton chemical shifts in related *cis–trans* isomers. The procedure developed here will predict absolute vinyl proton resonance positions in all mono-, di-, and trisubstituted isomers, and complements existing methods for assigning configurations to *cis* and *trans* isomer pairs based on the magnitude of H–H coupling constants.[4]

The method is based on the independence and additivity of vinyl substituent shielding effects,[1] a concept simultaneously evolved by Pascual, Meier, and Simon.[5] However, the model compound technique described in the latter part of this paper greatly improves the ability of the method to differentiate between closely related polysubstituted ethylenes in which specific steric and electronic interactions between functional groups occur.

The structure assignment method applies in its simplest form to those ethylenes which can be pictured as being constructed from a relatively open, rigid >C=C< rack and a set of small, symmetrical substituents. The substituents must cause relatively little distortion of the molecular framework when attached to the ethylenic backbone, and be able to assume a geometry relative to the vinyl protons which is unaffected by the introduction of other functional groups. Such substituents will generally be smaller in size than Br, and have threefold (C_3) or greater symmetry with respect to rotation about the bond joining them to the ethylenic backbone.

Goldstein showed[2] that, in several simple ethylenes, introduction of such symmetrical substituents caused characteristic shifts in the nmr positions of nearby vinyl protons. It turns out that in a molecule bearing a number of symmetrical substituents the total shielding experienced by a vinyl proton is simply the sum of the shielding effects exerted by all the substituents present. The resonance position of the vinyl proton in such molecules (**1**) can be accurately calculated from eq 1.



1

$$\delta_{ppm} = -5.27 + \sigma_{cis\text{-}X} + \sigma_{trans\text{-}Y} + \sigma_{gem\text{-}Z} \quad (1)$$

In this equation −5.27 ppm represents the resonance position of $CH_2{=}CH_2$[6,7] and $\sigma_{cis\text{-}X}$, $\sigma_{trans\text{-}Y}$, and $\sigma_{gem\text{-}Z}$

(1) (a) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, Division of Organic Chemistry, Abstracts of Papers, S24. Taken in part from Chapter VI of the Ph.D. Thesis of S. W. T., University of Wisconsin, Jan 1965. (b) National Institutes of Health Predoctoral Fellow, University of Wisconsin, 1961–1964.

(2) (a) E. B. Whipple, J. H. Goldstein, and L. Mandell, *J. Amer. Chem. Soc.*, **82**, 3010 (1960); (b) E. B. Whipple, J. H. Goldstein, and G. R. McClure, *ibid.*, **82**, 3811 (1960); (c) G. S. Reddy, J. H. Goldstein, and L. Mandell, *ibid.*, **83**, 1300 (1961); (d) G. S. Reddy and J. H. Goldstein, *ibid.*, **83**, 2045 (1961); (e) E. B. Whipple, W. E. Stewart, G. S. Reddy, and J. H. Goldstein, *J. Chem. Phys.*, **34**, 2136 (1963).

(3) (a) L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," The Macmillan Co., New York, N. Y., 1959, pp 119–125; (b) L. M. Jackman and R. H. Wiley, *Proc. Chem. Soc.*, 196 (1958); (c) L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2881, 2886 (1960); (d) ref 3a, pp 729–741.

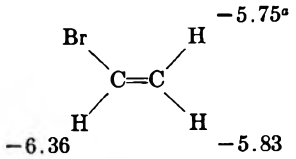
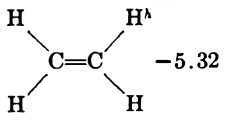
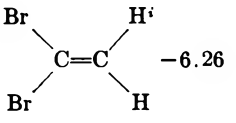
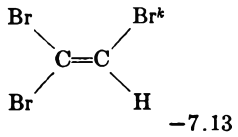
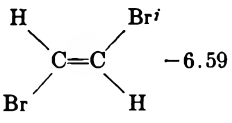
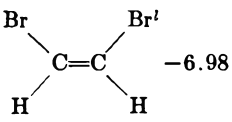
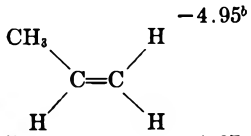
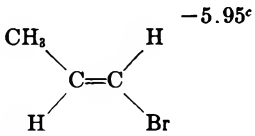
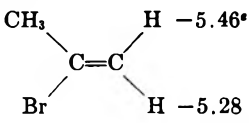
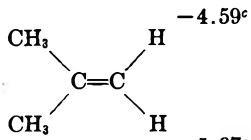
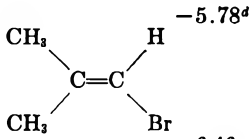
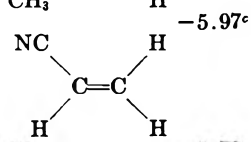
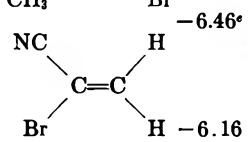
(4) (a) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Pergamon Press Ltd., London, 1966, pp 711–735; (b) P. Laszlo and P. von R. Schleyer, *Bull. Soc. Chim. Fr.*, 87 (1964); (c) J. Niwa, *Bull. Chem. Soc. Jap.*, **40**, 2192 (1967).

(5) C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, **49**, 164 (1966).

(6) Vinyl proton resonances for simple ethylenes occur anywhere between −4.0 and −8.0 ppm (below) tetramethylsilane. A saturated 35° solution of $CH_2{=}CH_2$ in CCl_4 containing 5 vol. % TMS internal reference resonates at −5.323 ppm. Values obtained under different conditions are tabulated in ref 5.

(7) Ethylene is unique in that it bears no vinyl substituents. From an analysis of nmr data on a large number of substituted ethylenes, ethylene is predicted to resonate at −5.27 ± 0.10 ppm.

TABLE I
NMR σ VALUES (PARTS PER MILLION) FOR Br

		−0.43	−0.51	−1.04
		−0.43[f]	−0.51	
				−0.87
		−0.23		−0.84
			−0.51	
			−0.64	−1.15
		−0.15		
		−0.31		−1.00
		−0.41	−0.51	
				
				−1.19
		−0.37	−0.49	
		-0.33 ± 0.09[g] $\sigma_{cis\text{-Br}}$	-0.53 ± 0.04 $\sigma_{trans\text{-Br}}$	-1.02 ± 0.11 $\sigma_{gem\text{-Br}}$

[a] R. E. Mayo and J. H. Goldstein, *J. Mol. Phys.*, **14**, 173 (1964). [b] A. A. Bothnerby and C. Naar-Colin, *J. Amer. Chem. Soc.*, **83**, 231 (1961). [c] G. S. Reddy and J. H. Goldstein, *ibid.*, **83**, 2045 (1961); 40 MHz. [d] L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2881 (1960); 40 MHz. [e] V. S. Watts and J. H. Goldstein, *J. Chem. Phys.*, **42**, 228 (1965). [f] The upper number in these sets is obtained by comparing the resonance position of the disubstituted ethylene with that of the monosubstituted derivative. The lower number is obtained by comparing the resonance position of the disubstituted ethylene with that of the trisubstituted derivative. Chemical shifts without literature references were obtained on a Varian Associates A56/60 spectrometer on 5–10 vol. % solutions in CCl_4 or $CDCl_3$ at 35° with 2% tetramethylsilane internal standard and side-band bracketing of resonance positions. [g] The indicated uncertainty is the root mean square deviation of the individual σ values from the mean. See H. Margenau and G. M. Murphy, "The Mathematics of Physics and Chemistry," 2nd ed, D. Van Nostrand Co., Inc., Princeton, N. J., 1956, pp 504–516. Registry numbers are as follows: [h] 74-85-1. [i] 593-92-0. [j] 590-12-5. [k] 2597-45-7. [l] 590-11-4.

are the shielding constants of X, Y, and Z from the *cis*, *trans*, and *gem* substituent locations.[8–12]

Actually, additivity in functional group shielding effects is not altogether surprising. The composition of each substituent on a molecule, its distance and orientation relative to a nearby proton, and the nature of the framework connecting the substituent and the proton are the critical molecular factors which determine the magnitude of the nmr shielding effect produced by each substituent on that proton, *whatever* the shielding mechanism.[13]

(8) The independence and additivity of nmr shielding effects apply to other open, rigid framework systems. The magnitude of the substituent effects depends, of course, on the nature of the molecular framework. The first study of the additivity principle was carried out on polysubstituted methanes by Shoolery.[9a] Additivity has since been demonstrated with varying degrees of success for several other systems.[10–12]

(9) (a) J. N. Shoolery, Technical Information Bulletin, Vol. 2, No. 3, Varian Associates, Palo Alto, Calif., 1959, pp 4–6; (b) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1963, pp 87–89; (c) H. Primas, R. Arndt, and R. Ernst, *Advan. Mol. Spectrosc.*, 1246 (1962).

(10) R. F. Zurcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

(11) P. L. Corio and B. P. Dailey, *J. Amer. Chem. Soc.*, **78**, 3043 (1956); (b) J. S. Martin and B. P. Dailey, *J. Chem. Phys.*, **39**, 1723 (1963); (c) G. W. Smith, *J. Mol. Spectrosc.*, **12**, 146 (1964).

(12) (a) K. Takahashi, T. Sone, Y. Matsuki, and G. Hazato, *Bull. Chem. Soc. Jap.*, **38**, 1041 (1965); (b) K. Takahashi, I. Ito, and Y. Matsuki, *ibid.*, **40**, 605 (1967); (c) S. Gronowitz and R. A. Hoffman, *Ark. Kemi*, **16**, 539 (1960).

(13) Reference 4a, pp 120–151, gives mathematical models of various nmr shielding processes. The additivity principle breaks down when specific steric and electronic interactions between substituents occur. When such interactions are properly taken into account the utility of the additivity principle is preserved (see below).

For each small symmetrical functional group X three vinyl shielding values can be established. These σ values depend on the chemical constitution of X and its location relative to the vinyl proton in question. $\sigma_{cis\text{-}X}$, $\sigma_{trans\text{-}X}$, and $\sigma_{gem\text{-}X}$ are defined as the average parts per million shifts in resonance position of a vinyl proton caused by introducing X *cis*, *trans*, or *gem* to that proton. One set of σ values can be estimated by comparing the totally analyzed ABC spectrum of a monosubstituted ethylene $CH_2{=}CHX$[14] with ethylene. Taking vinyl bromide from the first line of Table I, we see that introducing a bromine on the ethylene backbone lowers the resonance position of the *gem* proton -1.04 ppm relative to ethylene. Therefore, $\sigma_{gem\text{-}Br} = -6.36 - (-5.32) = -1.04$ ppm. Similarly, $\sigma_{cis\text{-}Br} = -0.43$ and $\sigma_{trans\text{-}Br} = -0.51$ ppm.

Since the totally analyzed spectra of monosubstituted ethylenes are not always available, and because steric and electronic interactions do occur, even between symmetrical substituents, values obtained solely by this method are not always reliable. σ values are best obtained, as shown in Table I, by averaging the apparent shielding effects of a given functional group in a series of compounds bearing substituents of varying size and electron-donating or -withdrawing ability. Note that from all three positions on the ethylenic backbone Br moves the proton resonance downfield, that this effect is greatest from the *gem* position, and that $\sigma_{trans\text{-}Br}$ is significantly greater than $\sigma_{cis\text{-}Br}$.[15] Note also that an average uncertainty of ± 0.1 ppm (6 Hz) for each σ_{Br} value does exist.[16]

Tables II, III, and IV derive the σ values for Cl, CH_3, and CN, three other common small symmetrical substituents. Although the value of $\sigma_{gem\text{-}Cl}$ from Table II is essentially the same as $\sigma_{gem\text{-}Br}$, $\sigma_{cis\text{-}Cl}$, and $\sigma_{trans\text{-}Cl}$ are much smaller in magnitude than the values for Br, and are *not* significantly different.[15] Table III shows that, whereas the *gem* methyl group causes a large downfield shift in vinyl proton resonance,[17a] *cis* and *trans* methyl groups cause equal upfield displacements. The data in Table IV show that the CN group causes a significantly different downfield displacement in the vinyl proton resonance position from each location. Unlike Br and Cl this effect is *smallest* from the *gem* position.[17b]

Taken altogether, the data in Tables I–IV show clearly that irrespective of the sign or magnitude of σ, the effective shielding values of all small symmetrical groups show uncertainties of ± 0.1 ppm depending on the substituent environment. However, within these limits σ values can be treated as constants, readily transferable from one ethylenic compound to another. That this is so is shown in Figure 1. Insertion of the 12 σ values from Tables I–IV into eq 1 faithfully reproduces the 50 nmr positions of the 39 compounds in the tables.

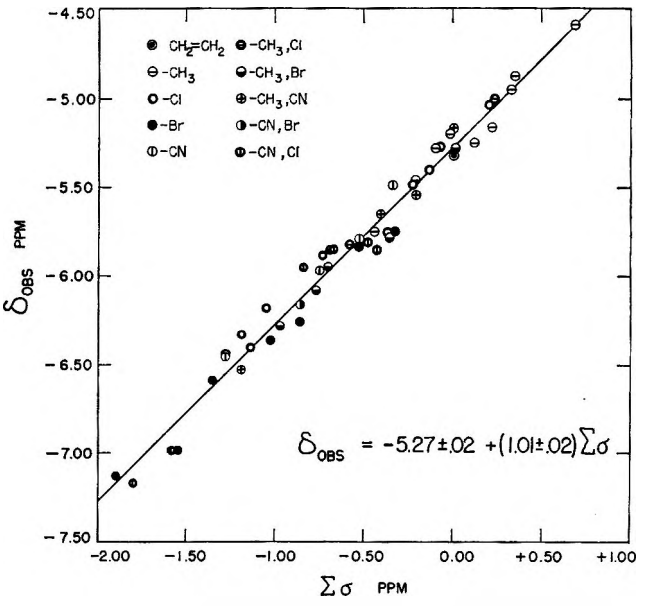


Figure 1.—Plot of the 50 values of δ_{obsd} *vs.* $\Sigma\sigma$ for the 39 substituted ethylenes in Tables I–IV. The substituents present on the various ethylenes are indicated by the key.

If the additivity relationship were perfect, the calculated points would all fall on a line of slope 1.00 and pass through -5.32 ppm (ethylene) at $\Sigma\sigma = 0.0$. The best least-squares line through the data actually has slope 1.00 ± 0.02, the mean deviation of the points from this line is ± 0.09 ppm, and, at $\Sigma\sigma = 0.0$, $\sigma = -5.27$ ppm.[6,7] This shows that at least for the compounds used in constructing the tables the additivity approximation is valid. Furthermore, the plot shows that uncertainties in σ values *tend to compensate rather than propagate* when used additively.

The most meaningful assessment of the σ additivity principle simply involves finding out how well compounds having the same substituents and similar resonance positions can be differentiated. For example, *cis*- and *trans*-dichloroethylene resonate at -6.40 and -6.33 ppm. Using the average σ values for Cl in eq 1, *cis*-dichloroethylene is predicted to resonate at -6.39 ± 0.16 ppm, and the *trans* isomer at -6.43 ± 0.14 ppm. Although both the observed resonances lie well within the uncertainty limits set on the predicted values, thus easily fulfilling the *correlation* requirement outlined by Pascual, Meier, and Simon,[5] *differentiation* between the two compounds using σ values alone is not possible.[18] This is due simply to the fact that $\sigma_{cis\text{-}Cl}$ and $\sigma_{trans\text{-}Cl}$ are not significantly different. Actually, the predicted resonance positions are in inverted order from the observed values.

As a general rule, geometric isomers of related polysubstituted ethylenes having resonance positions within 0.2 ppm (12 Hz) cannot be differentiated using σ values alone, owing to the σ uncertainty of ± 0.1 ppm. Outside this limit, the σ additivity principle provides a rapid and reliable method for establishing the proton resonance positions and/or geometric structures of many polysubstituted olefins.

(14) See E. W. Garbisch, Jr., *J. Chem. Educ.*, 45, 402 (1968), for an excellent discussion of the analysis of three-spin systems.

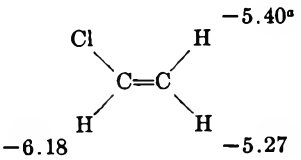
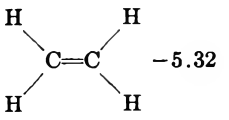
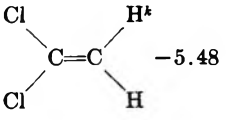
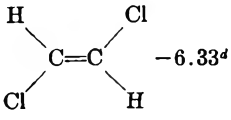
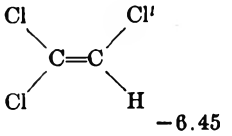
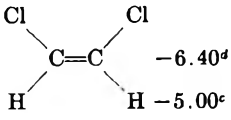
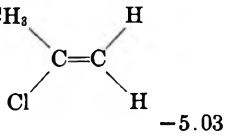
(15) For a discussion of vinyl halogen shielding effects and nmr data on a few vinyl iodides, see (a) F. Hruska, H. M. Hutton, and T. Schaefer, *Can. J. Chem.*, **43**, 2392 (1965); (b) F. Hruska, D. W. McBride, and T. Schaefer, *ibid.*, **45**, 1081 (1967); (c) R. C. Neuman, Jr., and D. N. Roark, *J. Mol. Spectrosc.*, **19**, 421 (1966).

(16) To minimize uncertainties due to taking literature data from many different sources, data were chosen from recent results obtained at 60 MHz on 5–20 vol. % solutions in CCl_4, $CDCl_3$, or cyclohexane at 30–35° with internal TMS standard. Some 40-MHz data were necessarily used, and are so indicated.

(17) (a) Possible origins of this remarkable *gem*-CH_3 effect have been investigated by Bothnerby and Naar-Colin. See ref *b*, Table I. (b) See ref 2c for a discussion of the CN group effect.

(18) *cis*- and *trans*-dichloroethylene can be readily differentiated by their H–H coupling constants, obtained from analysis of the ^{13}C side-band spectra. See R. M. Lynden-Bell and N. Sheppard, *Proc. Roy. Soc.* (London), **A269**, 385 (1962).

TABLE II
NMR σ VALUES (PARTS PER MILLION) FOR Cl

		−0.08	+0.05	−0.86
		−0.21[k]	−0.08	
		−0.15		−0.97
			−0.12	−0.93
			−0.22	−1.13
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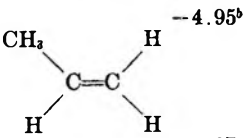
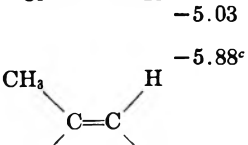
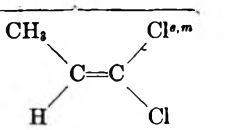
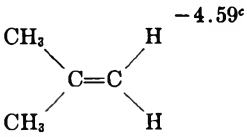
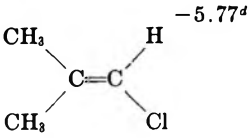
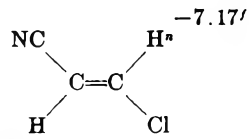
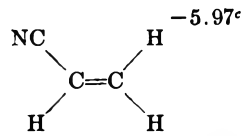
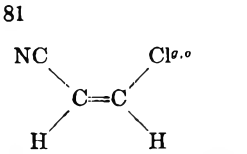
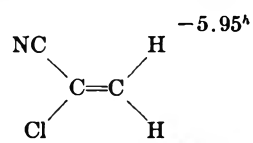
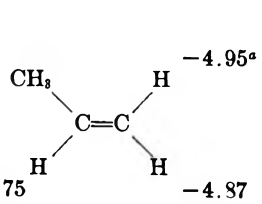
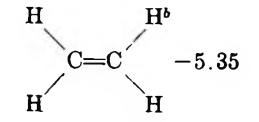
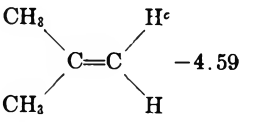
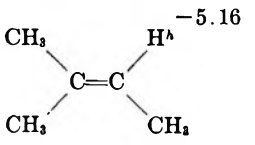
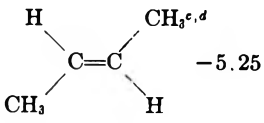
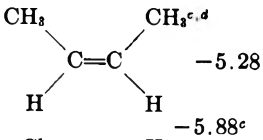
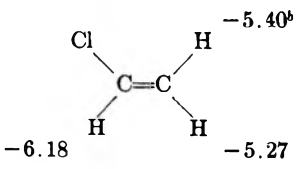
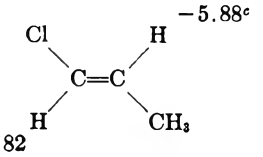
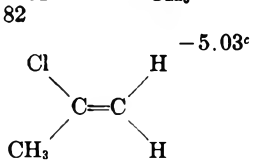
		−0.16	−0.05	
		−0.07		−0.93
			+0.03	
				−1.18
		−0.33		−1.20
			−0.37	−1.20
		−0.06	+0.02	
		-0.14 ± 0.08^{i} $\sigma_{cis\text{-}Cl}$	-0.09 ± 0.11 $\sigma_{trans\text{-}Cl}$	-1.05 ± 0.13 $\sigma_{gem\text{-}Cl}$

[a] See Table I, footnote *a*. [b] See Table I, footnote *b*. [c] See Table I, footnote *c*. [d] N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962. [e] J_{CH_3-H} = 6.9 Hz. [f] J_{H-H} = 14.0 Hz. See F. Scotti and E. J. Frazza, *J. Org. Chem.*, **29**, 1800 (1964). [g] J_{H-H} = 7.6 Hz. [h] V. S. Watts, G. S. Reddy, and J. H. Goldstein, *J. Mol. Spectrosc.*, **11**, 325 (1963). [i] See Table I, footnote *f*. [j] See Table I, footnote *g*. Registry numbers are as follows. [k] 75-35-4. [l] 79-01-6. [m] 563-58-6. [n] 37213-8-8. [o] 3721-37-7.

TABLE III

NMR σ VALUES (PARTS PER MILLION) FOR $-CH_3$

		+0.40	+0.48	−0.40
		+0.28[f]	+0.36	
				−0.60
		+0.50		−0.30
			+0.09	
			+0.47	−0.41
		+0.12		
		+0.36		−0.48
				
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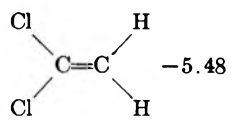
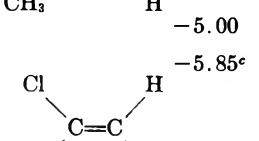
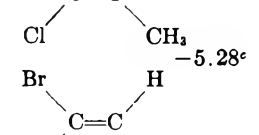
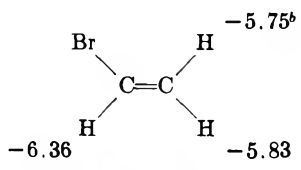
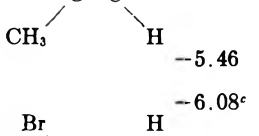
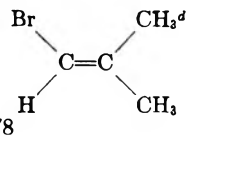
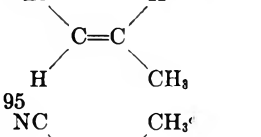
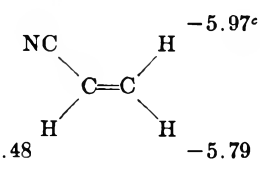
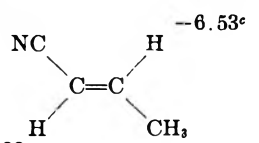
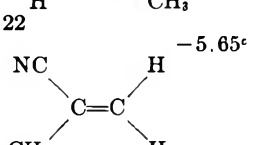
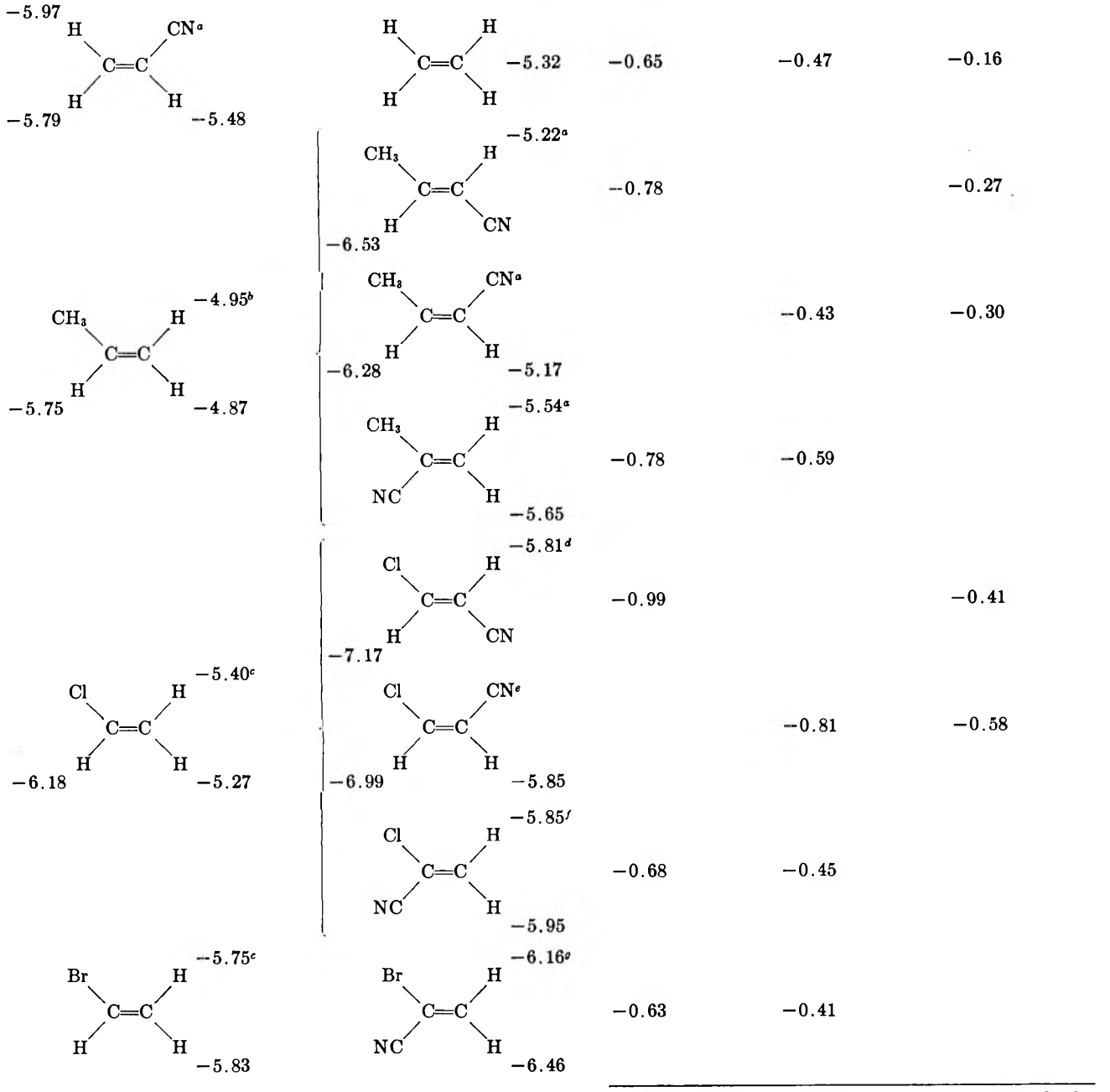
				−0.37
		+0.37	+0.47	
		+0.41		−0.33
			+0.17	
			+0.31	−0.49
		+0.26		−0.56
				
		+0.25	+0.32	

$+0.32 \pm 0.09$[g]	$+0.34 \pm 0.10$	-0.44 ± 0.09
$\sigma_{cis\text{-}CH_3}$	$\sigma_{trans\text{-}CH_3}$	$\sigma_{gem\text{-}CH_3}$

[a] See Table I, footnote *b*. [b] See Table I, footnote *a*. [c] See Table I, footnote *c*. [d] See Table I, footnote *d*. [e] See Table II, footnote *e*. [f] See Table I, footnote *f*. [g] See Table I, footnote *g*. [h] Registry number: 513-35-9.

TABLE IV
NMR σ VALUES (PARTS PER MILLION) FOR -CN



[a] See Table I, footnote *c*. [b] See Table I, footnote *b*. [c] See Table I, footnote *a*. [d] See Table II, footnote *f*. [e] See Table II, footnote *g*. [f] See Table II, footnote *h*. [g] See Table I, footnote *e*. [h] See Table I, footnote *g*.

Table V illustrates one such case. Even though the methyl group shields both protons equally, $\sigma_{cis\text{-Br}}$ is sufficiently different from $\sigma_{trans\text{-Br}}$ to indicate that the vinyl proton resonance assignments for 2-bromopropene (**2**) should be the reverse of those indicated in the Varian catalog, spectrum 23.[19]

Table VI illustrates a second case. Hydrolysis of tetrachlorocyclopropene in aqueous ammonia produces a single dichloroacrylonitrile (**3**) in 25% yield.[20] This product shows vinyl proton resonance at −7.23 ppm. The β,β-dichloro structure can be eliminated, and **3** can confidently be assigned the *cis*-dichloro structure in preference to the *trans*.

The structure assignment method can also be applied in a straightforward way to ethylenes bearing symmetrical planar substituents such as the phenyl group. The distribution of nuclei and electrons in all planar substituents is markedly different in the plane of the group from that above or below the plane, and the magnetic and electronic properties of all such substituents are inherently anisotropic. Irrespective of the mechanism by which any planar substituent shields nearby protons, this shielding will depend not only on the location of the substituent relative to the vinyl pro-

(19) (a) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962. (b) N. S. Bhacca, D. P. Hollis, L. F. Johnson, and E. A. Pier, "NMR Spectra Catalog," Vol. 2, Varian Associates, Palo Alto, Calif., 1963.

(20) (a) S. W. Tobey and R. West, *Tetrahedron Lett.*, 1179 (1963); (b) S. W. Tobey and R. West, *J. Amer. Chem. Soc.*, **86**, 56 (1964); (c) S. W. Tobey and R. West, *ibid.*, **86**, 4215 (1964); (d) S. W. Tobey and R. West, *ibid.*, **88**, 2478, 2481 (1966).

TABLE V
ASSIGNMENT OF VINYL PROTON RESONANCE POSITIONS IN 2-BROMOPROPENE (2)

Literature assignment[a]	Predicted δ's using σ values
CH_3 H −5.33	$\delta_{H_A}{}^a = -5.48 \pm 0.10$ ppm[b]
Br H −5.52	$\delta_{H_B}{}^c = -5.26 \pm 0.14$ ppm[d]

[a] $\delta_{H_A} = -5.27 + \sigma_{cis\text{-}CH_3} + \sigma_{trans\text{-}Br} = -5.27 + (+0.32 \pm 0.09) + (-0.53 \pm 0.04) = -5.48 \pm 0.10$. [b] This uncertainty is the square root of the sum of the squares of the uncertainties in the δ values used in calculating δ. See Table I, ref *g*, p 515. [c] $\delta_{H_B} = -5.27 + \sigma_{trans\text{-}CH_3} = \sigma_{cis\text{-}Br} = -5.27 + (+0.34 \pm 0.10) + (-0.33 \pm 0.09) = -5.26 \pm 0.14$. [d] The correct assignment for 2-bromopropene has previously been deduced from the 1.4- and 0.8-cps *cis* and *trans* H–CH_3 coupling constants. See ref 2a. [e] See ref 19.

TABLE VI
ASSIGNMENT OF STRUCTURE TO THE DICHLOROACRYLONITRILE (3) OBTAINED IN THE AMMONOLYSIS OF TETRACHLOROCYCLOPROPENE HAVING δ = −7.23

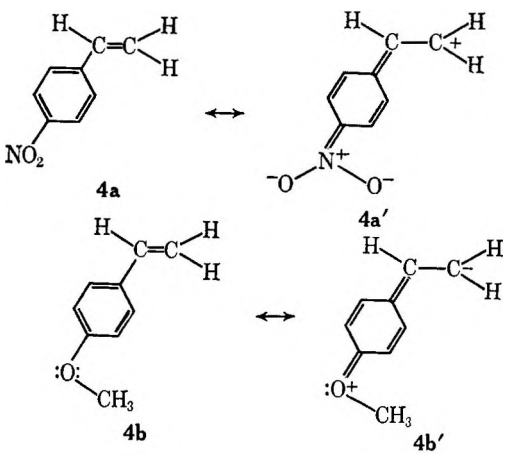
Structure	Predicted δ, ppm	Observed δ, ppm[a]
Cl, H^b, Cl, CN	−5.84 ±0.18	
H, Cl^c, Cl, CN	−6.99 ±0.18	−7.02
Cl, Cl^d, H, CN	−7.16 ±0.18	−7.23

[a] J. E. Lancaster, American Cyanamid Co., Stamford, Conn., private communication. Registry numbers are as follows. [b] 7436-85-3. [c] 19647-20-2. [d] 3533-66-2.

tons, but also on the time-averaged *angular orientation* of the group relative to the plane of the ethylenic backbone. Since an unsubstituted or *para*-substituted phenyl group has twofold (C_2) symmetry with respect to the bond joining it to the ethylenic backbone, the orientation of such phenyl groups is adequately specified by the dihedral angle between the substituent and ethylenic planes. This angle can have values between 0 and 90° and depends on the steric environment of the phenyl group.

Table VII shows data used to determine the three σ values for a phenyl group in an *uncrowded* environment. Theory and experiment both indicate[21] that protons near the plane of a phenyl group experience a downfield shift in resonance position which decreases quite rapidly with increasing distance of the proton from the ring center, but which is relatively insensitive to the angular location of the proton relative to the ring plane as long as this angle is less than about 20°. The observed σ_{PH} values in Table VII are consistent with these conclusions. A phenyl group free to lie approximately coplanar with the ethylenic backbone causes a very large (−1.42 ppm) downfield shift in resonance position of a vinyl proton from the *gem* position, a modest (−0.38 ppm) downfield shift from the *cis* position, but very little shift (~0.0 ppm) from the *trans* position. Note that in *all* of the polyphenylated ethylenes each phenyl substituent exerts a shielding effect which is indistinguishable from that which a single phenyl group exerts in styrene. This clearly implies that in polyphenylated ethylenes each phenyl group is capable of assuming a time-averaged orientation which is within 20° of the coplanar orientation of the phenyl group in styrene. This conclusion is quite different from that reached by Jackman.[3a]

Superimposed on the magnetic shielding of nearby protons by the phenyl ring is shielding arising from electronic interaction between the ring and C=C π systems. The data on *para*-substituted styrenes in Table VIII show clearly that electron-withdrawing groups (*e.g.*, *p*-NO_2 and *p*-Cl) on the benzene ring lead to enhanced deshielding of all the vinylic protons, and that electron-donating groups (*e.g.*, *p*-OCH_3) cause net shielding. Interestingly, the effect of a *para* substituent is much smaller on the *gem* proton than on the more distant *cis* and *trans* proton, while the effect on these two latter protons is essentially *equal*. These facts suggest that the resonance forms **4′** contribute heavily to the interaction between the ring and ethylenic π systems. These interactions alter the electron density only at the β carbon. Protons attached to this center should be affected more than at the α carbon. Because the β protons are symmetrically placed relative to the β carbon, changes in electron density at this center should affect them equally.[22]



Twisting the phenyl group more than about 20° out of the ethylenic plane causes dramatic changes in the shielding effects of this group on nearby protons.[21] This distortion is most easily accomplished by introduction of a bulky substituent *cis* to the phenyl group.[23] As Table IX shows, $\sigma_{gem\text{-}Ph}$ for the phenyl group in *cis*-β-bromostyrene (**5**) falls from its normal −1.42 value to −1.09 ppm. Although enforced loss of phenyl coplanarity necessarily decreases resonance interaction of the type **4**–**4′**, this is not the major reason for the di-

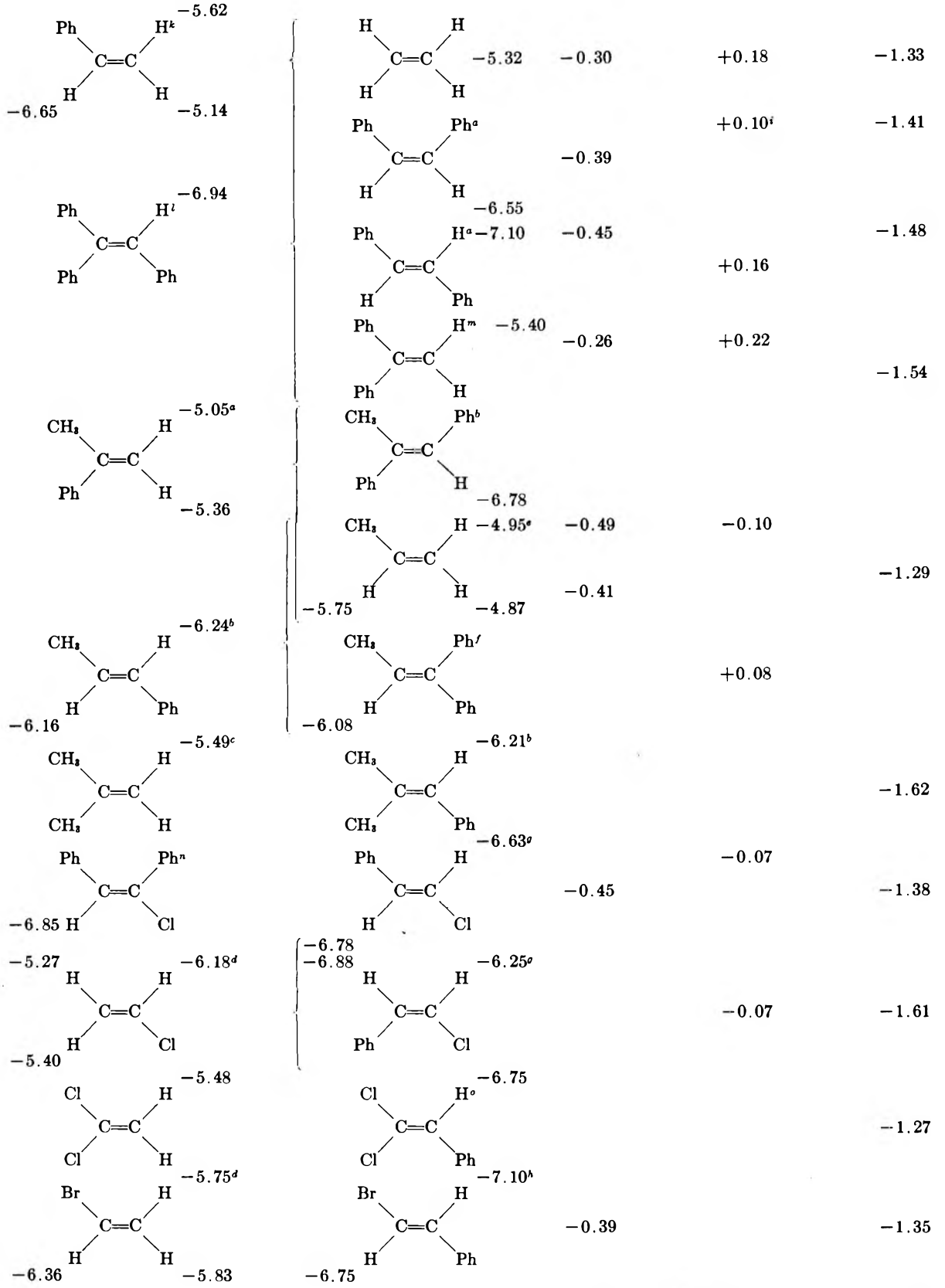
(21) (a) D. G. Farnum and C. F. Wilcox, *J. Amer. Chem. Soc.*, **89**, 5379 (1967); (b) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958); (c) J. S. Waugh and R. W. Fessenden, *J. Amer. Chem. Soc.*, **79**, 846 (1957), and correction in **80**, 6697 (1958).

(22) See Gurudata, J. B. Stothers, and J. D. Talman, *Can. J. Chem.*, **45**, 731 (1967), and T. A. Wittstruck and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **89**, 3803 (1967), for additional discussion.

(23) *ortho* substitution on the phenyl ring can also prevent coplanarity. See ref *b*, Table VIII, and ref *f*, Table VII.

TABLE VII

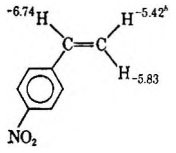
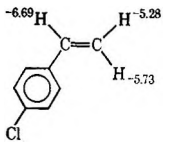
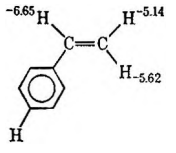
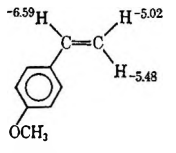
NMR σ VALUES (PARTS PER MILLION) FOR A STERICALLY UNCROWDED PHENYL GROUP



-0.39 ± 0.08[j]	$+0.06 \pm 0.12$	-1.43 ± 0.12
$\sigma_{cis\text{-Ph}}$	$\sigma_{trans\text{-Ph}}$	$\sigma_{gem\text{-Ph}}$

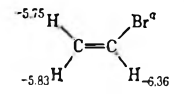
[a] See Table II, footnote *d*. [b] H. Rottendorf, S. Sternhell, and J. R. Wilmhurst, *Aust. J. Chem.*, **18**, 1759 (1965). [c] See Table I, footnote *c*. [d] See Table I, footnote *a*. [e] See Table I, footnote *b*. [f] R. van der Linde, O. Korver, P. K. Korver, P. J. van der Haak, J. Veenland, and Th. deBoer, *Spectrochem. Acta*, **21**, 1893 (1965). [g] L. J. Dolby, C. Wilkins, and T. G. Frey, *J. Org. Chem.*, **31**, 1110 (1966). [h] The data reported here are from ref *d*, Table II. See also ref *g*, Table VII, and D. T. Witiak and B. P. Chaudhari, *J. Org. Chem.*, **30**, 1467 (1964). [i] See Table I, footnote *f*. [j] See Table I, footnote *g*. Registry numbers are as follows. [k] 100-42-5. [l] 58-72-0. [m] 530-48-3. [n] 948-98-1. [o] 698-88-4.

TABLE VIII
EFFECT OF *para* SUBSTITUENTS ON THE NMR SHIELDING PROPERTIES OF THE PHENYL GROUP

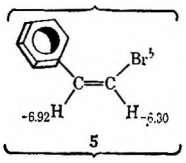
	$\Delta\sigma_{cis\text{-Ph}}$[a]	$\Delta\sigma_{trans\text{-Ph}}$	$\Delta\sigma_{gem\text{-Ph}}$
	−0.21	−0.28	−0.09
	−0.11	−0.14	−0.04
	0.00	0.00	0.00
	+0.14	+0.12	+0.06

[a] $\Delta\sigma$ is the difference in resonance position (ppm) between a vinyl proton in the *para*-substituted styrene and the corresponding vinyl proton in styrene itself. [b] Data for this table taken from R. H. Wiley and T. H. Crawford, *J. Polym. Sci., Part A*, **3**, 829 (1965).

TABLE IX
THE EFFECT OF Br ON σ VALUES FOR NEIGHBORING PHENYL GROUPS

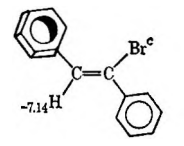


$\sigma_{gem\text{-Ph}} = -1.09$



5

$\sigma_{trans\text{-Ph}} = +0.06$



6

$\sigma_{cis\text{-Ph}} = -0.22$

[a] See Table I, footnote *a*. [b] See Table VII, footnotes *g* and *h*, and also D. Seyferth, L. G. Vaughan, and R. Suzuki, *J. Organometal. Chem.*, **1**, 437 (1964). The data of L. A. Singer and N. P. Kong [*J. Amer. Chem. Soc.*, **89**, 5251 (1967)] appear to be in error. [c] H. H. Freedman and G. A. Doorakian, The Dow Chemical Co., Eastern Research Laboratory, private communication.

minished $\sigma_{gem\text{-Ph}}$ effect in **5**. A 30° dihedral angle between the phenyl group and ethylenic backbone should decrease resonance interaction between the π systems by only about 15%,[24] and the effects of this perturbation should show up primarily as an altered $\sigma_{trans\text{-Ph}}$ value. No such effect is observed. On the other hand, a 30° dihedral angle should, according to theory,[21] move the *gem*-vinyl proton into a region near the phenyl ring where it will experience essentially *no* magnetic deshielding. We can therefore estimate that the phenyl group *cis* to Br in **5** lies somewhere near 25° out of plane.

Table IX also shows that phenyl *gem* to Br is *not* forced appreciably out of coplanarity. Comparing bromo-*trans*-stilbene (**6**) with **5**, a $\sigma_{cis\text{-Ph}}$ value of −0.22 ppm is obtained. Although this value falls among the lowest entries for $\sigma_{cis\text{-Ph}}$ in Table VII (uncrowded phenyls), it is not significantly different from them. Therefore the conformation of **6** can adequately be pictured as shown in Table IX. The following calculations support this view.

The resonance position of the vinyl proton in bromo-*trans*-stilbene calculated assuming normal σ values for both phenyls is −7.60 ppm. If the phenyl *cis* to Br in **6** is assumed to have the same crowded environment as the phenyl group in **5**, and is assigned a $\sigma_{gem\text{-Ph}}$ value of −1.09, while the phenyl *gem* to Br is presumed to be sterically uncrowded and have a normal −0.38-ppm $\sigma_{cis\text{-Ph}}$ value, **6** is predicted to show vinyl proton resonance at −7.27 ± 0.16 ppm, in satisfying agreement with the −7.14-ppm observed value. In other ethylenes bearing sterically crowded phenyl groups similar perturbation of $\sigma_{gem\text{-Ph}}$ values should be anticipated.

The data and principles outlined above permit rapid confirmation of a number of rather arduously assigned styrene structures. Davis and Roberts have synthesized both isomers of α-methyl-β-bromostyrene, shown in Table X.[25] As pointed out by the original authors the relative magnitudes of J_{H-CH_3} in the two isomers are *not* a reliable indicator of structure, and the *cis–trans* structure assignments were made on the bases of relative chemical reactivity, mechanism of synthesis, and relative boiling point and uv absorption characteristics. The excellent agreement between the calculated and observed vinyl proton resonance positions provides unambiguous proof of these structures. In this case both the relative and absolute vinyl proton resonance positions help in assigning the structures. In cases where only one isomer is reported the absolute value of the predicted resonance position alone often suffices.

Reed has reported[26] that halogenation of α-methylstyrene with N-chlorosuccinimide provides, in addition to α-chloromethylstyrene, a single α-methyl-β-chlorostyrene (**8**) with the nmr spectrum summarized in Table XI. From the predicted resonance positions **8** can confidently be assigned the *trans* structure. It is instructive to note that J_{CH_3-H} in this *trans* compound happens to be the same as J_{CH_3-H} in the *cis* Br isomer of **7**![27]

It is, of course, possible to tabulate functional group shielding parameters for an almost endless variety of vinyl substituents. Pascual, Meier, and Simon[5] list 30 vinyl substituents and their σ values, calculated from the spectra of 1070 compounds! It should be noted that the independent compilations of σ values for the substituents Br, Cl, CH_3, CN, and Ph agree very well. Pascual, Meier, and Simon's results are summarized here for convenience in Table XII.

Pascual, Meier, and Simon recognize that specific interactions between vinyl substituents can profoundly alter their effective group σ values. They have con-

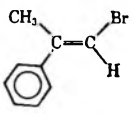
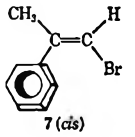
(24) M. J. S. Dewar, *J. Amer. Chem. Soc.*, **74**, 3345 (1952).

(25) D. R. Davis and J. D. Roberts, *ibid.*, **84**, 2252 (1962).

(26) S. F. Reed, Jr., *J. Org. Chem.*, **30**, 3258 (1965).

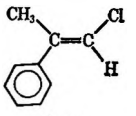
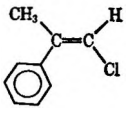
(27) See W. A. Nasutavicus, S. W. Tobey, and F. Johnson, *ibid.*, **32**, 3325 (1967), for assignment of structures to several phenyl alkylacrylonitriles using the technique outlined here.

TABLE X
NMR DATA FOR *cis*- AND *trans*-α-METHYL-β-BROMOSTYRENE 7[a]

α-Methyl-β-bromostyrene	δ_{CH_3}, ppm	J_{CH_3-H}, Hz	$\delta_{H_{obsd}}$, ppm	$\delta_{H_{calcd}}$, ppm
 7 (*trans*)	−2.12	1.25 ± 0.04	−6.30	−6.33 ± 0.17
 7 (*cis*)	−1.97	1.50 ± 0.04	−6.03	−5.92 ± 0.19

[a] See ref 25.

TABLE XI
ASSIGNMENT OF STRUCTURE TO THE α-METHYL-β-CHLOROSTYRENE (8) OBTAINED IN NCS CHLORINATION OF α-METHYLSTYRENE

α-Methyl-β-chlorostyrene 8[b]	$\delta_{H_{calcd}}$, ppm	$\delta_{H_{obsd}}$,[a] ppm
 *trans*	−6.36 ± 0.18	−6.34
 *cis*	−5.94 ± 0.20	

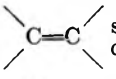
[a] δ_{CH_3} = −2.15, J_{CH_3-H} = 1.51 ± 0.02 Hz. [b] See ref 26.

jugation are present together (conj). The resonance positions for vinyl protons in all compounds containing such substituents are still calculated using eq 1.

We feel this approach is oversimplified. The cooperative shielding properties of two functional groups capable of conjugative interaction can easily be shown to depend *heavily* on the relative geometries of the two substituents. The data in Table XIII illustrate this point for $-OCH_3$[28] and $-CO_2CH_3$.[29] Five of the six σ values show variations of more than 0.5 ppm. It seems clear that strong dipole–dipole and steric interactions (in addition to conjugative interactions) must be operating between these highly polar, anisotropic substituents.

TABLE XII
VINYL SUBSTITUENT SHIELDING PARAMETERS AS OBTAINED BY PASCUAL, MEIER, AND SIMON
(δ_H −5.27 + Σσ PPM)

Substituent	σ_{cis}, ppm	σ_{trans}, ppm	σ_{gem}, ppm
-H			
H	0.00	0.00	0.00
CH_3–, C_2H_5–, etc.	+0.26	+0.29	−0.44
Alkyl ring[a]	+0.33	+0.30	−0.71
-Cl	−0.19	−0.03	−1.00
-Br	−0.40	−0.55	−1.04
−CN	−0.78	−0.58	−0.23
-C≡C-	−0.35	−0.10	−0.50
-Ph	−0.37	+0.10	−1.35
$-CH_2O-$, CH_2I	+0.02	+0.07	−0.67
$-CH_2S-$	+0.15	+0.15	+0.53
$-CH_2Cl$, $-CH_2Br$	−0.12	−0.07	−0.72
-O-alkyl	+1.06	+1.28	−1.18
-OAr, -O-conj	+0.65	+1.05	−1.14
-OCOR	+0.40	+0.67	−2.09
$-N(alkyl)_2$	+1.19	+1.31	−0.69
$-N(Ar)_2$, $-N(conj)_2$	+0.73	+0.81	−2.30
-SR	+0.24	+0.04	−1.00
$-SO_2R$	−1.15	−0.95	−1.58

Substituent		σ_{cis}, ppm	σ_{trans}, ppm	σ_{gem}, ppm
	solo[b]	+0.04	+0.21	−0.98
	conj	−0.08	+0.01	−1.26
	solo	−1.13	−0.81	−1.10
	conj	−1.01	−0.95	−1.06
	solo	−1.35	−0.74	−1.00
	conj	−0.97	−0.39	−0.69
	solo	−1.15	−0.56	−0.84
	conj	−1.02	−0.33	−0.68
		−0.97	−1.21	−1.03
		−1.41	−0.99	−1.10
		−0.93	−0.35	−1.37

[a] The "alkyl ring" increment is used when the C=C bond being studied forms part of a ring. [b] The increment for "R conj" is used instead of the "R solo" value when either the R substituent *or* the double bond being studied is further conjugated with other substituents.

cluded that these perturbations are primarily due to conjugative interaction between substituents.[5] They have attempted to take this into account by listing two sets of σ values for carbonyl and other unsaturated substituents. One set is to be used when such substituents are present alone on the double bond (solo). The other is to be used when two or more groups capable of con-

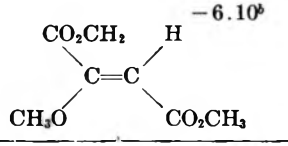
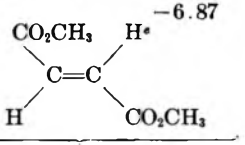
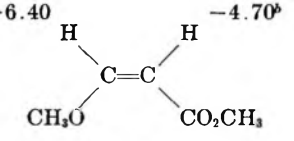
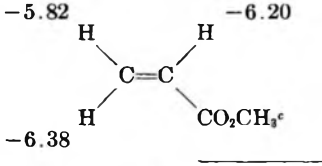
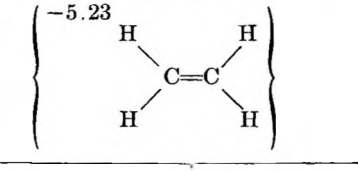
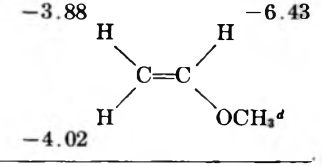
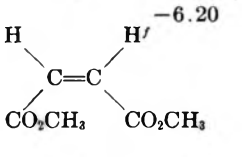
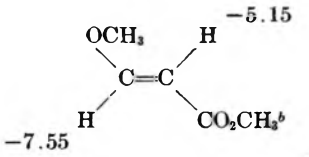
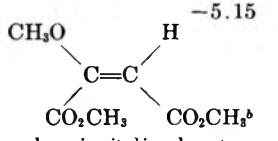
In general, when two asymmetric (C_s or lower symmetry) substituents are present together on an ethylenic

(28) (a) C. N. Banwell and N. Sheppard [*Mol. Phys.*, **3**, 351 (1960)]; (b) J. Feeney, A. Ledwith, and L. H. Sutcliffe [*J. Chem. Soc.*, 2023 (1962)], and (c) W. Brügell, Th. Ankel, and F. Krückeberg [*Z. Elektrochem.*, **64**, 1121 (1960)] discuss the origin of $-OCH_3$ shielding effects.

(29) See ref 3a, pp 121–125, and G. J. Karabatsos, G. C. Sonnichsen, N. Hsi, and D. J. Fenoglio, *J. Amer. Chem. Soc.*, **89**, 5067 (1967), for discussion of carbonyl shielding effects.

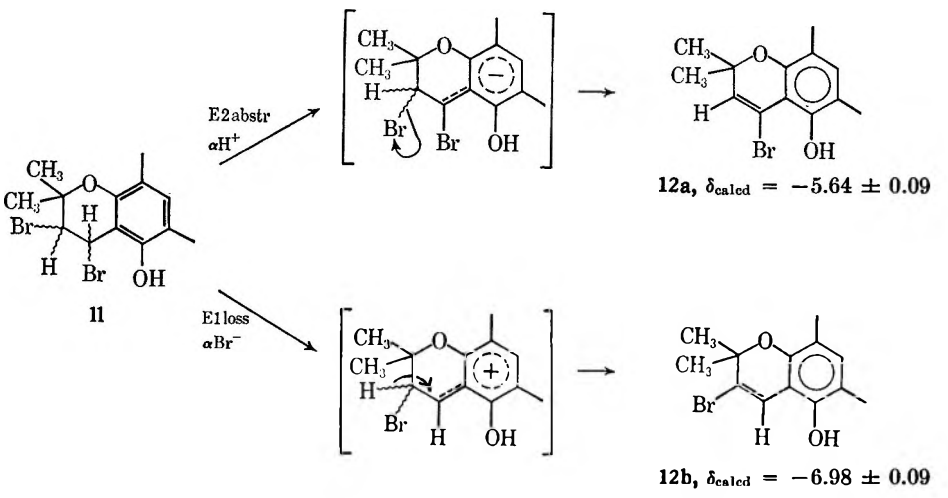
Table XIII

Effect of Relative Geometry and Substituent Environment on the Apparent σ Values for $-CO_2CH_3$ and $-OCH_3$

	σ_{OCH_3}, ppm			$\sigma_{CO_2CH_3}$, ppm		
	cis	*trans*	*gem*	*cis*	*trans*	*gem*
		*+0.77*[a]		*−1.40*		
 		+1.50	*−0.58*	*−0.67*	*+0.03*	*−0.49* −0.82
  	+1.30 (+1.06)	+1.44 (+1.28)	−1.11 (−1.18)	(−1.15) −1.06 (−1.02) c	(−0.56) −0.50 (−0.33) c	(−0.84) −0.88 (−0.68) c
 	+1.05		−1.17	 −1.12	±0.00	*−0.38* *−1.13*
	+1.05				±0.00	

[a] σ values in *italics* denote gross departure from "normal" behavior. Data in parentheses are σ values listed by Pascual, Meier, and Simon[c] for these groups in solo, and conjugative (c) situations. [b] E. Winterfeldt and H. Preuss, *Chem. Ber.*, **99**, 450 (1966). [c] See Table II, footnote *d*. [d] R. T. Hobgood, Jr., G. S. Reddy, and J. H. Goldstein, *J. Phys. Chem.*, **67**, 110 (1963). [e] Registry number: 624-49-7. [f] Registry number: 624-48-6.

SCHEME I

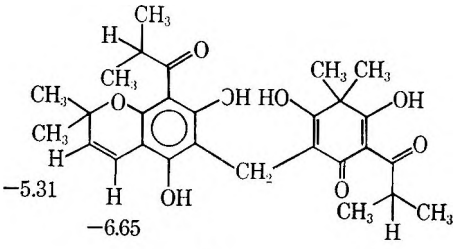


backbone, neither one retains the angular orientation it assumes if present alone. Also, the average orientation and effective σ values of each asymmetric group *vary*, depending on the exact nature and relative location of the other asymmetric group with which it is paired. Therefore, attempts to tabulate σ "constants" for asymmetric substituents that will be of any great use in differentiating between closely related ethylenes are ordinarily fruitless.

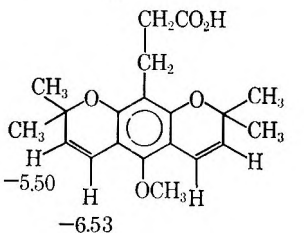
In predicting the resonance positions of vinyl protons in trisubstituted ethylenes bearing two asymmetric substituents most of the problems just discussed are avoided by use of a "model compound" approach. A compound is chosen from the literature which bears the asymmetric substituents in the appropriate geometry and environment, and in which the vinyl proton resonance positions can be unambiguously assigned. This model compound is then "transformed" into the desired trisubstituted ethylene by applying the σ value for one of the small, highly symmetric groups listed in Tables I–IV. This procedure automatically takes into account most of the major interactions between asymmetric groups.

The remainder of this paper describes several structural assignment problems which cannot be unambiguously solved using the simple additivity principle, but which can be simply solved using the model compound technique. Where relevant, the chemical implications of the assignments are discussed.

Bromouliginosin-B.—Uliginosin-B (**9**), an antibiotic isolated from a Central American herb, has been under investigation by a group in this laboratory.[30] The structure of **9** was initially deduced from a painstaking study of its nmr, ir, uv, and mass spectra.[30a] However, it was desired to confirm structure **9** by a single crystal X-ray diffraction study on a heavy atom derivative.[30b] To this end the carbon–carbon double bond in a sample of **9** was brominated in CCl_4 to dibromide **11** and dehydrobrominated in pyridine without purification to provide a single bromouliginosin-B (**12**) which showed singlet vinyl proton resonance at −7.04 ppm. The nmr spectrum of uliginosin-B includes two doublet resonances (J_{HH} = 9.9 Hz) in the vinyl region at −6.65 and −5.31 ppm[30a] which can be unambiguously assigned to the protons shown in structure **9** by their similarity to those in eriostoic acid (**10**).[31]



9



10

The question arose as to whether the bromine in **12** was α or β to the phenyl ring (**12a**) or (**12b**). Mechanisms leading to both derivatives from the intermediate dibromide seemed plausible. E2 abstraction of the acidic α proton by pyridine would lead to **12a** *via* a bromobenzylic anion, whereas E1 ionization of α bromine, would lead to **12b** *via* a benzylic cation.[32] This problem was quickly laid to rest using the σ additivity principle. (See Scheme I.)

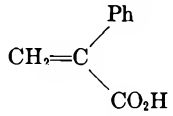
Application of $\sigma_{cis\text{-}Br}$ from Table I (−0.33 ± 0.09 ppm) to the two resonance positions in **9** shows that the vinyl proton in **12a** should resonate at −5.64 ± 0.09 ppm, whereas the vinyl proton in **12b** should resonate at −6.98 ± 0.09 ppm. This latter value is in excellent agreement with the observed −7.04-ppm value for **12**, and the β-Br structure was subsequently confirmed in the X-ray study.

(30) (a) W. L. Parker and F. Johnson, *J. Amer. Chem. Soc.*, **90**, 4716 (1968); (b) W. L. Parker, J. J. Flynn, and F. P. Boer, *ibid.*, **90**, 4723 (1968).

(31) Reference 19, spectrum 344.

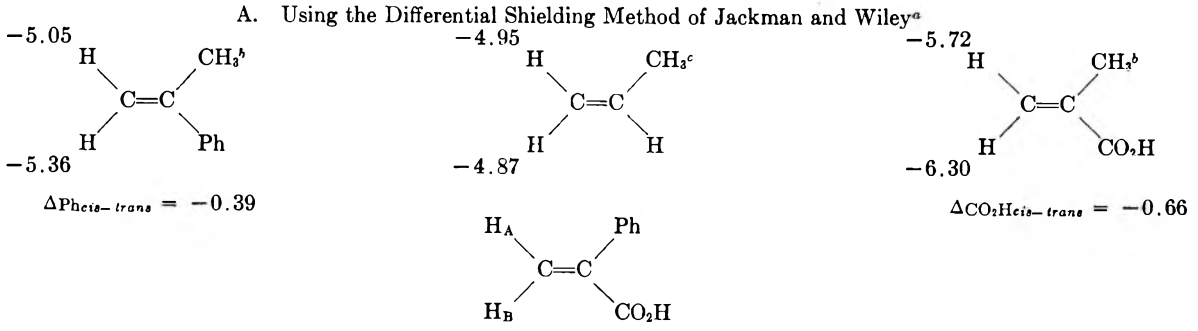
(32) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, New York, N. Y., 1959, Chapter 12, pp 472–485.

TABLE XIV
ASSIGNMENT OF THE VINYL PROTON RESONANCES IN ATROPIC ACID (**13**)



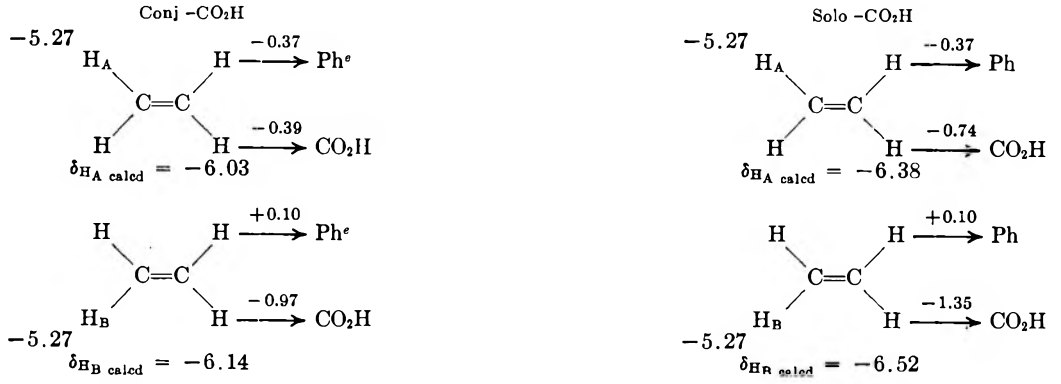
$\delta_{H_A\ obsd} = -5.95$ ppm
$\delta_{H_B\ obsd} = -6.52$ ppm
$J_{HH} = 1.5$ Hz

A. Using the Differential Shielding Method of Jackman and Wiley[a]



$\Delta_{(H_B-H_A)} = -0.66 - (-0.39) = -0.27$ ppm, therefore H_B downfield

B. Using Eq 1 and σ Data from Table XII[d]



C. Using β-Methylatropic Acids as Models[f] and σ_{gem-CH_3} Data from Table III

[a] See ref 3. [b] See Table II, footnote *d*. [c] See Table I, footnote *b*. [d] See ref 5. [e] The model compound used in the calculation is shown at the center of each block, along with the resonance position of its key vinyl proton. The vinyl substitutions required to "transform" the model compound into the desired compound are shown by arrows, and the shifts in resonance position of the key vinyl proton caused by such substitution are shown along the arrows. [f] See ref 34.

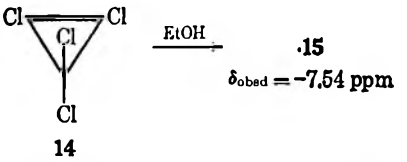
Atropic Acid.—Atropic acid (**13**)[33,34a] shows doublet vinyl proton resonances at −5.95 and −6.52 ppm, as shown at the top of Table XIV. Part A of the table illustrates the assignment of these resonances to the appropriate vinyl protons by the "differential shielding" method of Jackman and Wiley.[3] Comparing α-methylstyrene with propene (the standard reference compound used in this method) the phenyl group causes a −0.49-ppm downfield shift in the resonance position of the proton *cis* to phenyl, whereas the resonance position of the proton *trans* to phenyl is only moved downfield −0.10 ppm. Therefore, according to Jackman and Wiley, the phenyl group exerts a differential (*cis vs. trans*) shielding of −0.39 ppm. By a similar comparison of methacrylic acid with propene, the carboxyl group "differential shielding" is −0.66 ppm. In atropic acid, the β-vinyl protons experience *both* these differential shieldings but in *opposition* to one another. Therefore, one predicts that the proton *cis* to carboxyl in atropic acid will resonate −0.27 ppm (downfield) from the proton *cis* to phenyl. This prediction is qualitatively correct (see below) and serves as the basis for the assignment of the vinyl proton resonances in atropic acid given by Nilsson and Sternhell.[34]

Despite its success in this case the differential shielding method has two drawbacks. First, the differential shielding exerted by a group is always calculated using a model compound in which the group under considera-

(33) Prepared from atrolactic acid following the explicit directions of W. A. Bonner and R. T. Rewick, *J. Amer. Chem. Soc.*, **84**, 2334 (1962), mp 107–108°. The vinyl proton resonances in atropic acid are doublets, J_{HH} = 1.5 Hz. See ref 34a also.

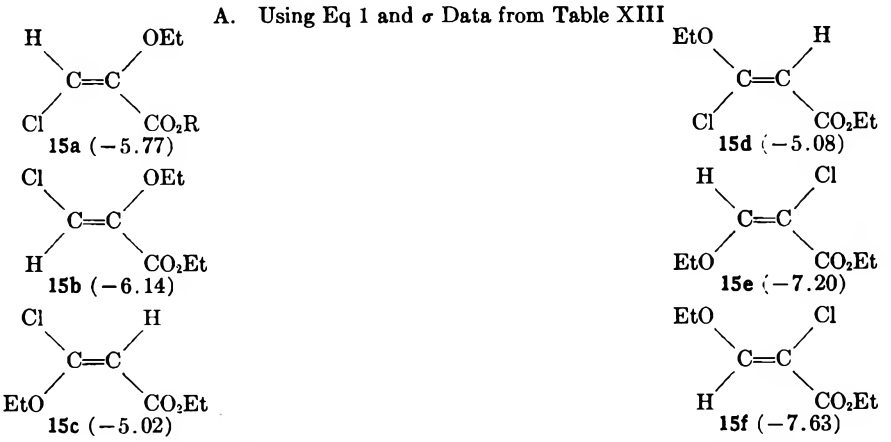
(34) (a) K. Nilsson and S. Sternhell, *Acta Chem. Scand.*, **19**, 2441 (1961); (b) K. Nilsson, *ibid.*, **19**, 612 (1965).

TABLE XV
PREDICTIONS OF THE RESONANCE POSITION FOR THE ETHYL CHLOROALKOXYACRYLATE ESTER 15 OBTAINED IN THE ETHANOLYSIS OF TETRACHLOROCYCLOPROPENE[a,b]

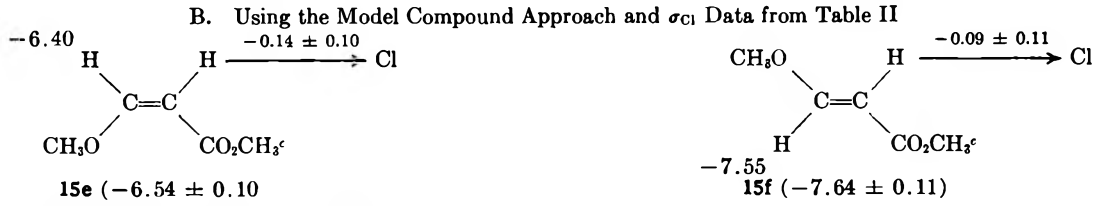


14

A. Using Eq 1 and σ Data from Table XIII



B. Using the Model Compound Approach and σ_{Cl} Data from Table II



[a] See ref 20. [b] δ_{obsd} values are given in parentheses. [c] See Table XIII, footnote *b*.

tion is *gem* to $-CH_3$. Since the shielding properties of a group *are* affected by its environment (both steric and electronic), sole reliance on the propenes as model compounds gives a false sense of consistency in group shielding behavior. This deficiency manifests itself in this instance as a grossly underestimated value of the differential shielding (−0.27 ppm calculated *vs.* −0.57 ppm observed). A second and more serious shortcoming of the technique is simply that it fails to make full use of the data at hand. No information on the *absolute* locations of the resonance positions is obtained, despite the fact that all the data required to make such a prediction must be obtained in order to make the differential shielding calculation.

Part B of Table XV shows the vinyl proton resonance positions for **9** predicted using the σ additivity data of Pascual, Meier, and Simon from Table XII.[5] The results of calculations assuming both "solo" and "conjugated" σ values for the $-CO_2H$ group are shown. Definitionally,[5] only the σ_{conj} values should have been employed, since the ethylenic system "stands in conjugation"[5] with the phenyl group. However, the reason for using σ_{conj} values is presumably to take into account conjugative interactions between the $-CO_2H$ and $-Ph$ groups. In atropic acid these groups are *cross*-conjugated rather than conjugated. The fact is that neither set of calculations satisfactorily fits the observed data. One set skews both resonances upfield, the other set downfield.

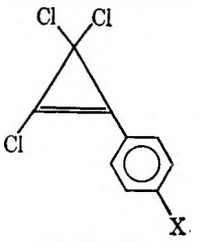
Since the differential between the calculated δ values in each set is sufficiently small, and so far within the (overlapping) uncertainty limits which must reasonably be assigned to each δ, assignment of the observed resonances to the appropriate vinyl protons in atropic acid using Pascual, Meier, and Simon's method is simply not possible.

The failure of the simple σ additivity calculation derives primarily from its inability to evaluate properly the highly specific interactions which undoubtedly occur between geminal $-CO_2H$ and $-Ph$ groups. For the purposes of the model compound nmr structural assignment technique, illustrated in part C of Table XV, it is not essential to understand in detail either the origin or exact nature of these interactions, but only to appreciate that they exist. Nilsson[34] has unambiguously assigned structures to the *cis* and *trans* β-methylatropic acids used as the models in part C from detailed consideration of their uv, ir (and nmr) spectra. Simply by applying the −0.44 ± 0.09 ppm $\sigma_{gem\text{-}CH_3}$ correction from Table III to the nmr data on the β-methylatropic acids, the proton *cis* to $-Ph$ in atropic acid is predicted to resonate at −5.96 ± 0.09 ppm, in excellent agreement with the −5.95-ppm observed value. Similarly the proton *cis* to $-CO_2H$ is predicted to resonate at −6.6 ± 0.2 ppm in excellent agreement with an observed −6.52-ppm value. The larger uncertainty in this latter prediction arises from the fact that the vinyl proton resonance in the model compound is buried in a broad phenyl resonance region.

Tetrachlorocyclopropene Solvolysis Products.—When tetrachlorocyclopropene (**14**) is solvolyzed in ethanol, one of the minor reaction products is a chloroalkoxyacrylate ester **15** which shows vinyl proton resonance at −7.54 ppm.[20] Given the extent of molecular rearrangement and substitution required to convert **14** into **15**, none of the six possible geometric isomers of **15** can be disregarded as being impossible. Part A of Table XV shows predicted resonance positions for the six

TABLE XVI

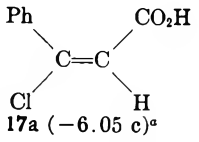
PREDICTION OF THE VINYL PROTON RESONANCE POSITIONS IN PHENYLCHLOROACRYLIC ACIDS 17 AND 19[a]



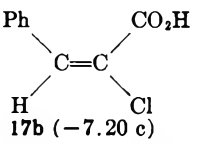
$\xrightarrow{H_2O}$ 17, X = H; $\delta_{obsd} = -7.57$
19, X = F; $\delta_{obsd} = -7.72$

16, X = H
18, X = F

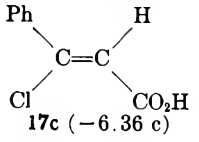
A. Using Eq 1 and σ Data from Table XII[b]



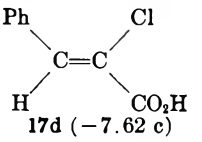
17a (−6.05 c)[a]



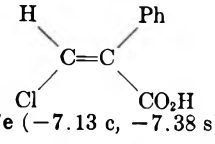
17b (−7.20 c)



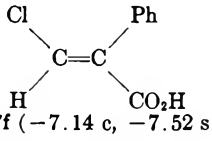
17c (−6.36 c)



17d (−7.62 c)

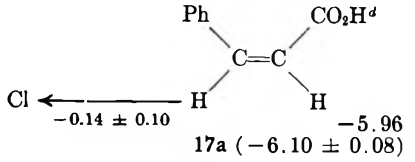


17e (−7.13 c, −7.38 s)[c]

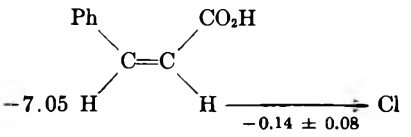


17f (−7.14 c, −7.52 s)

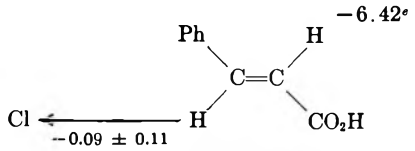
B. Using *cis*- and *trans*-Cinnamic[f] and Atropic Acids[g] as Models and σ_{Cl} Data from Table II



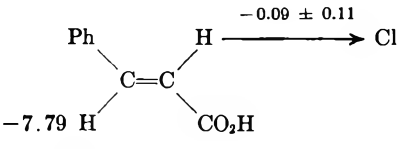
17a (−6.10 ± 0.08)



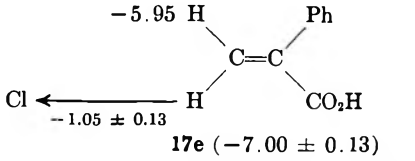
17b (−7.19 ± 0.08)



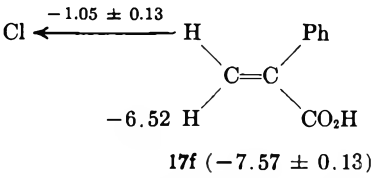
17c (−6.51 ± 0.11)



17d (−7.88 ± 0.11)



17e (−7.00 ± 0.13)



17f (−7.57 ± 0.13)

[a] δ_{calcd} values are given in parentheses. [b] See ref 5. [c] c denotes δ_{calcd} using $\sigma_{conj\ CO_2H}$; s denotes δ_{calcd} using $\sigma_{solo\ CO_2H}$. [d] J_{HH} = 12.9 Hz. [e] J_{HH} = 16.1 Hz. See ref 19, spectrum 230 also. [f] See ref 37. [g] See ref 33.

possible isomers of **15** using eq 1 and σ_{solo} values from Table XII. The first four structures can be eliminated immediately since the predicted δ values deviate so greatly from the observed resonance position. Bearing in mind the uncertainties in σ values which occur when -OR and $-CO_2R$ are present together, **15f** (δ_{calcd} = −7.63) would be judged the more likely structure, though **15e** (δ_{calcd} = −7.20) could not be excluded.

That structure **15f** is indeed correct is demonstrated by model compound calculations shown in part B of the table. Using the Winterfeldt and Preuss data[35] for *cis*- and *trans*-methyl 2-methoxyacrylate and applying corrections for *cis* and *trans* Cl, **15f** is predicted to resonate at −7.64 ± 0.11 ppm. On the other hand, **15e** is predicted to resonate at −6.54 ± 0.10 ppm, *considerably* removed from both the observed resonance, and the −7.20-ppm resonance position calculated assuming simple σ additivity.

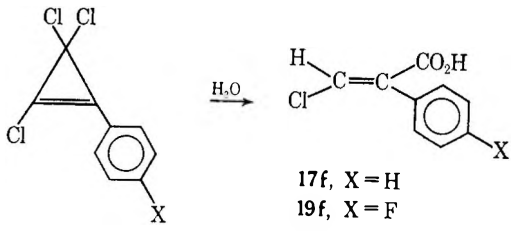
Phenyltrichlorocyclopropene Hydrolysis Products.—Hydrolysis of 1-phenyl-2,3,3-trichlorocyclopropene (**16**) provides a phenylchloroacrylic acid (**17**) which shows vinyl proton resonance at −7.57 ppm.[36] Hydrolysis of 1-*p*-fluorophenyl-2,3,3-trichlorocyclopropene (**18**) produces a *p*-fluorophenylchloroacrylic acid (**19**) showing vinyl proton resonance at −7.72 ppm.[20] Table XVI, part A, shows the vinyl proton resonances predicted for the six possible isomers of **17** using simple σ additivity.[5] Structures **17a** and **c** can be quickly discarded. However, *no* choice from among the remaining four isomers

(35) See footnote *b*, Table XIII.

(36) D. C. Zecher and R. West, University of Wisconsin, private communication.

can be made, especially if it is (reasonably) assumed that in the chlorocinnamic derivatives (**17a–d**) $\sigma_{conj\ CO_2H}$ values should be used, whereas in the chloroatropic acids (**17e** and **f**) $\sigma_{solo\ CO_2H}$ values should be employed.

Part B of Table XVI shows the contrasting results of predicting the vinyl proton resonances for **17a–f** using *cis*-[37,38] and *trans*-cinnamic and atropic acids[33] as model compounds. Structure **17f** is uniquely indicated.



16, X = H
18, X = F

17f, X = H
19f, X = F

Comparison of **17** and **19** shows that introduction of *p*-fluorine has caused a −0.15-ppm downfield shift in the vinyl resonance. This observation corroborates assignment of structure **17f** to the hydrolysis product and decisively excludes structures **17b** and **d**, the only two which have predicted resonances anywhere near **17f**. **17b** and **d** have hydrogen α to the phenyl, whereas **17f** has hydrogen β to the ring. From the data in Table VIII, introduction of *p* fluorine should have negligible effect on the resonance position of α hydrogen[39]—a prediction contrary to the fact presuming either structure **17b** or **d** but should cause an approximately −0.10 ± 0.05 ppm downfield shift in resonance position of β hydrogen—clearly in agreement with fact assuming structure **17f**.

α-Cyanocinnamic Ester Geometry.—In their paper,[5] Pascual, Meier, and Simon list several compounds for which the difference between the observed vinyl proton resonance position and that calculated assuming σ additivity exceeds 0.5 ppm. Among them is one taken from the Varian catalog, spectrum 290:[19] ethyl α-cyanocinnamate, **20**. This compound shows vinyl proton resonance at −8.22 ppm and is assigned a *cis* geometry. As shown in part A of Table XVII, *cis* **20** is actually predicted to resonate at −7.74 using Pascual, Meier, and Simon's data, while the *trans* isomer is predicted to resonate at −8.22 ppm. That the compound listed in the Varian catalog should be reassigned the *trans* **20** structure seems clear, particularly since the analogous methyl ester, spectrum 576, showing vinyl proton resonance at −8.27 ppm, is assigned *trans*.

A recent paper by Hayashi,[40] in which both *cis* and *trans* **20** are discussed, supports this conclusion; the vinyl proton resonance for *trans* **20** is given as −8.22 ppm. However, the paper makes the disconcerting assertion that *cis* **20** resonates at −7.26 ppm, 0.5 ppm *up*field from the location predicted using σ additivities!

(37) *cis*-Cinnamic acid was obtained as a 1:2 mixture with the *trans* isomer by photoisomerization for 2 hr.[38]

(38) Photoisomerizations were carried out on 5–10% w/v solutions in clear Pyrex nmr tubes (uv cutoff 3000 Å) centrally suspended in a Southern New England Ultraviolet Co. Rayonet RPR-100 photochemical reactor fit with RPR 3000-Å lamps.

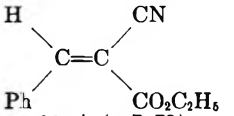
(39) The combined inductive and resonance effects of *p*-fluorine are comparable with those with Cl. See (a) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 709, 3146 (1963); and (b) ref 32, Chapter 7, especially p 221.

(40) T. Hayashi, *J. Org. Chem.*, **31**, 3253 (1966).

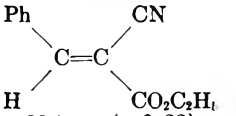
Because the applicability of simple σ additivities to compounds of type **20** is open to question (particularly for the *cis* isomer in which space-filling models suggest that neither the $-CO_2Et$ nor −Ph groups can achieve normal coplanarity with the ethylenic backbone), it seemed worthwhile to prepare model compounds of *trans* and *cis* **20**. Methyl *trans*-cinnamate (**21**) was therefore photoisomerized for 3 hr in $CDCl_3$ to an approximately 2:1 mixture of *trans*:*cis* **21** and the nmr data shown in part B of Table XVII were recorded.[41]

TABLE XVII
PREDICTION OF THE VINYL PROTON RESONANCE POSITIONS IN ETHYL α-CYANO-*cis*- AND -*trans*-CINNAMATES[a]

A. Using Eq 1 and σ Data from Table XII

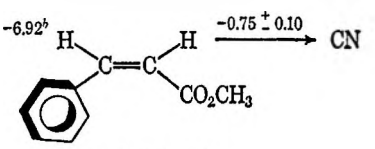


20 *cis* (−7.73)



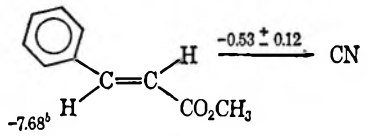
20 *trans* (−8.22)

B. Using *cis*- and *trans*-Methyl Cinnamate (**21**) as Models and σ_{CN} Data from Table IV



cis **20** (−7.67 ± 0.10)

δ_{obsd} = −7.64



trans **20** (−8.21 ± 0.12)

δ_{obsd} = −8.22

[a] δ_{calcd} values (parts per million) are given in parentheses. [b] The proton *gem* to $-CO_2CH_3$ in *cis*-methyl cinnamate resonates at −5.92 ppm and J_{HH} = 12.5 Hz. The methyl group resonates at −3.79 ppm. In the *trans* compound the vinyl proton *gem* to $-CO_2CH_3$ resonates at −6.41 ppm and J_{HH} = 16.2 Hz. The methyl group resonates at −3.68 ppm. The difference in σ values for $-CO_2CH_3$ and $-CO_2C_2H_5$ is negligible.

Application of the σ constants for −CN to these data leads to vinyl proton resonance positions for *cis* and *trans* **20** of −7.67 ± 0.10 and −8.21 ± 0.12 ppm, respectively. Two conclusions seemed inescapable: *trans* **20** should indeed be assigned the −8.22-ppm resonance position, and Hayashi's data for *cis* **20** must be in error.

Hayashi's nmr spectrum[40] of the photoequilibrated mixture of methyl α-cyanocinnamates is reproduced below in Figure 2. The −8.22- and −7.26-ppm "vinyl proton" resonances are of comparable intensity, whereas the methyl resonances (which should be of the same relative intensities) are *not*. The spectrum in Figure 2 was obtained on a $CDCl_3$ solution of the ester mixture isolated from the benzene solution in which it was prepared by photoisomerization. We concluded that the −7.26-ppm resonance assigned to *cis* **20** was in reality due to the small amount of $CHCl_3$ (δ = −7.27 ppm)[19]

(41) The data of A. J. Speziale and C. C. Tung [*ibid.*, **28**, 1353 (1963)] would have been very useful but for the fact that the nmr data were taken on the neat liquids in which horrendous solvent shifts occur.

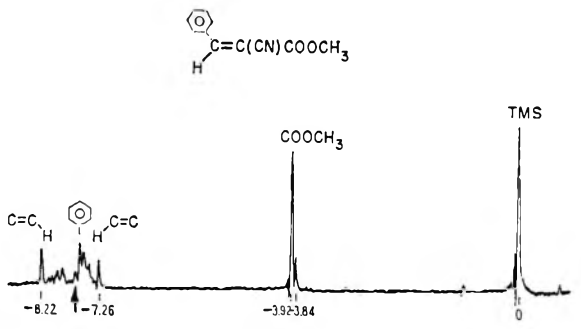


Figure 2.—The $CDCl_3$ nmr spectrum of *cis*- and *trans*-methyl α-cyanocinnamates photoequilibrated in benzene. Reprinted from T. Hayashi, *J. Org. Chem.*, **31**, 3253 (1966). Copyright 1966 by the American Chemical Society. Reprinted by permission of the copyright owner. Note the relative sizes of the −7.26 and −8.22 resonances assigned by Hayashi to the vinyl protons in the *cis* and *trans* isomers *vs.* the relative sizes of the methyl resonances at −3.84 and −3.92 ppm. Note also the resonance at −7.64 ppm indicated by the arrow.

normally present in $CDCl_3$, and the small, unassigned blip at −7.64 ppm was due to *cis* **20**.

To prove this point **20** was synthesized from benzaldehyde and ethyl cyanoacetate,[42] and photoisomerized for 24 hr in deuteriobenzene.[43] Figure 3A shows the $CDCl_3$ nmr spectrum of the resulting product mixture. In addition to the vinyl proton resonance for *trans* **20** at −8.22 ppm the spectrum shows a strong singlet at −7.64 ppm in the position predicted for *cis* **20** using model compounds. That this resonance is indeed due to the vinyl proton in *cis* **20** (and not to a phenyl resonance) is demonstrated by the spectrum shown in Figure 3B. This latter spectrum was taken on a photoisomerized sample of **20** prepared from benzaldehyde containing 50% aldehydic deuterium.[44-46] The peaks at −8.22 and −7.64 ppm are reduced to half-intensity while all other bands in Figures 3A and B are of comparable size. It is thus clear that *trans* and *cis* **20** *do* resonate in the positions accurately predicted by the model compound calculations.

It is worthwhile noting here that the original photoisomerized solution of *cis* and *trans* **20** in C_6D_6 showed *no* peak at −7.64 ppm. The −8.22 peak for *trans* **20** was observed at −7.99, shifted upfield +0.23 ppm. The −7.64 peak for *cis* **20** was subsequently shown by the deuterium labeling experiment to fall at −7.07 ppm in C_6D_6, shifted upfield +0.57 ppm into the complex phenyl region (which also moves upfield in C_6D_6).

(42) Benzaldehyde and cyanoacetic ester (0.1 mol each) were refluxed in 50 ml of benzene containing 1 ml of piperidine and 20 g of Linde Mclecular Sieve 4A for 3 hr.

(43) Photoisomerization of **20** in $CDCl_3$ and cyclohexane does not occur to any measurable extent in 3 hr.

(44) Benzaldehyde-*d* has been synthesized by a variety of routes.[45] The material used in this work was made[46] by stirring 0.1 mol (10.6 g) of benzaldehyde with 100 ml of D_2O, 1 g of NaCN, and 350 ml of tetrahydrofuran at room temperature for 48 hr. The resulting solution was saturated with K_2CO_3; the upper THF layer was drawn off and dried over additional K_2CO_3. Filtration, followed by removal of solvent under vacuum, left a white crystalline powder (presumably benzoin) moist with benzaldehyde. Trituration of this material with 25 ml of petroleum ether, filtration, and removal of solvent under vacuum provided 3.2 g of high-purity benzaldehyde showing 50 ± 5% deuterium incorporation in the carbonyl position by nmr analysis.

(45) (a) R. A. Olofson and D. M. Zimmerman, *J. Amer. Chem. Soc.*, **89**, 5057 (1967); (b) J. C. Craig and L. R. Kray, *J. Org. Chem.*, **33**, 871 (1968); (c) D. Seebach, B. W. Erickson, and G. Singh, *ibid.*, **31**, 4303 (1966).

(46) The synthesis suggests itself immediately from a consideration of the probable mechanism of the benzoin condensation. See ref 32, pp 394–397, and references cited there.

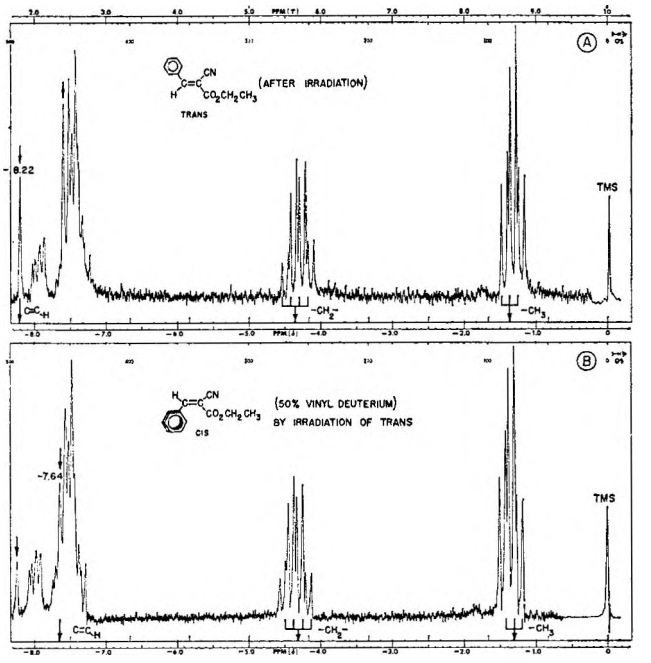


Figure 3.—(A) The $CDCl_3$ spectrum of *cis*- and *trans*-methyl α-cyanocinnamate after 24-hr photoequilibration at 300 mμ in C_6D_6. The vinyl and ethyl group resonances characteristic of the initial *trans* isomer are indicated at the base of the spectrum. Note the −8.22- and (photogenerated) −7.64-ppm resonance lines. (B) An analogous spectrum of photoequilibrated ester containing 50% vinyl deuterium. Note the essentially identical sizes of the ethyl group resonances in spectra A and B and the much smaller (due to deuteration) sizes of the −8.22- and −7.64-ppm resonances in spectrum B.

This differential shielding of the vinyl protons in *cis* and *trans* **20** in C_6D_6 *vs.* $CDCl_3$ is only one example of a very general effect produced by such strongly anisotropic solvents as pyridine and benzene.[47] The important point to keep in mind is that the σ parameters and additivity calculations used in this paper are *only* applicable to dilute solutions in isotropic solvents. Vinyl proton nmr positions predicted from data obtained on neat,[41] concentrated, or anisotropic solvent solutions[5] may be in considerable error.

The examples given in this paper illustrate the ease with which structures can be assigned to a wide variety of simple polysubstituted ethylenes using the σ additivity principle,[48] and demonstrate the distinct advantages of the model compound approach to solving trisubstituted ethylene structure assignment problems in which specific polar, steric, and resonance interactions between substituents must be taken into account.

Registry No.—**2**, 557-93-7; **5**, 588-73-8; **6**, 15022-93-2; **7** (*trans*), 16917-35-4; **7** (*cis*), 19647-26-8; **8** (*trans*), 16917-32-1; **8** (*cis*), 16917-31-0; **12a**, 19713-69-0; **12b**, 19647-29-1; **13**, 492-38-6; **15a**, 19647-31-5; **15b**, 19647-45-1; **15c**, 19647-46-2; **15d**, 19647-47-3;

(47) For an excellent explanation of this effect and leading references to numerous specific examples, see T. Ladaal, *Tetrahedron Lett.*, 1683 (1968).

(48) A number of other papers in which the σ additivity principle has or can be used in assigning structures to trisubstituted ethylenes are (a) A. N. Kurtz, W. E. Billups, R. B. Greenlee, H. F. Hamil, and W. T. Pace, *J. Org. Chem.*, **30**, 3141 (1965); (b) M. Barbieux, N. Defay, J. Pecher, and R. H. Martin, *Bull. Soc. Chim. Belges*, **73**, 716 (1964); (c) C. Rappe, T. Nilsson, G. B. Carlsson, and K. Anderson, *Ark. Kemi*, **24**, 95 (1965); (d) C. Rappe, *Acta. Chem. Scand.*, **19**, 31 (1965); (e) C. Rappe and K. Anderson, *ibid.*, **21**, 1741 (1967); (f) A. W. Douglas and J. H. Goldstein, *J. Mol. Spectrosc.*, **16**, 1 (1965).

15e, 19647-48-4; **15f**, 19713-70-3; **17a**, 18819-63-1; **17b**, 705-55-5; **17c**, 18819-66-4; **17d**, 705-54-4; **17e**, 19647-53-1; **17f**, 19647-54-2; **20** (*cis*), 14533-87-0; **20** (*trans*), 2169-69-9; **21** (*cis*), 19713-73-6; **21** (*trans*), 1754-62-7; *cis*-methyl α-cyanocinnamate, 14533-85-8; *trans*-methyl α-cyanocinnamate, 14533-86-9.

Acknowledgments.—The author wishes to thank the National Institutes of Health for a Predoctoral Fellowship at the University of Wisconsin, and the several donors of unpublished nmr data used in the tables. Numerous helpful discussions were held during the course of this work with Professors Robert West of the University of Wisconsin, Norbert Muller of Purdue University, David M. Lemal of Dartmouth College, Sidney L. Gordon of Georgia Institute of Technology, and Drs. Francis Johnson and W. Lawrence Parker of the Dow Chemical Co. Eastern Research Laboratory.

Photolyses of Trienes. III. Photoreactions of 2,3,7,7-Tetramethylcycloheptatriene

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Received August 26, 1968

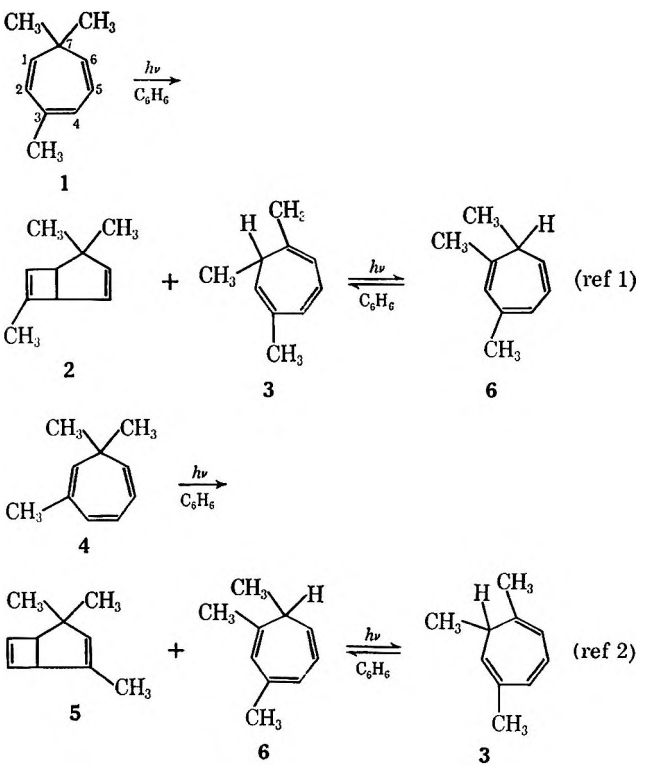
Irradiation of a benzene solution of 2,3,7,7-tetramethylcycloheptatriene (**7**) in a Pyrex tube with a Hanovia medium-pressure mercury arc lamp yields a complex mixture. The major reaction products were identified as 2,2,6,7-tetramethylbicyclo[3.2.0]hepta-3,6-diene (**9**) and 1,2,6,7-tetramethylcycloheptatriene (**13**). Secondary photoproducts (**10** and **11**) were also produced. These reaction products are the result of a selective (1,7) sigmatropic methyl migration and electrocyclization reaction.

Previous studies[1,2] have indicated that methyl substituents attached to vinyl carbon atoms in various cycloheptatrienes exert a strong directive influence on the course of photochemical cyclization and methyl and hydrogen migration reactions. Specifically, irradiation of 3,7,7-trimethylcycloheptatriene[1] (**1**) induces an electrocyclization reaction across C_1 and C_4 to give **2** and promotes methyl migration from C_7 to C_1 to give the new cycloheptatriene **3**. On the other hand, when 2,7,7-trimethylcycloheptatriene (**4**) is irradiated,[2] a methyl shift from C_7 to C_6 is observed to give **6**, and cyclization occurs across C_3 and C_6 to give **5**. Secondary photoproducts were observed in each reaction arising from selective hydrogen migration in the new triene photoproducts to give **6** in the case of **1**, and **3** in the case of **4**. These reactions are summarized in Chart I. The selectivity noted in the methyl and hydrogen migration reactions was rationalized on the basis of a series of molecular orbital calculations, and the selectivity of the cyclization reactions was accounted for primarily on the basis of steric considerations.[1,2]

Based on our observations that the direction of these photochemical cyclization and migration reactions is dependent upon whether the methyl group is located at C_2 or C_3, it was of interest to prepare a cycloheptatriene with methyl substituents located both at positions 2 and 3 to determine which substituent exerts the stronger effect. It was anticipated that the photochemistry of 2,3,7,7-tetramethylcycloheptatriene (**7**) would be more complex and that the selectivity would be less than that observed during photolysis of either **1** or **4**. With this in mind, we have studied the photolysis of **7** in benzene solution with a 450-W Hanovia medium-pressure mercury arc lamp.

2,3,7,7-Tetramethylcycloheptatriene (**7**) was prepared by the addition of methylmagnesium bromide to eucarvone, followed by acid-catalyzed dehydration.[3,4]

CHART I



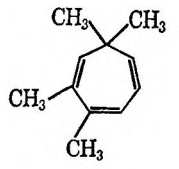
As observed by Conrow,[4] this procedure gives rise to a mixture of **7** (the predominant component) and 2-methylene-3,7,7-trimethyl-3,5-cycloheptadiene (**8**). These materials are readily separable by vapor phase chromatography (vpc).

As anticipated, the photoisomerization reactions of **7** proved to be extremely complex. Irradiation of a benzene solution of **7** to 40% reaction gave a mixture which upon vpc[5] was shown to consist of 1% a group of minor bicyclic products, 11% a group of major bicyclic

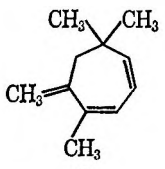
(1) L. B. Jones and V. K. Jones, *J. Amer. Chem. Soc.*, **89**, 1880 (1967).
(2) L. B. Jones and V. K. Jones, *ibid.*, **90**, 1540 (1968).
(3) E. J. Corey, H. J. Burke, and W. A. Remers, *ibid.*, **78**, 180 (1956).
(4) K. Conrow, *ibid.*, **83**, 2958 (1961).

(5) A column packed with SE-30 suspended on base-washed Chromosorb P was employed.

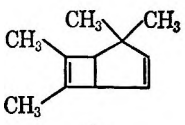
products, 60% unreacted **7**, and 9% new cycloheptatrienes (determined using an internal standard and known thermal conductivity ratios). Further analysis[6] showed the major bicyclic products to consist of three peaks in the relative amounts of 84, 9, and 7%, in order of elution. The structures **9**, **10**, and **11**, respectively,



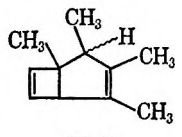
7



8



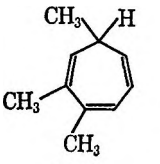
9



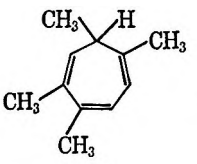
10, 11

have been assigned to these peaks on the basis of arguments presented below. Further analysis[7] of the new trienes showed four peaks in the relative amounts of ~3%, 13% A, 64% B, and 3% C, in order of elution.[8] Irradiation of **7** to almost complete reaction gave a mixture which vpc[5] showed to consist of 7% minor bicyclic products, 35% major bicyclic products, 6% unreacted starting material, and 10% new cycloheptatrienes (determined using an internal standard and known thermal conductivity ratios). Further analysis[6] showed the major bicyclic products to consist of 64% **9**, 20% **10**, and 16% **11**. Analysis[7] of the new trienes showed four peaks in the relative amounts of ~2%, 34% A, 58% B,[9] and 6% C, in order of elution. As A and B are the major new trienes formed, we centered our attention on the elucidation of their structures. Peak C shows aromatic hydrogen absorptions in the nmr spectrum (7 ppm) and no absorption above 2 ppm. Because of its apparent aromatic nature and the absence of alkyl groups attached to saturated carbon atoms, it is felt that this material is not a photoproduct, but arises from either an acid-catalyzed isomerization or a thermal reaction (reaction temperature 35–40°) during the irradiation.

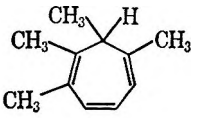
The nmr spectrum of a sample of A shows a three-hydrogen doublet at 0.88 (J = 7.5 Hz), a multiplet at 1.30–2.0 (10 H), a multiplet at 4.50–4.90 (1 H), a multiplet at 5.30–5.60 (1.3 H), and a multiplet at 5.80–6.70 ppm (0.7 H). This spectrum would be consistent with a cycloheptatriene such as **12a** or **12b**, which has one upfield, one midfield, and one low field hydrogen. The ultraviolet (uv) spectrum of the material having this nmr spectrum shows λ_{max} 265 mμ (log ε 3.65), which is typical of cycloheptatrienes.[10] The nmr spectrum of a sample of B shows absorption at 0.75–1.20 ppm on which is superimposed a doublet at 0.96 (J = 7.5 Hz, total integration 3 H), absorption at 1.4–2.1 (10 H), a multiplet at 4.8–5.2 (0.5 H), a multiplet at 5.6–5.9 (1 H), and a multiplet at 6.18–6.38 ppm (1.5 H). This spectrum would be consistent with a cycloheptatriene such as **13**, which would have no upfield, one midfield, and two downfield hydrogens. The uv spectrum of this material shows λ_{max} 266 mμ (log ε 3.59).



12a



12b



13

The proposed structures **12a** and **13** for A and B would be logical if, upon irradiation of **7**, a selective (1,7) sigmatropic methyl shift occurred from C_7 to C_1 to give **13**, which could then undergo a selective (1,7) sigmatropic hydrogen shift to give **12a**. If this were the case, then B would be expected to equilibrate upon photolysis to A. In fact, no noticeable equilibration of either A or B could be detected.

On the other hand, structure **12b** would not be expected to photoequilibrate with **13**. The formation of **12b** upon irradiation of **7** could be rationalized as follows: methyl migration from C_7 to C_6 followed by hydrogen migration. This result would be consistent with our previous results.[1,2] The predominant methyl migration reaction of **7** leads to **13**, while methyl migration in the opposite direction transforms **7** into the carbon skeleton of **12b**.

In view of these inconclusive data, it would appear that A and B, as they appear upon vpc, are in fact a mixture of trienes, the major component of B which is structure **13**. This conclusion is further substantiated by other evidence presented below. A control experiment indicated that trienes A and B do not isomerize under the analytical conditions employed (see Experimental Section). It has been reported[11] that certain column materials cause rearrangement of substituted cycloheptatrienes during their gas chromatographic analysis, either by way of an acid-catalyzed mechanism or *via* hydride exchange. The columns used in our work do not fall in the category of columns which cause this type of rearrangement. It has also been demonstrated that thermally induced 1,5-hydrogen migrations occur in cycloheptatrienes.[12] In our system, this possibility is excluded both by the control experiment and by the apparent structure of the new cycloheptatrienes. In our previous work,[1,2] 1,5-hydrogen shifts were not observed in the glpc analyses of the trienes **3** and **6**, which were carried out at detector temperatures of *ca.* 200°. In addition, activation energies determined for thermal 1,5-hydrogen migrations in several substituted cycloheptatrienes are much too high[12] to permit such isomerizations to take place at the temperatures employed for our analyses.

The identification of the bicyclic compound **9** was straightforward. The nmr spectrum shows two three-hydrogen singlets at 0.70 and 0.77 (*gem*-dimethyl), a broadened six-hydrogen singlet at 1.30 (vinyl CH_3), a broadened one-hydrogen singlet at 2.30 (monoallylic bridgehead hydrogen), a broadened one-hydrogen singlet at 3.06 (doubly allylic bridgehead hydrogen), a one-hydrogen doublet at 5.04 (J = 6 Hz) further split

(6) A column packed with Carbowax 20M suspended on base-washed Chromosorb P was employed.

(7) A column packed with 1,2,3-tri-(β-cyanoethoxy)propane (TCEP) suspended on Chromosorb P was employed.

(8) Peaks A and B are not completely resolved.

(9) Here, peak B has a small shoulder.

(10) J. A. Berson and M. R. Willcott, III, *J. Amer. Chem. Soc.*, **88**, 2494 (1966).

(11) K. Conrow and L. L. Reasor, *J. Org. Chem.*, **30**, 4368 (1965).

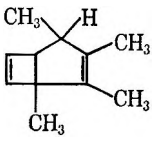
(12) A. P. ter Borg and H. Kloosterziel, *Rec. Trav. Chim.*, **82**, 741 (1963); R. W. Egger, *J. Amer. Chem. Soc.*, **89**, 3688 (1967).

by the bridgehead hydrogen (J = 1.5 Hz), and a one-hydrogen doublet of doublets at 5.36 and 5.45 ppm (J = 2 Hz). The uv spectrum shows only end absorption [210 mμ (ε 3397)].

The 100-Mc nmr spectrum of **10** shows a three-hydrogen doublet at 0.96 (J = 7 Hz), a three-hydrogen singlet at 1.30 (bridgehead methyl), a six-hydrogen absorption at 1.45–1.90 (vinyl CH_3), a broadened one-hydrogen quartet at 2.15 (J = 7 Hz), a one-hydrogen singlet at 2.88, and two one-hydrogen doublets at 6.02 and 6.45 ppm (J = 2.5 Hz). Double irradiation at 0.96 ppm caused the broad quartet at 2.5 ppm to collapse to a singlet.

The 100-Mc nmr spectrum of **11** shows a three-hydrogen doublet at 0.95 (J = 7 Hz), a three-hydrogen singlet at 1.18, a six-hydrogen absorption at 1.40–1.80, a broadened one-hydrogen absorption at 2.1–2.4, a one-hydrogen singlet at 2.92, and two one-hydrogen doublets at 6.08 and 6.30 ppm (J = 2.5 Hz). Double irradiation of the broad absorption at 2.1–2.4 ppm caused the doublet at 0.95 ppm to collapse to a singlet and caused the absorption at 2.92 ppm to sharpen slightly. Double irradiation at 2.92 ppm caused the broad absorption at 2.1–2.4 ppm to collapse to a singlet resembling the singlet at 2.92 ppm.

Thus, the nmr spectra of **10** and **11** are in agreement with the structure of 2,3,4,5-tetramethylbicyclo[3.2.0]-hepta-3,6-diene, epimeric at C_2. The strongest evidence against the isomeric structure **14** is the almost identical



14

chemical shift of the bridgehead hydrogen in **10** and **11**. In compound **9**, the difference in the chemical shifts of the monoallylic and doubly allylic bridgehead hydrogens corresponds to *ca.* 40 Hz. In 2,2,6-trimethylbicyclo-[3.2.0]hepta-3,6-diene (**2**),[1] the difference in chemical shifts between the double allylic and monoallylic hydrogens also amounts to *ca.* 40 Hz. In addition, the ratio of **10** and **11** stays approximately the same at various stages of photolysis. The most consistent interpretation of these data is that both **10** and **11** arise from the same triene. If they were arising from electrocyclization of two tautomeric trienes, their ratio should change during the course of the irradiation, because the ratio of tautomeric trienes would change.

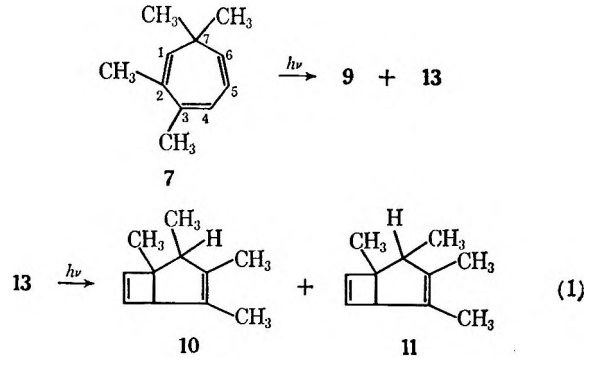
To help to elucidate the structures of the photoproducts of **7**, 1-deuterio-2,3,7,7-tetramethylcycloheptatriene (**7**-d_1) was synthesized from eucarvone-d_2.[1] The nmr spectra of the new trienes, A-d_1 and B-d_1, were inconclusive (see Experimental Section). In the nmr spectrum of **9**-d_1, the singlet at 2.30 ppm has disappeared. The remainder of the spectrum is virtually unchanged. The 60-Mc nmr spectra of **10**-d_1 and **11**-d_1 each show a broadened singlet at 0.97 ppm. The absorption at 2.0–2.4 ppm has disappeared, and the remainder of the spectra are unchanged. Thus, **10** and **11** can only arise from electrocyclization of the cycloheptatriene **13**, which must result from a (1,7) sigmatropic methyl shift from C_7 to C_1 in compound **7**.

As evidence that photoproduct B must consist predominantly of **13**, a sample consisting of *ca.* 10% A and 90% B was irradiated to complete disappearance of A and B. Analysis of the bicyclics showed the presence of six peaks in the relative amounts of 2, 10 (two peaks), 6, 49, and 33%. The 49 and 33% peaks had the retention times of **10**, and **11**, respectively. Irradiation of a sample consisting of *ca.* 25% A and 75% B was carried out to 75% reaction. Analysis of the bicyclic mixture showed seven peaks in the relative amounts of 1, 6, 3, 9, 12, 39, and 25%. The 39 and 25% peaks had the retention times of **10** and **11**.

The bicyclic compounds **10** and **11** were further subjected to selective catalytic hydrogenation. Both **10** and **11** could be selectively reduced at the cyclobutenyl double bond to give the corresponding bicyclo[3.2.0]-hept-3-ene, as indicated by the loss of the cyclobutenyl hydrogen absorption in the nmr spectrum. The nmr spectra of the reduced compounds are very similar. The mass spectra of the reduced compounds are virtually identical and show highest m/e at 150, with the base peak at m/e 122. This is in agreement with the 1,2,3,4-tetramethylbicyclo[3.2.0]hept-3-ene structure, the positive ion of which could easily split out ethylene to give a stable C_9 fragment corresponding to m/e 122.

It is interesting to compare the hydrogenation results of **10** and **11** with those obtained for **9**. After the uptake of 1 mol of hydrogen, the nmr spectrum shows loss of the cyclopentenyl hydrogen absorption. Selective reduction of the cyclopentenyl double bond is reasonable, as *cis* reduction of the cyclobutenyl double bond would result in serious steric interactions of the methyl substituents.

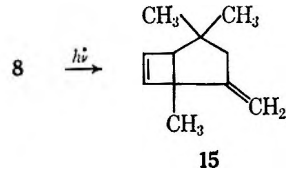
Based on these data, we suggest that the predominant photoreaction of **7** is that indicated in eq 1. The



(1)

methyl substituent at C_3 in **7** exhibits a stronger directive influence (in the methyl migration reaction) than the C_2 methyl group and, hence, the predominant mode of migration is from C_7 to C_1. This is consistent with the HMO treatment discussed previously.[1,2] The preferred mode of cyclization involves bond formation across C_1–C_4 to produce the more highly substituted olefinic system. This mode of cyclization avoids placing a methyl group at the bridgehead which would be eclipsed with the adjacent bridgehead hydrogen.

Compound **8** (a by-product in the preparation of **7**) was also irradiated in benzene solution with a Pyrex filter. As anticipated, a single product corresponding to 2,2,5-trimethyl-4-methylenebicyclo[3.2.0]hept-6-ene



8 (2)

15

(15) was produced (eq 2). This diene (15) was identified on the basis of spectroscopic data, deuterium labeling, and elemental analysis data (see Experimental Section).

Experimental Section[13]

2,3,7,7-Tetramethylcycloheptatriene (7) and 2-Methylene-3,7,7-trimethyl-3,5-cycloheptadiene (8).—The procedure followed was essentially that described earlier.[4] Following the addition of 10 g (0.067 mol) of eucarvone to an excess of methylmagnesium bromide and decomposition with aqueous ammonium chloride, the crude alcohol was dehydrated by dropwise addition to 1 g of potassium hydrogen sulfate at a bath temperature of 150–160° and water aspirator pressure. The material having bp 110–115° (60–70 mm) was collected. The water layer was removed, and after drying the organic layer amounted to 7 g. Gas chromatography[5] showed the material to consist of two products in the relative amounts of 75 and 25%, in order of retention. Each peak was collected. The nmr spectrum of the major product showed a *gem*-dimethyl group at 0.95, two vinyl methyl groups at 1.88 and 2.01, a two-hydrogen absorption at 4.80–5.1, and a two-hydrogen absorption at 5.6–6.25 ppm, and is in agreement with the spectrum of 3 published by Conrow.[4] The nmr spectrum of the minor product showed a *gem*-dimethyl group at 0.98, a vinyl methyl group at 2.00, the saturated methylene group at 2.05, a one-hydrogen absorption centered at 4.90, a one-hydrogen absorption at 5.25, and a two-hydrogen absorption centered at 5.60 ppm, and is in agreement with the spectrum of 4 published by Conrow.[4]

1-Deuterio-2,3,7,7-tetramethylcycloheptatriene (7-d_1) and 1-Deuterio-2-methylene-3,7,7-trimethyl-3,5-cycloheptadiene (8-d_1).—Eucarvone-d_2 was prepared as previously described[1] from 10 g of eucarvone. The crude eucarvone-d_2 was treated with methylmagnesium bromide and dehydrated as described above. The material boiling at 100–110° (30–40 mm) was collected and, after separation of water and drying of the organic layer, amounted to 3 g of material consisting of 42% 7-d_1 and 58% 8-d_1. The compounds were collected by gas chromatography.[6] The nmr spectrum of 7-d_1 showed a *gem*-dimethyl group at 0.96, two vinyl methyl groups at 1.88 and 2.01, a one-hydrogen absorption at 4.80–5.10, and a two-hydrogen absorption at 5.6–6.25 ppm. The spectrum of 8-d_1 showed loss of the saturated methylene group at 2.05 ppm. The remainder of the spectrum is unchanged.

Irradiation of 2,3,7,7-Tetramethylcycloheptatriene (7).—A solution of 53.4 mg of 7 in 2 ml of benzene was irradiated in a Pyrex tube with a 450-W Hanovia mercury arc lamp for 16 hr. At the end of irradiation, 31.4 mg of 2-methylene-3,7,7-trimethyl-3,5-cycloheptadiene (8) was added as an internal standard, and the mixture was concentrated at room temperature and water aspirator pressure, then analyzed by gas chromatography[5] to show 60% unreacted 7. The results are presented in the text.

A solution of 59.9 mg of 7 in 0.3 ml of benzene was irradiated in a Pyrex tube for 24 hr. After addition of 16.4 mg of 8 and concentration, analysis[5] showed 6% unreacted 8. The results are presented in the text.

A solution of 1.4 g of 7 in 60 ml of benzene was irradiated in a Pyrex tube for 16 hr. The reaction mixture was concentrated at water aspirator pressure and room temperature and analyzed by gas chromatography[5] to show 78% bicyclic products, 1% 7, and 21% new trienes as determined from relative peak areas. The bicyclic products and the new trienes were collected. Further chromatography[6] showed the bicyclic products to consist of 16% at least five peaks (minor bicyclics) and 37% 9, 25% 10, and 22% 11, in order of elution as determined from relative peak areas. The peaks corresponding to 9, 10, and 11 were collected. Further chromatography[7] of the triene mixture showed three partially resolved peaks in the approximate relative amounts of 8, 42% A, and 50% B, in order of elution, as determined from peak areas. Because of only partial resolution, the central portion of the new triene peaks A and B were collected.

The nmr and uv spectra of 9, 10, 11, and the triene mixtures A and B are described in the text. *Anal.* Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found for 9: C, 89.28; H, 10.84. Found for 11: C, 89.05; H, 11.09. The mass spectrum of 10 showed highest *m/e* at 148. Found for a mixture of *ca.* 20% A and 80% B: C, 89.22; H, 10.92. The ir spectrum[14] of 9 showed medium bands at 3010 and 3030 (CH of olefin) and a strong band at 765 cm^{-1}.

Irradiation of 1-Deuterio-2,3,7,7-tetramethylcycloheptatriene (7-d_1).—A solution of 320 mg of 7-d_1 in 5 ml of benzene was irradiated for 7 hr. Gas chromatography[5] showed *ca.* 80% bicyclics and 20% new trienes as determined from the relative areas of the peaks. Analysis of the collected bicyclics showed 15% minor bicyclics, 43% 9-d_1, 23% 10-d_1, and 19% 11-d_1, as determined from relative peak areas. Analysis[7] of the collected triene mixture showed *ca.* 30% A and 70% B. Samples of 9-d_1, 10-d_1, 11-d_1, A-d_1, and B-d_1 were collected and their nmr spectra were determined using the microcell described previously.[2] The nmr spectra of 9-d_1, 10-d_1, and 11-d_1 are described in the text. A 100-Mc spectrum of a sample of *ca.* 60% A-d_1 and 40% B-d_1 showed absorption at 0.55–1.0 (2.3 H) consisting of two broadened peaks and absorption at 1.25–2.00 (11.3 H), 4.4–4.7 (0.34 H), 5.3–5.6 (0.52 H), and 5.8–6.0 ppm (0.46 H). A 100-Mc spectrum of a sample consisting of 30% A-d_1 and 70% B-d_1 showed multiplet absorption at 0.6–1.0 (2.24 H) and absorption at 1.25–2.00 (11 H), 4.4–4.8 (0.24 H), 5.3–5.6 (0.6 H), and 5.75–6.10 ppm (0.65 H). A 100-Mc spectrum of a sample of B-d_1 showed broad absorption at 0.6–1.0 on which was superimposed a broadened singlet at 0.95 (2.3 H) and absorption at 1.4–1.7 (11 H), 4.7–4.9 (0.14 H), 5.4–5.6 (0.8 H), and 5.8–6.1 ppm (1.07 H).

Irradiation of Trienes A and B to Bicyclics.—A 20-mg sample consisting of *ca.* 90% B and 10% A in 0.2 ml of cyclohexane was irradiated for 24 hr to disappearance of the starting trienes. The mixture was concentrated and analyzed by gas chromatography[15] to show six peaks in the relative amounts of 2, 10 (two peaks), 6, 49, and 33%, in order of elution. The 49 and 33% peaks had the retention times of 10 and 11, respectively. A 130-mg sample consisting of *ca.* 25% A and 75% B in 1 ml of benzene was irradiated for 19 hr to 75% reaction. Analysis[16] of the bicyclics showed seven peaks in the relative amounts of 1, 6, 3, 9, 12, 39, and 29%, in order of retention. The 39 and 25% peaks had the retention times of 10 and 11, respectively.

Attempted Photoequilibration of A and B.—A 10-μl sample consisting of *ca.* 90% A and 10% B was irradiated in 0.20 ml of benzene for 10 hr. Analysis showed loss of material but no apparent change in peak composition. A 10-μl sample consisting of *ca.* 90% B and 10% A was irradiated in 0.18 ml of benzene for 10 hr. Analysis showed loss of material, but no apparent change in peak composition.

Control Experiment to Determine Presence of Triene Isomerization under Conditions of Analysis.—A sample of trienes which glpc[7] showed to consist of A and B in the relative amounts of *ca.* 80 and 20%, respectively, was collected under the following conditions: inlet temperature, 230°; oven temperature, 130°; detector temperature, 210°. The collected material from glpc[7] analysis consisted of *ca.* 80 and 20% A and B, respectively.[16]

The nmr[17] of the collected material showed a multiplet at 0.65–1.0 (2H), absorption at 1.30–1.90 (11 H), a multiplet at

(13) All boiling points are uncorrected. Magnesium sulfate was employed as a drying agent. Ultraviolet spectra of solutions in 95% ethanol were determined with a Cary Model 14 recording spectrophotometer. Nuclear magnetic resonance spectra of carbon tetrachloride solutions with tetramethylsilane as internal reference were determined at 60 Mc with a Varian Model A-60 spectrometer and at 100 Mc when so indicated with a Varian Model HA-100 spectrometer. Integrations of the 100-Mc spectra were carried out manually with a planimeter. Infrared spectra were determined with a Perkin-Elmer Model 337 ir recording spectrophotometer. Vapor phase chromatography was carried out on an Aerograph Model A-90-P3 gas chromatograph. The mass spectra were determined with a Hitachi Perkin-Elmer RMV-6 E mass spectrometer. The microanalyses were performed by Huffman Laboratories, Inc., Wheatridge, Colo.

(14) Determined as a film.

(15) A column packed with 4-methyl-4-nitropimelonitrile (NMPN) suspended on Chromosorb P was employed.

(16) A more precise estimate of the relative amounts of these peaks is difficult as they are only partially resolved.

(17) The nmr spectrum was determined at 100 Mc using the microcell described previously[2] with the triene mixture in the capillary and tetramethylsilane in carbon tetrachloride surrounding the capillary.

4.2–4.9 (0.8 H), a multiplet at 5.3–5.5 (1 H), and a multiplet at 5.7–6.0 ppm (1.2 H). This material was reinjected under conditions identical with those above and collected. The nmr of the collected material, which glpc[7] showed to consist of *ca.* 80 and 20% A and B, respectively,[16] was identical and superimposable with the one described above.

Irradiation of 2-Methylene-3,7,7-trimethyl-3,5-cycloheptadiene (8) and (8-d_2).—A solution of 200 mg of **8** in 3 ml of benzene was irradiated in a Pyrex tube for 9 hr. Gas chromatography[5] showed 95% **15** and 5% **8** as determined from relative peak areas. The new product was collected. The nmr spectrum of **15** showed two singlets at 0.58 and 0.74 (6 H, *gem*-dimethyl), a singlet at 1.08 (3 H, bridgehead CH_3), two one-hydrogen doublets at 1.64 and 2.44 (J = 15 Hz, $=CH_2$), a singlet at 2.18 (1 H, bridgehead H), a two-hydrogen absorption at 4.50–4.60 consisting of two peaks, and a two-hydrogen doublet of doublets at 5.72 and 5.84 ppm (J = 2.5 Hz, cyclobutenyl hydrogens). The uv spectrum of **15** showed only end absorption [210 mμ (ϵ 2476)]. The ir spectrum[18] of **15** showed a weak band at 1645 and a strong band at 885 cm^{-1} ($=CH_2$). *Anal.* Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.28; H, 10.82.

A solution of 350 mg of 8-d_1 in 5 ml of benzene was irradiated for 14 hr. Analysis[5] showed 55% **15**-d_1 and 45% **8**-d_1. The mixture was concentrated and a sample of **15**-d_1 was collected. The nmr spectrum of **15**-d_1 showed loss of the doublets at 1.64 and 2.44 ppm. The absorption at 4.50–4.60 ppm had collapsed to a singlet. The remainder of the spectrum is unchanged.

Reduction of 9.—A solution of 172 mg (1.165 mmol) of **9** in 5 ml of carbon tetrachloride containing the catalyst from 40 mg of platinum oxide was permitted to absorb 0.9 equiv of hydrogen. The reaction mixture was filtered and concentrated. Gas chromatography[15] showed one major component (*ca.* 95%) which was collected. The 100-Mc nmr spectrum of this material showed singlets at 0.58 and 0.82 (*gem*-dimethyl), absorption at 1.0–1.5, and singlets at 2.65 and 3.10 ppm (bridgehead hydrogens). The cyclopentenyl absorption at 5.0–5.4 ppm had disappeared. Mass spectrum (80 eV) showed m/e (rel intensity) 150 (15), 135 (80), 122 (38), 107 (100), etc.

Reduction of 10.—A solution of 38 mg (0.27 mmol) of **10** in 1 ml of carbon tetrachloride containing the catalyst from 10 mg of platinum oxide was permitted to absorb 1.1 equiv of hydrogen. The reaction mixture was filtered and concentrated. Gas chromatography[15] showed one major component (*ca.* 85%) which was collected. The nmr spectrum of this material showed loss of the cyclobutenyl hydrogen absorption. The allylic hydrogen could not be distinguished. Mass spectrum (80 eV) showed m/e (rel intensity) 150 (11), 135 (24), 122 (100), 107 (78), etc.

Reduction of 11.—A solution of 65 mg (0.44 mmol) of **11** in 1 ml of carbon tetrachloride containing the catalyst from 30 mg of platinum oxide was permitted to absorb 0.9 equiv of hydrogen. The mixture was filtered and concentrated. Gas chromatography[15] showed one major compound (*ca.* 95%) which was collected. The nmr spectrum of this material showed loss of the cyclobutenyl hydrogen absorption. The allylic hydrogen could not be distinguished, and the spectrum was very similar to that of reduced **10**. Mass spectrum (80 eV) showed m/e (rel intensity) 150 (13), 135 (25), 122 (100), 107 (77), etc.

(18) Determined as a solution in carbon tetrachloride.

Registry No.—**7**, 19566-41-7; **8**, 19566-42-8; **9**, 19566-43-9; **10**, 19566-44-0; **11**, 19566-45-1; **13**, 19566-47-3; **15**, 19566-48-4.

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Stereochemistry of Radical Additions of Bromotrichloromethane to Some Cyclic Olefins[1]

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Received October 3, 1968

In order to assess the importance of some factors which may influence the stereochemistry of additions of reagents which are sources of carbon radicals to alkenes, we have investigated the photoinitiated additions of bromotrichloromethane to several cycloalkenes. Nmr data have been used to assign stereochemistry to the 1-bromo-2-trichloromethylcycloalkane adducts. Like cyclooctene,[2] cyclohexene affords a mixture of *cis* and *trans* adducts. *trans*-1,4,5,6,7,8,9,10-Octahydronaphthalene, cyclopentene, indene, and norbornene yield only *trans* adducts, and cycloheptene only the *cis* adduct. The over-all stereochemical results are most readily rationalized in terms of addition of both portions of the addend (in separate steps) from an axial-like direction. Abstraction of Br from $BrCCl_3$ by the intermediate 2-trichloromethylcycloalkyl radical may occur before or after ring flipping in flexible systems, but it does not occur to form product with eclipsed Br and CCl_3 substituents.

Recent investigation of the photoinitiated addition of bromotrichloromethane to *cis*-cyclooctene demonstrated that the 1,2-addition product consists of a 1:1 mixture of *cis*- and *trans*-1-bromo-2-trichloromethylcyclooctane.[2,3] While a mixture of geometrical isomers was expected for this radical addition reaction, the 1:1 proportion obtained was surprising. Both highly stereoselective and nonselective radical additions of hydrogen bromide, halogens, thiols, and hydrogen sulfide have been reported.[4] Reaction conditions, identity of substituents on the alkene linkage, and steric factors have been found to affect significantly the stereoselectivity of these additions.[4] Few data are available however, on the stereochemistry of additions of carbon tetrahalide (or of other reagents which are sources of carbon radicals) to alkenes.[5] Therefore, in order to assess the importance of some factors which may influence the stereochemistry of such additions, we have

(1) (a) We gratefully acknowledge partial support of this research by a grant from the National Science Foundation (Grant No. GP 5749). (b) Presented in part at the Southwest Regional Meeting of the American Chemical Society, Little Rock, Ark., Dec 1967, paper 170.

(2) J. G. Traynham, T. M. Couvillon, and N. S. Bhacca, *J. Org. Chem.*, **22**, 529 (1967). Although the addition product appeared to be a single component by gas chromatographic (gc) analysis, nuclear magnetic resonance (nmr) data clearly established it to be a mixture.

(3) The 1,2-addition product formed in minor amounts (3%) from addition of carbon tetrachloride to *cis*-cyclooctene was likewise shown to be a 1:1 mixture of *cis* and *trans* isomers: J. G. Traynham and T. M. Couvillon, *J. Amer. Chem. Soc.*, **89**, 3205 (1967).

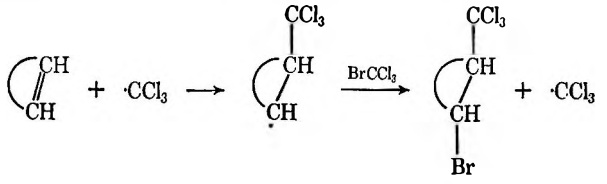
(4) For brief reviews, with references, see (a) W. A. Pryor, "Free Radicals," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, pp 206–218; (b) B. A. Bohm and P. I. Abell, *Chem. Rev.*, **62**, 599 (1962).

(5) (a) E. S. Fawcett, *ibid.*, **47**, 219 (1950). (b) E. Tobler and D. J. Foster, *J. Org. Chem.*, **29**, 2839 (1964). (c) J. Weinstock (Abstracts, 128th National Meeting of the American Chemical Society, Minneapolis, Minn., Sept 1955, p 19-20) reported that radical addition of $BrCH_2COOEt$ to norbornene appeared to give the *exo-cis* product. (d) NOTE ADDED IN PROOF.—L. H. Gale [*J. Org. Chem.*, **34**, 81 (1969)] has reported radical additions of $BrCCl_3$ to cycloalkenes (ring sizes 5–8, γ radiation). He reports single adducts with cyclopentene and cycloheptene but does not identify them as *cis* or *trans* isomers. He does report *cis* and *trans* adducts with cyclohexene.

cis-1-Bromo-2-trichloromethylcyclohexane	$J_{xa} + J_{xb} = 7.8$; $J_{mx} = 2.2$; $J_{mc} = 3.3$; $J_{md} = 10.5$
trans-1-Bromo-2-trichloromethylcyclohexane	$J_{xa} = 5.5$; $J_{xb} = 3.5$; $J_{mx} = 4.0$; $J_{mc} = 6.0$; $J_{md} = 6.0$
trans 2	$J_{xa} + J_{xb} + J_{mx} \simeq 10$; $J_{md} = 6.0$; $J_{mx} + J_{mc} \simeq 5$
cis-1-Bromo-2-trichloromethylcycloheptane	$J_{mx} = 3.0$; $J_{ma} = 11.0$; $J_{mb} = 3.0$
trans-1-Bromo-2-trichloromethylcyclopentane	$J_{xa} = 3.0$; $J_{xb} = 6.0$; $J_{mx} = 3.0$; $J_{mc} = 8.0$; $J_{md} = 8.0$
trans-1-Bromo-2-trichloromethylindane	$J_{mx} = 3.2$; $J_{mc} = 8.8$; $J_{md} = 5.0$; $J_{od} \simeq 18$
trans-2-*endo*-Bromo-3-trichloromethylnorbornane	$J_{2ev,3en} = 6.0$; $J_{2,ex1} = 4.0$; $J_{2ex,6ex} = 1.5$; $J_{3en,4} = 0.0$; $J_{3en,7a} = 1.7$; $J_{7a,1} = 1.3$; $J_{7a,4} = 1.3$; $J_{7a,7s} = 11.0$

Figure 1.—Summary of vicinal coupling constants (in hertz). The subscripts designate hydrogens according to the following key: H_x is HCBr, H_m is $HCCCl_3$, H_a and H_b are geminal hydrogens vicinal to CCl_3; H_c and H_d are geminal hydrogens vicinal to Br; *ex*, *en*, *s*, and *a* refer to *exo*, *endo*, *syn*, and *anti* hydrogens, respectively.

extended this study to include other cycloalkenes and bicycloalkenes, chosen to reveal the influence of steric effects and relative ease of ring flipping in different ring systems. The over-all stereochemical results are most readily rationalized in terms of addition of both portions of the addend (in separate steps) from an axial-like direction. After initial addition of $\cdot CCl_3$ to the cycloalkene, the second step (abstraction of Br from $BrCCl_3$ by the substituted cycloalkyl radical) may occur before or after ring flipping in flexible systems, but it does not occur to form product with eclipsed Br and CCl_3 substituents.

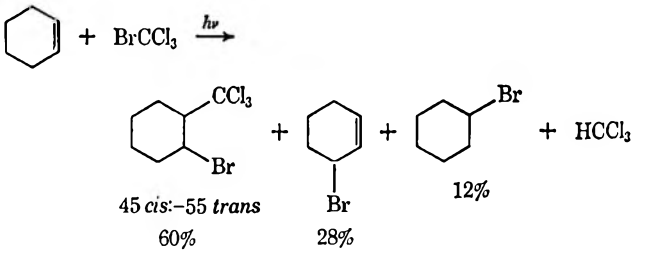


Each addition was carried out under an atmosphere of nitrogen by irradiating a deoxygenated mixture of cycloalkene and $BrCCl_3$ (1:2 or 1:4 molar ratio) with 3500-Å light for a few hours.[2] Nmr spectra periodically obtained on small samples of the mixture were used to estimate the progress of the reaction. After irradiation, excess $BrCCl_3$ was removed, and nmr spectra (60, 100, and 220 MHz) of the 1,2-addition product(s) were recorded. These spectra clearly revealed whether the 1,2-addition product consisted of a single compound or was a mixture of geometrical isomers.[2] The stereochemistry of individual 1,2-addition products was assigned by comparing the relative magnitude of the experimental coupling constants with that expected from application of the Karplus relation[6] to molecular models of the isomeric products.

Results

Cyclohexene.—Additions of $BrCCl_3$ to cyclohexene have been described previously.[5d,7] Although monosubstituted cyclohexane derivatives were reported to be among the products, no hint is given in these papers[7] that the 1,2 adduct was regarded as anything other than a single isomer. Dehydrohalogenation rate data[7a,b] and acid hydrolysis[7c] were used to identify the adduct as the *trans* isomer.

Our addition product from photoinitiated addition of $BrCCl_3$ to cyclohexene possessed the same physical properties as those previously reported for 1-bromo-2-trichloromethylcyclohexane.[7] Its nmr spectrum, however, is quite similar to that of the 1,2-adduct mixture obtained from cyclooctene.[2] Decoupling and selective dehydrohalogenation[2] experiments were used to establish that this product is also a mixture and consists of *cis*- and *trans*-1-bromo-2-trichloromethylcyclohexane (45:55).[8] The nmr spectrum includes four



multiplet signals downfield from −2.55 ppm, each of which has an area equivalent to approximately $^1/_{20}$ of the total area of the spectrum. (The adduct has ten protons per molecule.) In accord with our study of cyclooctene adducts,[2] we assign the more upfield pair of these signals (M) to $HCCCl_3$ and the more downfield pair (X) to HCBr. The decoupled spectra not only revealed that the outer pair of these four signals (X_c and M_c) are coupled, as are the inner pair (X_t and M_t), but also afforded the coupling constants which we used to assign *cis* and *trans* labels to the isomeric components of the mixture. The single large J_{vic} ($J_{md} = 10.5$ Hz) for one isomer, and the lack of a $J_{vic} > 6$ Hz for the other isomer, together with the relative magnitude of the other coupling constants (Figure 1), permit us to assign the signals X_c and M_c to the *cis* isomer and the signals X_t and M_t to the *trans* isomer. While the coupling constants are consistent with a chair conformation for the *cis* isomer (with the bulky CCl_3 substituent equatorial), they are not consistent with a chair conformation with both substituents equatorial for the *trans* isomer (J_{ax}, J_{md}, each expected to be *ca.* 10–11 Hz). These coupling constants require that the *trans* isomer exist either in the sterically unfavorable chair conformation with both substituents axial or in a twist (flexible) form.[9]

Electrical repulsions between the *trans* (diequatorial) Br and CCl_3 substituents, and unfavorable axial substituent–axial H interactions, are relieved by the change

(6) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963). Most of our applications were qualitative rather than quantitative; that is, we examined models to see if the probable dihedral angle led one to expect a "large" or a "small" vicinal coupling constant.

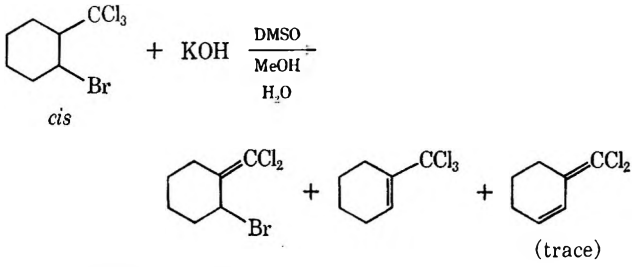
(7) (a) M. S. Kharasch and H. N. Friedlander, *J. Org. Chem.*, **14**, 239 (1949). (b) M. S. Kharasch and M. Sage, *ibid.*, **14**, 537 (1949) (these authors used ultraviolet irradiation). (c) E. I. Heiba and L. C. Anderson, *J. Amer. Chem. Soc.*, **79**, 4940 (1957) (these authors used γ radiation). While this reference reports the hydrolysis of the addition product to the previously known *trans*-2-bromocyclohexanecarboxylic acid, the authors do not ever label the addition product *trans*, and they mildly disfavor the *trans* label earlier in the paper.

(8) This mixture is apparently that formed by kinetic control, for, in a separate experiment (by Dr. F. Schweinsberg), a sample of *cis*- and *trans*-1-bromo-2-trichloromethylcyclohexane (approximately 28:72) in $BrCCl_3$ did not change composition when irradiated under the addition reaction conditions for 22 hr.

(9) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, pp 36–42.

from chair to twist conformation, but the repulsions are probably increased by the similar change for the *cis* isomer. The only monocyclic cyclohexanes known to exist largely in the flexible form have a *t*-butyl substituent which would have to be axial if the chair form were used.[9] Although the conformation energy of the trichloromethyl substituent apparently has not been estimated,[10a] it is probably at least as large as that of *t*-butyl.[10b] We favor the twist (flexible) conformation, rather than the diaxial chair, for *trans*-1-bromo-2-trichloromethylcyclohexane.[10c]

In experiments paralleling those with the mixed 1,2 adducts obtained from cyclooctene,[2] treatment of the mixture of *cis*- and *trans*-1-bromo-2-trichloromethylcyclohexane with 0.5 molar equiv of base under essentially E2 conditions led to the selective dehydrohalogenation of the *cis* isomer and the subsequent isolation of pure *trans* isomer.[11,12] The dehydrohalogenation products were analyzed and characterized by use of gc, infrared (ir), and nmr data. The *cis* isomer was partially separated from the *trans* isomer by repeated fractional distillation at reduced pressure.



In addition to the mixture of *cis* and *trans* addition products, reaction of $BrCCl_3$ with cyclohexene produced substantial amounts of products arising from hydrogen abstraction processes,[7c] namely, 3-bromo-1-cyclohexene (28%) and chloroform in approximately equimolar amounts during the progress of the reaction. The product mixture also contained another product, tentatively identified by nmr data as bromocyclohexane (12%), and whose origin is, at best, speculative.[13]

(10) (a) J. A. Hirsch in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, New York, N. Y., 1967, pp 199–222. (b) E_s values: *t*-Bu, −1.54, and CCl_3, −2.06 (R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 598). (c) Professor M. Hanack, University of Tübingen, has informed us, by private communication, that *trans*-1,2-di-*t*-butylcyclohexane exists in the diequatorial conformation. The twist conformation for *trans*-1-bromo-2-trichloromethylcyclohexane must be favored by electrical repulsions in the diequatorial conformer rather than by steric repulsions.

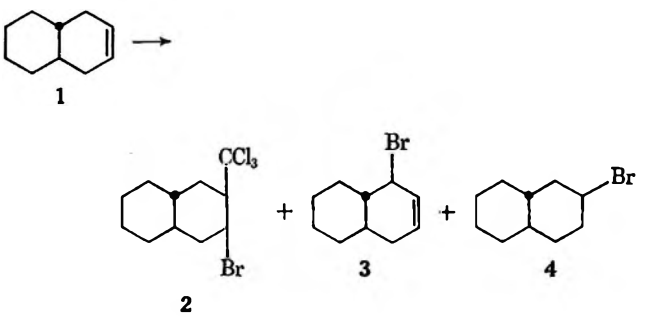
(11) The nmr spectrum of the recovered 1-bromo-2-trichloromethylcyclohexane included absorptions X_t and M_t of the original spectrum but not X_c and M_c. Treatment of this isomer with more base, under the same mild conditions which led to dehydrohalogenation of the other isomer, failed to bring about any dehydrohalogenation.

(12) Dehydrohalogenations of 1-bromo-2-trichloromethylcyclohexane (from cyclohexene + $BrCCl_3$) to 3-dichloromethylene-1-cyclohexene have been effected with 2 molar equiv of sodium ethoxide in ethanol.[7a,c] In one study, a 39% yield of diene was obtained, and 13% of starting material (which we presume to have been the less reactive *trans* isomer) was recovered.[7c]

(13) No proposal that has occurred to us for the formation of bromocycloalkane is uniquely or completely satisfying.

The reaction mixtures did contain an acidic gas, presumed to be HBr. Hydrogen abstraction by Br· (generated by dissociation of $BrCCl_3$) would lead to HBr and allylic radical, which could subsequently react with cyclohexene and with $BrCCl_3$, respectively, to give the observed bromides. Alternatively, Br· could add to cyclohexene to give an intermediate radical which abstracts hydrogen from cyclohexene (or chloroform) to form bromocyclohexane. The large amounts of bromocycloalkane formed in the several reactions observed here seem incompatible with the requirement that all Br· (and HBr) arise from dissociation of $BrCCl_3$, and substantial amounts of 1,2-dibromide would be expected if 2-bromocycloalkyl radical figured importantly in the over-all reaction.

trans-**1,4,5,6,7,8,9,10,-Octahydronaphthalene (1).**[14]—When a mixture of bromotrichloromethane and **1** was irradiated with 3500-Å light for 4 hr, 84% of the olefin was converted into a product mixture which consisted of $BrCCl_3$ addition product (**2**, 50%), allylic bromide (**3**, 20%), and HBr addition product (**4**, 30%).[13] Products **3** and **4** depend upon allylic hydrogen abstraction from **1**; their formation is competitive with but otherwise not related to the addition of $BrCCl_3$ to **1**.



The 60-, 100-, and 220-MHz nmr spectra of **2**, which included a single, narrow multiplet for HCBr (H_x) and a broad doublet for $HCCCl_3$ (H_m), revealed that this $BrCCl_3$ addition product was a single isomer. There are four possible geometrical isomers for this 2,3-disubstituted *trans*-decalin: two *trans* (both substituents axial or both equatorial) and two *cis* (one substituent axial, one equatorial). Figure 1 summarizes the coupling constants from the nmr spectrum of **2**. The magnitudes of these coupling constants are correct for the *trans*, diaxial isomer, but they are too small for any of the other possible isomers. If either or both of the substituents were equatorial, at least one coupling constant would be expected to be about 10 Hz.[15] (See earlier discussion about cyclohexene adduct.)

Cycloheptene.—Irradiation of a mixture of cycloheptene and $BrCCl_3$ for 16 hr led to an 81% yield of products consisting of the adduct, 1-bromo-2-trichloromethylcycloheptane (32%), and hydrogen-abstraction products (3-bromo-1-cycloheptene, 40%, and trichloromethylcycloheptane, 28%).[16] The nmr spectra of the adduct demonstrated that it was a single isomer; in contrast to the spectra for the cyclooctene and cyclohexene adducts, only single multiplet absorptions were recorded for HCBr (H_x) and $HCCCl_3$ (H_m). The coupling constants obtained by decoupling experiments are summarized in Figure 1. On the basis of molecular models and the probable conformation of a vicinally substituted

(14) Prepared from benzoquinone–butadiene adduct by the procedure of W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. D. Dreger, and W. M. Hubbard, *J. Amer. Chem. Soc.*, **83**, 606 (1961). The mixture of *cis*- and *trans*-octahydronaphthalene obtained in this procedure is conveniently separated by fractional distillation through an annular Teflon spinning-band column.

(15) A referee suggested that the twist form for the substituted ring in **2** should be considered. While Dreiding models indicate that one ring of a *trans*-decalin can be twist rather than chair, the twist form is not so flexible as it is for cyclohexane. The models indicate that, in the twist form for **2**, the Br and CCl_3 substituents are about as close together as in a diequatorial conformation and at least one large (~10 Hz) coupling constant would be expected.

(16) The relative amounts of addition and hydrogen abstraction reactions vary greatly with ring size and probably depend in part on the relative stabilities of the different allylic radicals.[2] Trichloromethylcycloheptane may arise from hydrogen abstraction from cycloheptene by 2-trichloromethylcycloheptyl radical or by the radical addition of $HCCl_3$, itself formed by hydrogen abstraction by $\cdot CCl_3$.

cycloheptane (chair or twist-chair),[17] we were led to expect H_m in *cis*-1-bromo-2-trichloromethylcycloheptane to exhibit two small (J_{mx} and J_{mb}) and one large (J_{ma}) vicinal coupling constants, and H_m in the *trans* isomer to exhibit one small (J_{mb}) and two large (J_{mx} and J_{ma}) ones. The experimental J values are consistent with those expected for the *cis* isomer but not the *trans*.

Cyclopentene and Indene.—Radical additions of $BrCCl_3$ to cyclopentene and to indene have been reported to give single vicinal addition products,[7a,c] but the stereochemistry of the products received no comment or was only tentatively assigned. We have repeated these photoinitiated additions and obtained nmr data which confirm that each of these olefins yields a single adduct and establish that *trans* addition of $Br-CCl_3$ does occur.[5a]

For both the 1-bromo-2-trichloromethylcyclopentane and 1-bromo-2-trichloromethylindan[7c] products (isolated in 84 and 72% yields, respectively), each nmr spectrum includes only single absorptions for HCBr (H_x) and $HCCCl_3$ (H_m), with $J_{mx} \simeq 3$ Hz. This small vicinal coupling constant is that expected for the *trans* isomer (vicinal torsion angle approximately 120°) but not for the *cis* isomer (vicinal hydrogens substantially eclipsed). The nmr spectrum of the indene adduct easily confirms its identity as *trans*-1-bromo-2-trichloromethylindan; the signal for H_x is a sharp doublet while that for H_m is a complex multiplet.

Norbornene.—Radical additions of $BrCCl_3$ to norbornene have been reported by several investigators, but the stereochemistry of the adduct has not been firmly established.[18] The photoinitiated addition is much more rapid than the previous reports led us to expect; after 15 min, addition was essentially complete, and the mixture had become quite warm. The product, 2-bromo-3-trichloromethylnorbornane,[5b] was obtained in 95% yield and was shown by 60- and 100-MHz nmr spectra to be a single adduct. The coupling constants, which are summarized in Figure 1 and which are comparable to those reported for the CCl_4 addition product,[5b,18c] establish the complete identity as *trans*-2-*endo*-bromo-3-trichloromethylnorbornane. The greater multiplicity in the signal for H-2, compared to that for H-3, as well as the relative magnitudes of the coupling constants, clearly requires the *exo*-H-2,*endo*-H-3 configuration. That is, $BrCCl_3$ addition, like CCl_4[5b,18c] but unlike HBr[19a] additions, is *trans*, with the initial attack by $\cdot CCl_3$ from the *exo* direction.

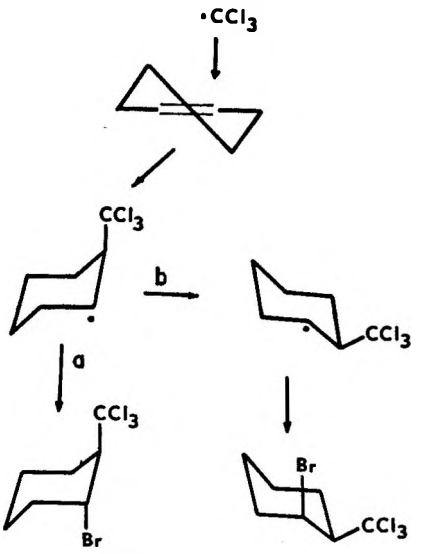


Figure 2.—Alternate pathways for the addition of $BrCCl_3$ to cyclohexene.

The dipole moment of the norbornene–$BrCCl_3$ adduct has previously been taken to indicate *cis* rather than *trans* addition.[19b] By using appropriate bond moments for C–Br (1.7 D) and C–CCl_3 (1.6 D),[19c] and the unit vectors proposed by Wilcox for calculating dipole moments of norbornane derivatives,[19d] one calculates that the dipole moment of the *cis* (*exo*) adduct will be near 3.1 D and that of the *trans* isomer near 1.5 D. The experimental dipole moment for the adduct is 2.6 D[20] and does indeed favor the *cis* isomer. We believe, however, that the nmr data are a more reliable revelation of stereochemistry in the rigid norbornane derivative than a comparison of calculated and experimental dipole moments. The applicability of the Wilcox parameters for dipole moment calculations is apparently more limited than initially proposed.[19d]

Discussion

Formation of *cis* and *trans* isomers by addition of bromotrichloromethane to cyclohexene could arise from either ring flipping or inversion of the radical center without ring flipping (or both) in the initially formed 2-trichloromethylcyclohexyl radical. Addition to a locked cyclohexene was investigated to distinguish between these possible paths. The rigid framework in *trans*-1,4,5,6,7,8,9,10-octahydronaphthalene (1) precludes ring flipping, but the remoteness of the saturated ring from the olefin site should minimize any other alterations in the radical addition reaction.

The flexible (monocyclic) cyclohexene adds $BrCCl_3$ to give geometrical isomers, but the rigid one (1) gives a single adduct, which is *trans* diaxial. These results seem to require that both portions of the addend ($Br-CCl_3$) add from an axial direction. The 2-*axial*-trichloromethylcyclohexyl radical initially formed from cyclohexene may abstract Br from $BrCCl_3$ directly (Figure 2, path a) to form the *trans* product, or it may do so after ring flipping, which puts the bulky CCl_3 substituent in the more favorable equatorial conformation

(17) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7043 (1967), and previous papers cited there.

(18) (a) See ref 5b for the brief summary of previous reports and references. Tobler and Foster[5b] report the use of nmr data to identify the norbornene–CCl_4 adduct as *trans*-2-*endo*-chloro-3-trichloromethylnorbornane and state that "a similar stereochemistry may be inferred for the addition of bromotrichloromethane to norbornene." The nmr spectrum of 2-bromo-3-trichloromethylnorbornane was not described. These additions were effected by refluxing mixtures of norbornene, carbon tetrahalide, and benzoyl peroxide for several hours. (b) L. E. Barstow and G. A. Wiley [*Tetrahedron Lett.*, 865 (1968)] report, without any details about identification, that $BrCl_3$ adds to benzonorbornadiene to form the *trans*-2-*endo*-bromo-3-trichloromethyl product in 95% yield. (c) After this paper had been submitted for publication, the stereochemistry of the norbornene–CCl_4 adduct was discussed in some detail by C. L. Osborn, T. V. Van Auken, and D. J. Trecker, *J. Amer. Chem. Soc.*, **90**, 5806 (1968); the magnitudes of $J_{2ez,1}$ and $J_{2ez,3}$ are reversed in that paper and in the present one.

(19) (a) N. A. LeBel, *J. Amer. Chem. Soc.*, **82**, 623 (1960); (b) V. A. Rolleri, *Dissertation Abstr.*, **19**, 960 (1958); (c) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman Co., San Francisco, Calif., 1963, pp 42, 56; (d) C. F. Wilcox, *J. Amer. Chem. Soc.*, **82**, 414 (1960).

(20) The experimental dipole moment was measured as a part of a class assignment by students in the physical chemistry laboratory at Louisiana State University, under the supervision of Professor J. H. Wharton, during the fall semester, 1967.

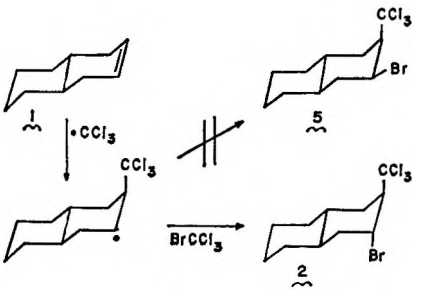


Figure 3.—Stereochemistry of the addition of $BrCCl_3$ to *trans*-1,4,5,6,7,8,9,10-octahydronaphthalene (1).

(Figure 2, path b), to form the *cis* product. By either path, the added substituents approach the ring from axial orientations.[21] The radical initially formed by axial approach of $\cdot CCl_3$ to **1**, however, cannot undergo ring flipping, and the single adduct is the *trans*-diaxial one (2). Were the geometric isomers formed from cyclohexene due to inversion at the radical center, rather than to ring flipping, one would expect that, with **1** as reactant, some *cis* isomer **5** would be formed along with (or instead of) the sterically unfavored *trans*-diaxial one actually obtained (see Figure 3).

Addition of $BrCCl_3$ to the nonflexible ring systems (cyclopentene, indene, and norbornene) is *trans*, probably because eclipsing approach of $BrCCl_3$ to the CCl_3 substituent in the product-forming step of the chain process is highly unfavored.[5a,b,18c] Two features of the cycloheptene addition require comment. Unlike the other flexible cycloalkenes (cyclooctene and cyclohexene), cycloheptene gives a single adduct, and unlike the other olefins for which a single adduct was obtained, cycloheptene gives the *cis* isomer, not the *trans* one. We believe that both of these features are directly associated with the very low energy barrier to conformation change (ring flipping) in cycloheptane compared to that in cyclooctane and cyclohexane.[22] We presume that every initially formed 2-trichloromethylcycloheptyl radical, with an axial-like substituent, undergoes conformational change to make the substituent equatorial-like before the product-forming step. Axial bonding to bromine (from $BrCCl_3$) by the new radical would produce *cis*-1-bromo-2-trichloromethylcycloheptane. While this picture accounts in a reasonable and qualitative way for the formation of only *cis* adduct from cycloheptene, the formation of *nearly equal* proportions of *cis* and *trans* isomers from cyclohexene and cyclooctene remains inexplicable. The slight preference for *trans* adduct (initially diaxial) from cyclohexene over cyclooctene is in accord with the higher energy barrier to conformation change with cyclohexene, but the actual outcome is undoubtedly dependent on several interrelated energy factors.

Experimental Section

Gc data were obtained with a Beckman Model GC5 instrument equipped with hydrogen flame and thermal conductivity detectors and with $^1/_8$-in. packed columns (either 6-ft SE-30 silicone or 10-ft Carbowax 20M). Ir spectra were obtained with Beckman IR-5 and IR-7 and Perkin-Elmer Model 137 instruments. Nmr spectra were obtained with Varian Associates A-60A, HA-100, and HR-220 spectrometers;[23] all chemical shifts are relative to internal tetramethylsilane reference (minus sign indicates downfield).

Addition of $BrCCl_3$ to Cyclohexene.—The general procedure used with each olefin is described only for cyclohexene. A solution of cyclohexene (1 mol) in bromotrichloromethane (2 mol) contained in a Pyrex tube was deoxygenated by a stream of nitrogen and then irradiated for 4 hr in a Rayonet photochemical reactor equipped with 3500-Å lamps. The composition of the mixture was determined periodically by gc, ir, and nmr methods. At the end of the irradiation, the conversion of cyclohexene into products was 86%, and the yield of 1-bromo-2-trichloromethylcyclohexane[7] was about 60%. The reaction mixture could be resolved by fractional distillation at reduced pressure. Gc and nmr data for the 1,2-addition product indicated that it was a mixture (45:55) of geometrical isomers: bp 73–84° (0.15 mm); $n^{20}D$ 1.5478; ir 12.8–13.5 μ (intense, CCl_3); nmr (CD_3COCD_3) −2.71 ($HCCCl_3$, *cis* isomer), −3.13 ($HCCCl_3$, *trans* isomer), −4.79 (HCBr, *trans* isomer), and −5.06 ppm (HCBr, *cis* isomer). *Anal.* Calcd for $C_7H_{10}BrCl_3$: C, 29.84; H, 3.58. Found: C, 30.3; H, 3.7.

Besides the addition product, the mixture was found to contain 3-bromocyclohexene[24,25] (28%), chloroform, and another product tentatively identified as bromocyclohexane (12%) [nmr −4.48 ppm (bm, 1 H, HCBr)]. During the course of the reaction, the molar amounts of chloroform and 3-bromo-1-cyclohexene were approximately equal.

Selective Dehydrohalogenation of 1-Bromo-2-trichloromethylcyclohexane.—During 1.5 hr, a solution of potassium hydroxide (0.02 mol) in a mixed solvent [20 ml of dimethyl sulfoxide (DMSO), 5 ml of methanol, and 5 ml of water] was added to a solution of 1-bromo-2-trichloromethylcyclohexane (0.04 mol, 45% *cis*, 55% *trans*) in a mixture of DMSO (40 ml) and methanol (10 ml).[2] The mixture was stirred at room temperature for 18 hr longer, diluted with water, and extracted three times with petroleum ether (bp 60–70°). Subsequent reduced pressure distillation of the organic material gave a mixture of dehydrohalogenation products and pure *trans*-1-bromo-2-trichloromethylcyclohexane [45% of original mixture; bp 92–99° (1.3 mm); nmr −3.05 (m, 1 H, $HCCCl_3$) and −4.80 ppm (m, 1 H, HCBr)].

The dehydrohalogenation products were shown by nmr, ir, and gc data to consist of mainly 1-bromo-2-dichloromethylenecyclohexane [ir, intense absorption at 6.23 and 11.2 μ ($C{=}CCl_2$); nmr −5.31 ppm (m, $HCBrC{=}CCl_2$)], 1-trichloromethyl-1-cyclohexene [ir, weak absorption at 6.23 ($C{=}C$) and 13.0 μ (CCl_3); nmr −5.47 ppm (m, $HC{=}CCCl_3$)], and a very small amount of 3-dichloromethylene-1-cyclohexane [nmr −6.43 (dt, J_{12} = 10 Hz, J_{26} = 1.5 Hz, $CH_2CH{=}CHC{=}CCl_2$) and −5.97 ppm (dt, J_{12} = 10 Hz, J_{16} = 4.0 Hz, $CH_2CH{=}CHC{=}CCl_2$)].

When a sample of the recovered *trans*-1-bromo-2-trichloromethylcyclohexane was treated with an equal molar amount of potassium hydroxide in the same mixed solvent used with the *cis*–*trans* mixture, the nmr spectrum of the organic material extracted from the diluted solution was almost totally devoid of absorptions for CH=C, but the absorptions characteristic of the *trans*-1-bromo-2-trichloromethylcyclohexane persisted.

A sample of mixed *cis*- and *trans*-1-bromo-2-trichloromethylcyclohexane spontaneously lost some hydrogen halide during storage for several weeks. Gc analysis of the sample indicated that the addition product had become contaminated with the same dehydrohalogenation product generated by potassium hydroxide treatment.

Addition to *trans*-1,4,5,6,7,8,9,10-Octahydronaphthalene (1).—Irradiation of a mixture of 1 (0.04 mol) and $BrCCl_3$ (0.16 mol) for 4 hr led to the consumption of 84% of the olefin and the formation of a product mixture consisting of *trans*-2-*axial*-bromo-3-trichloromethyl-*trans*-decahydronaphthalene (2, 42% yield), **3** (17%), and 4 (25%). The nmr spectrum of the mixture revealed

(21) (a) Radical additions of HBr to cyclohexenes for which stereochemistry can be discerned are also *trans*-diaxial additions; see ref 4. (b) This suggestion does not exclude the possibility of rapid inversion at the radical center nor even of a planar radical center, but only effective approach of $BrCCl_3$ to the radical from an equatorial orientation.

(22) Reference 9, pp 41, 209, 211, records the free energy barrier to conformation interconversion in cyclohexane as 10.1 kcal/mol, that in cyclooctane as 7.7 kcal/mol, and that in cycloheptane as 2.16 kcal/mol.

(23) The 60- and 100-MHz instruments are at Louisiana State University and were purchased with the aid of equipment grants from the National Science Foundation. The 220-MHz instrument is at Varian Associates, Palo Alto, Calif., and was generously made available to N. S. B. for this study.

(24) An authentic sample of 3-bromo-1-cyclohexene for identification use was prepared from cyclohexene and N-bromosuccinimide in refluxing CCl_4 solution,[25] nmr −5.83 ppm (m, 2 H, C=CH).

(25) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948).

that it also contained some chloroform, and an acidic gas (presumably HBr) was detected when the reaction flask was opened.

Adduct 2 distilled at 111–112° (0.08 mm). Its 60-MHz nmr spectrum included narrow multiplets at −5.19 (m, 1 H, HCBr) and −3.16 ppm (m, 1 H, $HCCCl_3$) which were not resolved at 100 and 220 MHz. Decoupling experiments led to the assignment of coupling constants summarized in Figure 1. *Anal.* Calcd for $C_{11}H_{16}BrCl_3$: C, 39.50; H, 4.82. Found: C, 39.75; H, 4.98.

The lower boiling components of the product mixture were not cleanly resolved by distillation, but the nearly pure distillate fractions were identified by nmr spectra. Compound **3** was the principal component in the fraction distilling at 56–60° (0.08 mm): nmr −5.72 (bm, 2 H, C=CH) and −4.52 ppm (bm, 1 H, HCBr). Compound 4 was obtained mixed with 2 and was identified by its nmr absorption at −4.67 ppm (m, HCBr); a small authentic sample for comparison was prepared in solution by the addition of hydrogen bromide to **1**.

Addition to Cycloheptene.—Irradiation of a mixture of cycloheptene (1.0 mol) and $BrCCl_3$ (4.0 mol) for 16 hr led to the formation of three products. In addition to lower boiling products tentatively identified as 3-bromo-1-cycloheptene [20% yield; decolorized Br_2 in CCl_4; ir 3.31 and 6.06 μ (olefin); nmr −5.83 (bm, 2 H, C=CH) and −4.90 ppm (m, 1 H, HCBr)] and trichloromethylcycloheptane [23% yield; did not decolorize Br_2 in CCl_4; ir 12.9–13.0 μ (intense, CCl_3)], the adduct, *cis*-1-bromo-2-trichloromethylcycloheptane, was obtained (26% yield) at 89–103° (0.1 mm). It was characterized by its ir (12.95 μ, intense, CCl_3) and nmr [C_6D_6, −4.78 (m, 1 H, HCBr) and −3.27 ppm (bm, 1 H, $HCCCl_3$)] spectra. The narrow multiplet absorption for HCBr was not resolved at 220 MHz.

Anal. Calcd for $C_8H_{12}BrCl_3$: C, 32.54; H, 4.37. Found: C, 32.89; H, 4.21.

Treatment of a sample of this adduct with a deficiency of potassium hydroxide in mixed solvent as described for the cyclohexene adduct led to a single dehydrohalogenation product, 1-bromo-2-dichloromethylenecycloheptane [ir 6.2 and 10.85 μ ($C=CCl_2$); nmr −5.15 ppm (m, HCBr), no absorption for C=CH], which was not separated from unconsumed adduct.

Addition to Cyclopentene.—A mixture of cyclopentene (0.18 mol) and $BrCCl_3$ (0.71 mol) afforded an 84% yield of *trans*-1-bromo-2-trichloromethylcyclopentane: bp 60° (0.05 mm); nmr −4.46 (m, 1 H, HCBr), −3.69 (m, 1 H, $HCCCl_3$), and −2.96 ppm (bm, 6 H, CH_2). Gc analysis of the product mixture revealed the presence of three minor products of significantly shorter retention time than the adduct; these products were not further characterized but are presumably hydrogen-abstraction products corresponding to those obtained from cyclohexene. When a portion of the adduct was treated with a deficiency of potassium hydroxide in mixed solvent as described for the cyclohexene adduct, it was partially dehydrochlorinated to 1-bromo-2-dichloromethylenecyclopentane: ir 6.23 and 11.1 μ ($C=Cl_2$); nmr −4.9 ppm (nm, HCBr). Gc analysis indicated that a single dehydrohalogenation product had been formed.

Addition to Indene.—When a mixture of indene (0.215 mol) and $BrCCl_3$ (0.86 mol) was irradiated for 6 hr, the nmr spectrum of the mixture revealed only a single component containing hydrogen, *trans*-1-bromo-2-trichloromethylindane: bp 125–129° (0.1 mm); nmr −5.72 (d, J = 3.2 Hz, 1 H, HCBr) and −4.02 ppm (m, 1 H, $HCCCl_3$).

Addition to Norbornene.—Periodic nmr spectra revealed that the addition of $BrCCl_3$ (0.64 mol) to norbornene (0.16 mol) was essentially complete after 15 min. Distillation of the mixture afforded a 95% yield of the adduct, *trans*-2-*endo*-bromo-3-trichloromethylnorbornane: bp 90–95° (0.4 mm); $n^{25}D$ 1.5516; nmr (C_6D_6) −4.06 (m, 1 H, HCBr), −2.63 (q, 1 H, $HCCCl_3$), −2.33 (m, 1 H, H-4), −2.19 (m, 1 H, H-1), −2.1 to −1.68 (bm, 2 H, H-5 *endo* + H-6 *endo*), −1.5 to −1.0 (bm, 3 H, H-5 *exo* + H-6 *endo* + H-7 *syn*), and −0.92 ppm (dq, 1 H, H-7 anti).

Anal. Calcd for $C_8H_{10}Cl_3Br$: C, 32.85; H, 3.45. Found: C, 33.01; 3.64.

Registry No.—Bromotrichloromethane, 75-62-7; *cis*-1-bromo-2-trichloromethylcyclohexane 17831-07-1; *trans*-1-bromo-2-trichloromethylcyclohexane, 17831-06-0; **2**, 19640-04-1; *cis*-1-bromo-2-trichloromethylcycloheptane, 19640-05-2; *trans*-1-bromo-2-trichloromethylcyclopentane, 19640-06-3; *trans*-1-bromo-2-trichloromethylindan, 19640-07-4; *trans*-2-*endo*-bromo-3-trichloromethylnorbornane, 19640-08-5.

Laser Photolysis of 2-Chloro-2-nitrosobutane. Kinetics and Mechanism

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The kinetics and mechanism of the photolysis of 2-chloro-2-nitrosobutane have been investigated using the 6328-Å emission from helium–neon lasers. Concentration, oxygen, and solvent have been found to affect the mechanism and kinetics of the photodecomposition. The use of a laser as light source simplified experimental problems and reduced total irradiation time so that complications from slow dark reactions were reduced. Selective production of 2-chloro-2-nitrobutane occurred on photolysis in the presence of oxygen.

The photochemistry of 2-chloro-2-nitrosobutane and similar compounds has been previously investigated[2,3] and reviewed.[4–6] Products of the photolysis in methanol of *gem*-chloronitrosoalkanes have been reported to be 2-butanone oxime, 2,3-butanedione monoxime, and a compound with $C_8H_{16}O_3N_2 \cdot HCl$ as the molecular formula,[2b] but Baldwin and Rogers[3] isolated a compound ($C_8H_{16}O_2N_2HCl$) which was shown to have a dinitrone structure. For 4-chloro-4-nitrosovaleric acid and 2-chloro-2-nitroso-1,4-diphenylbutane, Mitchell and coworkers[2a] found the primary products of the photolysis in methanol to be the respective oxime hydrochlorides. Kosinski[5] contended since experiments were carried out using light absorbed by the nitroso chromophore that the initial step of the photolysis must be the activation of the nitroso group and then its splitting off. A major role for the solvent was postulated. Artemiev[7] considered the initial step to be the formation of chlorine and nitrosoalkyl radicals. These radicals then participated in further reactions.

The photolysis of 2-chloro-2-nitrosobutane was reexamined to clarify the mechanism of the photodecom-

(1) Address inquiries to this author at Texas Woman's University, Box 3686, TWU Station, Denton, Texas 76204.

(2) (a) S. Mitchell, K. Schwarzwald, and G. K. Simpson, *J. Chem. Soc.*, 602 (1941); (b) S. Mitchell and J. Cameron, *ibid.*, 1964 (1938).

(3) J. E. Baldwin and N. H. Rogers, *Chem. Commun.*, 524 (1965).

(4) B. G. Gowenlock and W. Luttke, *Quart. Rev.* (London), **32**, 321 (1958).

(5) M. Kosinski, *Lodz. Towarz. Nauk., Wydzial III, Acta Chim.*, **9**, 93 (1964).

(6) J. H. Boyer, NASA-CR-79491, 1966, NASA Access N-67-11725.

(7) A. A. Artemiev and A. A. Stvelcova, *Khim. Nauka i Promy.*, **3**, 629 (1958).

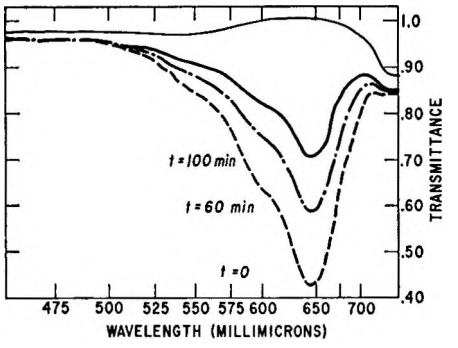

Figure 1.—Change in transmission of 2-chloro-2-nitrosobutane solution on irradiation (methanol, absence of oxygen).

position and to develop techniques for using lasers in photochemistry. Although it was not expected that the low power laser would produce photochemical effects different from other monochromatic light sources, it was anticipated that greater selectivity in products would be observed because of the narrow band width of the exciting light. The effect of coherence was presumed to be unimportant in this case. One of the major advantages of using a laser light source is the high-power density. Ordinary light sources usually provide intensities on the order of 10^{13} quanta/cm^3 sec.[8] An unfocused 3-mW helium–neon laser offers intensities greater than 10^{17} quanta/cm^3 sec. In a 1.0-cm cell containing 10^{-2} M solutions of 2-chloro-2-nitrosobutane, the change in absorption throughout a typical run was small so that the Lambert–Beer approximation for photobleaching systems gave accurate results.[9] The relatively high power density not only simplified the calculations but reduced the experimental time resulting in elimination of most interference from slow dark reactions that have been reported[2] to occur.

Experimental Section

Light sources were a Spectra Physics helium–neon laser Model 122 with emission at 6328 Å TEM_{00} with beam diameter of 0.7 mm at $1/e^2$ points and a Spectra Physics hilium–neon Model 125 with emission at 6328 Å TEM_{09} and a beam diameter of 2.0 mm at $1/e^2$ points. The detector was a Spectra Physics Model 401 power meter connected to an E. H. Sargent Model SR recorder. Beckman DK-2 and Perkin-Elmer 250 spectrophotometers were used to record ultraviolet and visible spectra. Infrared spectra were determined on a Perkin-Elmer 337 infrared spectrophotometer equipped with a specular reflectance attachment. An F & M Model 700 gas chromatograph with dual flame and electron capture detectors and F & M Model 200 gas chromatograph with flame and themistor detectors were used in analysis of reactants and products. An AEI MS 7 mass spectrometer was used to analyze gaseous products.

2-Chloro-2-nitrosobutane and 2-chloro-2-nitrobutane were prepared in good yield and purity by the method of Kosinski.[5] A variety of chlorinated butanes and butenes including 2,2-dichlorobutane were purchased from K & K Laboratories, Inc., Plainview, N. Y., for use as standards in the gas chromatographs and infrared instrument.

Experiments using the Model 122 laser were conducted in 1.0-cm quartz cells stirred magnetically. Temperatures were lowered by passing chilled water through a baffled brass block; temperatures were raised by heating the block with a hot plate while water circulated slowly through the block. The temperature was monitored with an iron–constantan thermocouple and maintained ±1° of the desired temperature. The block was fitted with two cell compartments with a hole 3 mm in diameter drilled through each compartment for the admission of the laser beam. The purpose of the second cell was to provide a comparison for the behavior of the solutions in the absence of laser irradiation.

Experiments using the Model 125 laser were conducted in cylindrical cells 6-mm i.d., varying in length, with ends ground optically flat.

As the rates of reaction and product distribution were markedly dependent on the concentration of oxygen in the system, precautions were taken to eliminate thoroughly dissolved oxygen by repeated vacuum freezing of stirred ampoules.[10] Cells were filled in a dry nitrogen atmosphere and sealed. Reactions conducted in the presence of oxygen were maintained saturated by constantly bubbling oxygen through the reaction cell.

Relative quantum yields were determined by comparing the yield of products to the number of quanta that could be absorbed by 2-chloro-2-nitrosobutane in the elapsed time.[11]

The photomultiplier was calibrated by reference to National Bureau of Standards calibrated tungsten–iodine standard light source. Calibration was checked at frequent intervals to maintain accuracy.

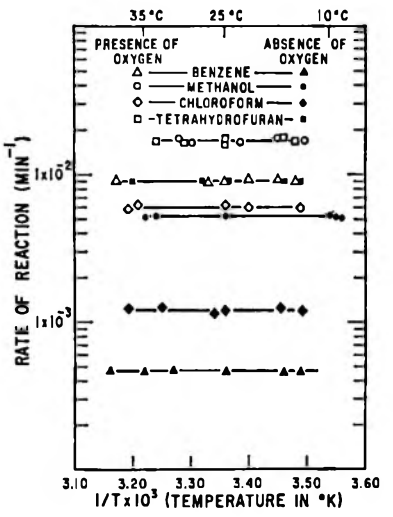

Figure 2.—Effect of changing temperature on rate of reaction.

Discussion and Results

Not only were the experimental techniques simplified by using the laser source, but the progress of the reaction could be followed directly by means of a photomultiplier system coupled directly to a recorder.

The applications of nulling potential at the start of each experiment permitted the use of maximum recorder sensitivity. When comparing recorder output with spectrophotometer measurements, the former was at least as accurate as the latter in determining changes in optical density on irradiation. The laser, after proper warm-up, proved to be a very constant source of energy.

The absorption spectrum of 2-chloro-2-nitrosobutane in the visible region was little affected by changes in solvent. Figure 1 illustrates the change in transmission of dilute solutions of 2-chloro-2-nitrosobutane in methanol on irradiation in the absence of oxygen. Spectrophotometric measurements on other dilute solutions were found to be very similar.

The kinetics of the photodecomposition of 2-chloro-2-nitrosobutane in dilute solution can be treated as first or pseudo first order. The rate of decomposition and quantum yield depend on the nature of the solvent as well as the presence or absence of oxygen (see Table I).

(8) J. G. Calvert, J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N. Y., 1966, p 722.

(9) H. C. Kessler, Jr., *J. Phys. Chem.*, **71**, 2736 (1967).

(10) See ref 8, p 583.

(11) See ref 8, p 588.

TABLE I

IRRADIATION OF 2-CHLORO-2-NITROSOBUTANE AT 6328 Å (3 mW)

Solvent	Concn, M	k, min^{-1}		Quantum yield		Product analysis (absence of O_2)
		Presence of O_2	Absence of O_2	Presence of O_2	Absence of O_2	
Benzene	$(1–9) \times 10^{-2}$	9×10^{-3}	4.6×10^{-4}	0.6	0.2	25% 2,2-dichlorobutane, 40% 2-chloro-2-nitrobutane
Benzene	8.25					0.4 mol of N_2/mol of 2-chloro-2-nitrobutane
Methanol	$(1–9) \times 10^{-2}$	1.6×10^{-2}	5.6×10^{-3}	1.3	0.6	90% 2-butanone oxime hydrochloride, trace of formaldehyde
Methanol	9.0					60% 2-butanone oxime hydrochloride, 24% 2,3-butanedione monoxime hydrochloride
Chloroform	$(3–9) \times 10^{-2}$	6.1×10^{-3}	1.2×10^{-3}	0.6	0.2	23% 2,2-dichlorobutane, 37% 2-chloro-2-nitrobutane
Tetrahydrofuran	$(3–6) \times 10^{-2}$	1.7×10^{-2}	9×10^{-3}	2.0	1.0	82% 2-butanone oxime hydrochloride, 12% complex mixture of unidentified compounds

That the rate-determining step of the photodecomposition is probably a primary process was indicated by the fact that the rate of reaction was observed to be independent of temperature[12] over the range of 8–45° in all solvents employed (Figure 2) and that the rate of reaction is found to be directly proportional to the intensity of light (Figure 3).[13] The rate of reaction is dependent on solvent and oxygen concentration and independent of temperature over the range investigated.

Three types of primary photochemical processes have been postulated for the photodecomposition of *gem*-chloronitrosoalkanes.[14]

$$\underset{\underset{NO}{|}}{RCClCH_2R'} + h\nu \longrightarrow HCl + \underset{\underset{NO}{|}}{RC{=}CHR'} \quad (1)$$

$$\underset{\underset{NO}{|}}{RCClCH_2R'} + h\nu \longrightarrow \underset{\underset{NO}{|}}{RCCH_2R'} + Cl\cdot \quad (2)$$

$$\underset{\underset{NO}{|}}{RCClCH_2R} + h\nu \longrightarrow \underset{\underset{Cl}{|}}{RCCH_2R'} + NO\cdot \quad (3)$$

In solutions high in concentration with respect to 2-chloro-2-nitrosobutane and in solvents from which hydrogen atoms are not readily abstracted, eq 3 appears to be the important primary process. That NO is the oxidizing agent in such solutions is shown by the effect of added nitric oxide on the reaction[15] (see Figure 4). The rate is increased 30-fold and the yield of 2-chloro-2-nitrobutane relative to 2,2-dichlorobutane approaches 100%. In experiments in which the solution was 1:1 2-chloro-2-nitrosobutane–benzene, nitrogen formation could be detected; analysis by mass spectrograph gave a ratio of about 0.4 mol of nitrogen for each mole of 2-chloro-2-nitrobutane produced. The addition of nitrosyl chloride to dilute benzene solutions affected the rate of reaction very little (see Figure 4) but increased the ratio of 2,2-dichlorobutane to 2-chloro-2-nitrobutane; the combined yield of 2,2-dichlorobutane and 2-chloro-2-nitrobutane changed from 65% in the absence of nitrosyl chloride to 97% on addition of nitrosyl chloride. These data support the mechanism given in Scheme I for the disproportionation of 2-chloro-2-nitrosobutane in benzene in the absence of oxygen.

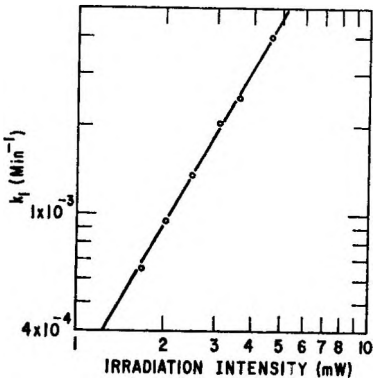

Figure 3.—Typical effect of intensity of light on the rate of reaction for chloroform solutions of 2-chloro-2-nitrosobutane in the absence of oxygen.

SCHEME I

$$CH_3CH_2\underset{\underset{Cl}{|}}{\overset{\overset{N=O}{|}}{C}}CH_3 \xrightarrow{h\nu} CH_3CH_2\underset{\underset{Cl}{|}}{\dot{C}}CH_3 + NO\cdot$$

$$CH_3CH_2\underset{\underset{Cl}{|}}{\overset{\overset{N=O}{|}}{C}}CH_3 + NO\cdot \longrightarrow CH_3CH_2\underset{\underset{Cl}{|}}{\overset{\overset{NO_2}{|}}{C}}CH_3 + 0.5N_2$$

$$CH_3CH_2\underset{\underset{Cl}{|}}{\overset{\overset{N=O}{|}}{C}}CH_3 + CH_3CH_2\underset{\underset{Cl}{|}}{\dot{C}}CH_3 \longrightarrow$$

$$CH_3CH_2\underset{\underset{Cl}{|}}{\overset{\overset{Cl}{|}}{C}}CH_3 + CH_3CH_2\underset{\underset{Cl}{|}}{\overset{\overset{NO}{|}}{C}}CH_3$$

$$CH_3CH_2\underset{\underset{Cl}{|}}{\overset{\overset{N=O}{|}}{C}}CH_3 \longrightarrow \text{other products}$$

(12) See ref 8, p 646.
(13) See ref 8, p 651.
(14) See ref 8, pp 475, 476.
(15) D. E. O'Connor and P. Tarrant, *J. Org. Chem.*, **29**, 1793 (1964).

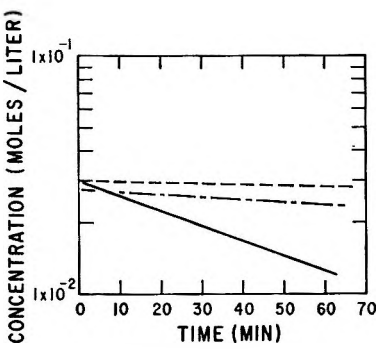

Figure 4.—Effect of the addition of nitric oxide and nitrosyl chloride on the rate of reaction of 2-chloro-2-nitrosobutane in benzene: ———, NO, $k = 1.4 \times 10^{-2}$ min^{-1}; – – – –, NOCl, $k = 4.3 \times 10^{-4}$ min^{-1}; –·–·–·, no addition, $k = 4.6 \times 10^{-4}$ min^{-1}. Experiments were conducted in the absence of oxygen.

In dilute solutions of 2-chloro-2-nitrosobutane in oxygen-free methanol, the primary process of greatest importance is eq 2. The radicals abstract hydrogen from the solvent to produce the oxime and hydrogen chloride. Not only is the oxime hydrochloride the dominant product, but traces of formaldehyde can be detected by gas chromatography of the reaction products.

In concentrated oxygen-free methanol solutions of 2-chloro-2-nitrosobutane, 2,3-butanedione monooxime was formed as well as 2-butanone oxime. The dinitrone reported by Baldwin and Rogers[3] was detected only if the photolysis products were not analyzed immediately.

In tetrahydrofuran the primary process of importance is probably eq 2. The rate of reaction and quantum yields are increased relative to the other solvents (see Table I). The abstraction of hydrogen from cyclic ethers results in the formation of an intermediate α-alkoxy radical which can then combine with another radical to form a stable product or ring opening can occur with the formation of a carbonyl compound.[16] These free-radical pathways result in the increase in reaction rate and apparent quantum efficiency.

The mechanism for the photodecomposition of 2-chloro-2-nitrosobutane solutions proceeds in essentially the same manner as the reaction in benzene (see Table I).

In summary, the fate of the excited 2-chloro-2-nitrosobutane molecule depends on solvent and concentration. The competing paths, eq 2 and 3, are the important primary processes. Selectivity in product occurs in oxygen-saturated solutions, but not in oxygen-free systems. In the absence of oxygen the excited molecule can either experience deactivating collisions or react to form free radicals. These free radicals undergo further reactions to produce products dependent on the nature of the radical, not the source of the free radical. In the presence of oxygen the excited molecule reacts very rapidly with oxygen to form 2-chloro-2-nitrobutane and only traces of products of free-radical origin.

The use of laser light sources removes many experimental problems encountered in ordinary photochemical work. As was to be expected, the low-power lasers used did not directly give rise to products different from common light sources, but the fact that the time of photolysis could be drastically shortened lessened the interference from dark side reactions and simplified product analysis.

Registry No.—2-Chloro-2-nitrosobutane, 681-01-6.

(16) R. S. Davidson, *Quart. Rev.* (London), **21**, 249 (1967).

Derivatives of Thiacyclobutene (Thiete). IV.[1] Thermal Decomposition of a Naphthothiete Sulfone. An Oxidation–Reduction Reaction and Formation of a Cyclic Sulfinate Ester (Sultine)[2-4]

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Received October 16, 1968

Pyrolysis of 3,8-diphenyl-2H-naphtho[2,3-*b*]thiete 1,1-dioxide, **1**, at 360–400° for 5 min in a nitrogen atmosphere gives two principal organic products which are thiophene derivatives: 14H-benzo[*b*]benzo[3,4]fluoreno-[2,1-*d*]thiophen-14-one (**2**) and 14H-benzo[*b*]benzo[3,4]fluoreno[2,1-*d*]thiophene (**3**). Sulfur dioxide is not evolved in any significant amounts and no evidence for formation of a naphthocyclopropene was observed. When the pyrolysis is done in the presence of 9,10-dihydroanthracene, the reaction took a completely different course yielding 78–81% cyclic sulfinate ester or sultine, 4,9-diphenyl-3H-naphth[2,3-*c*]-2,1-oxathiole 1-oxide (**6**). The cyclic sulfinate by itself decomposes on pyrolysis to the two thiophene derivatives obtained from the naphthothiete sulfone.

Pyrolysis of sulfones usually gives sulfur dioxide and products derived formally from radicals formed on the departure of sulfur dioxide.[5] Examples of pyrolysis of four-membered-ring sulfones (thietane sulfones) are limited. Dodson and Klose found that sulfur dioxide was lost from either *cis*- or *trans*-2,4-diphenylthietane 1,1-dioxide to give a mixture of *cis*- and *trans*-1,2-diphenylcyclopropane in which the *trans* isomer predom-

(1) Paper III: D. C. Dittmer and J. M. Balquist, *J. Org. Chem.*, **33**, 1364 (1968).

(2) This work was aided by Grant GP 5513 of the National Science Foundation and Grant CA08250 of the National Cancer Institute, National Institutes of Health.

(3) Reported at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p 101–O.

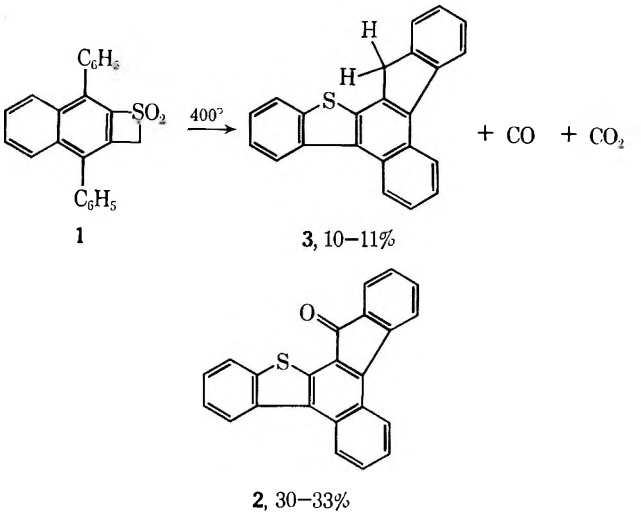
(4) For further details, see R. S. Henion, Ph.D. Thesis, Syracuse University, 1967.

(5) Reviewed in ref 4 and by J. L. Kice, "The Chemistry of Organic Sulfur Compounds," Vol. 2, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, London, England, 1966, p 115.

inated.[6] Truce and Norell pyrolyzed 2-phenyl-3,3-diethoxythietane 1,1-dioxide and obtained ethyl cinnamate, which they suggested was formed by way of 2-phenyl-1,1-diethoxycyclopropane.[7] Middleton pyrolyzed 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane 1,1-dioxide with loss of sulfur dioxide and formation of 2,2,3,3-tetrakis(trifluoromethyl)thiirane.[8] Hoffmann and Sieber heated naphtho[1,8-*bc*]thiete 1,1-dioxide and obtained perylene and unidentified carbonyl compounds; *in vacuo* a cyclic sulfinate ester was isolated.[9]

Rearrangement of acyclic sulfones and cyclic sulfones (five membered) to sulfinates was suggested to explain ions observed in the mass spectra of sulfones,[10] and other similar rearrangements have been reported.[11] Loss of carbon monoxide has been observed also.[11a,b]

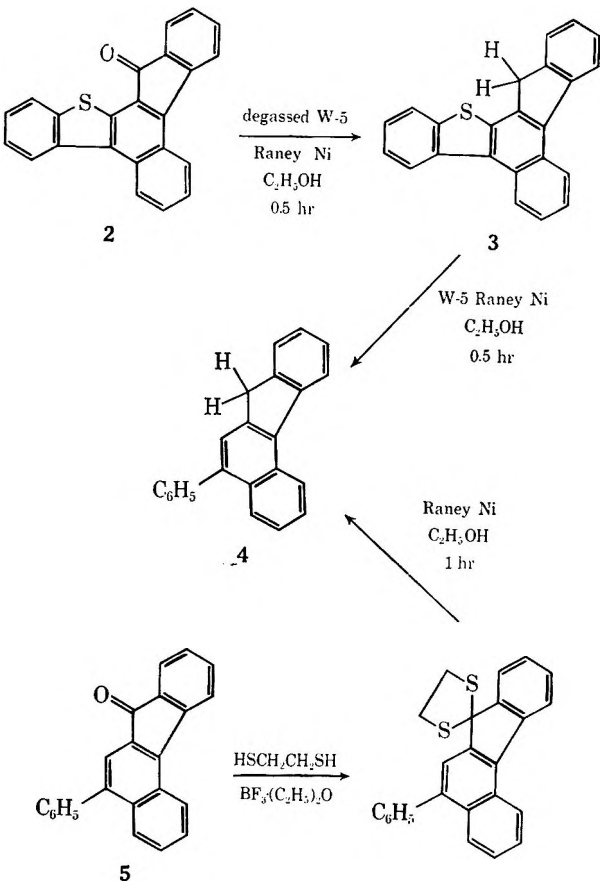
Pyrolysis of Naphthothiete Sulfone 1 Neat.—Heating 3,8-diphenyl-2H-naphtho[2,3-*b*]thiete 1,1-dioxide (**1**) for 5 min at 400° in a nitrogen atmosphere gave five organic products (indicated by thin layer chromatography) in addition to carbon monoxide which had been reported previously.[12] We now wish to report that the two major organic products are the scarlet 14H-benzo[*b*]benzo[3,4]fluoreno[2,1-*d*]thiophen-14-one (**2**) and colorless 14H-benzo[*b*]benzo[3,4]fluoreno[2,1-*d*]thiophene (**3**), the pyrolysis reaction taking an entirely different course from those reported earlier. Analysis of the gases evolved shows them to be mainly carbon monoxide (14–20% based on starting sulfone) and carbon dioxide (6–18%) with lesser amounts of water, hydrogen sulfide, carbon oxysulfide, and sulfur dioxide. Relatively more sulfur dioxide was obtained at lower temperatures. No evidence was obtained for a naphthocyclopropene which might have been expected if the pyrolysis had proceeded as observed with those five-membered cyclic sulfones which yield benzocyclobutene derivatives[13] and the four-membered sulfones which yield cyclopropanes.[6-8]



Structure Proof of Ketone 2 and Fluorene 3.—The infrared, ultraviolet, visible, and mass spectroscopic data are consistent with structures **2** and **3**, and chemical evidence provides further proof for them.[14]

When fluorene **3** was refluxed with W-5 Raney nickel (hydrogen rich) in ethanol, 5-phenyl-7H-benzo[*c*]fluorene, **4**, a known compound,[15] was formed which also was prepared by desulfurization of the ethylene dithioketal of 5-phenyl-7H-benzo[*c*]fluorenone (**5**) (Scheme I).

SCHEME I

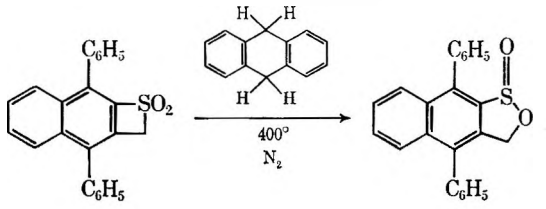


This fluorenone was prepared as described previously.[16] Fluorene **3** also was obtained when ketone **2** was refluxed with partially degassed W-5 Raney nickel in ethanol. Although reduction of a carbonyl group to a methylene group by Raney nickel is known,[17] this appears to be the first case where a carbonyl group is reduced without a concomitant desulfurization by the Raney nickel. Raney nickel also is reported to renuce alcohols to alkanes under mild conditions.[18] If fluorenone **2** was refluxed for 5 hr with hydrogen-rich Raney nickel, desulfurization occurred accompanied by reduction of the carbonyl group and the naphthalene

(6) R. M. Dodson and G. Klose, *Chem Ind.* (London), 450 (1963).
(7) W. E. Truce and J. R. Norell, *J. Amer. Chem. Soc.*, **85**, 3236 (1963).
(8) W. J. Middleton, U. S. Patent 3,136,781 (1964); *Chem. Abstr.*, **61**, 5612 (1964).
(9) R. W. Hoffmann and W. Sieber, *Angew. Chem. Intern. Ed. Engl.*, **4**, 786 (1965); *Ann. Chem.*, **703**, 96 (1967).
(10) S. Meyerson, H. Drews, and E. K. Fields, *Anal. Chem.*, **36**, 1294 (1964), and references cited therein.
(11) (a) E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.*, **88**, 2836 (1966); (b) J. H. Bowie, D. H. Williams, S.-O. Lawesson, J. Ø. Madsen, C. Nolde, and G. Schroll, *Tetrahedron*, **22**, 3515 (1966); (c) Q. N. Porter, *Aust. J. Chem.*, **20**, 103 (1967); (d) R. D. Chambers and J. A. Cunningham, *Chem. Commun.*, 583 (1967); (e) D. C. Dittmer and F. A. Davis, *J. Org. Chem.*, **32**, 3872 (1967).
(12) D. C. Dittmer and N. Takashina, *Tetrahedron Lett.*, 3809 (1964).
(13) M. P. Cava and A. A. Deana, *J. Amer. Chem. Soc.*, **81**, 4266 (1959).
(14) The physical data are given in the Experimental Section and are fully discussed in ref 4.
(15) A. Etienne and A. Le Berre, *C. R. Acad. Sci., Paris*, **239**, 176 (1954).
(16) R. Weiss and A. Abeles, *Monatsh.*, **61**, 162 (1932).
(17) G. N. Rao, B. D. Tilak, and K. Venkataraman, *Proc. Indian Acad. Sci., A*, **38**, 244 (1953); *Chem. Abstr.*, **49**, 1003 (1955).
(18) For examples, see W. A. Bonner, J. A. Zderic, and G. A. Casaletto, *J. Amer. Chem. Soc.*, **74**, 5086 (1952); J. A. Zderic, M. E. C. Rivera, and D. C. Linon; *ibid.*, **82**, 6373 (1960); E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 3363 (1962).

nucleus.[19] An impure red oil was obtained in which a carbonyl group was present (infrared absorption around 1710 cm^{-1}). A mass spectrum of this crude oil indicated the presence of ions at *m/e* 306 which is the mass to charge ratio for the molecular ion of ketone **5** expected from the desulfurization of ketone **2**.

Pyrolysis of Naphthothiete Sulfone 1 in the Presence of 9,10-Dihydroanthracene.—When thiete sulfone **1** was heated in the presence of a twofold excess of 9,10-dihydroanthracene, the reaction took a completely different course. A good yield (78–81%) of cyclic sulfinate[20] **6** (4,9-diphenyl-3H-naphth[2,3-*c*]-2,1-oxathiole 1-oxide) was obtained. Cyclic sulfinates or sultines are



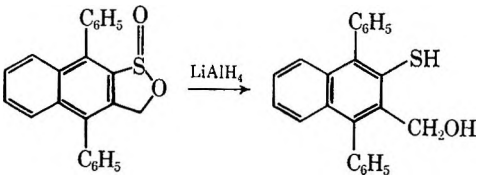
6

rare, only a few examples in addition to **6** having been reported.[9,21] Recently, treatment of a thietane sulfone with *t*-butoxymagnesium bromide was reported to yield a sultine.[21a] The rearrangement of sulfones to sultines may occur while the mass spectra of cyclic sulfones are being obtained[10,11] and in the pyrolysis of a thiete sulfone.[9] The reverse rearrangement of acyclic sulfinates to sulfones is fairly common[22a] although only one example of such a rearrangement involving a sultine is known.[9] The interconversion of a sulfoxide and a sulfenic ester has been postulated.[22b]

The infrared spectrum of sultine **6** shows absorption at 1120 and 940 cm^{-1} in agreement with absorptions reported for esters of sulfinic acids.[23] The ultraviolet absorption (λ_{max} 246, 304, 333 mμ) is similar to that of naphthothiete sulfone **1**, and the intense absorption of the diphenylnaphthalene chromophore overwhelms the weaker absorption around 240–250 mμ attributed to sulfinate esters.[23] The proton nmr spectrum ($CDCl_3$, relative to tetramethylsilane) shows a multiplet at δ 7.00–8.00 (aromatic protons, relative area 14) and an AB pattern (relative area 1.7), J = 14 Hz, with the low-field absorption centered at δ 5.98 and the high-field absorption centered at δ 5.31. The magnitude of the nonequivalence of the methylene protons may be attributed in part to the diamagnetic anisotropy of the S=O group which deshields the proton *cis* to the sulfinyl oxygen as has been observed in cyclic sulfite esters.[24]

Similarities exist between the mass spectra of sultine **6** and naphthothiete sulfone **1**, an indication that both have some structural features in common. The sulfone may rearrange to the sultine prior to fragmentation in the mass spectrometer. The base peak of the sultine is the parent ion at *m/e* 356, but that of thiete sulfone **1** is at *m/e* 291, the latter fragment possibly representing a naphthocyclopropenium cation analogous to similar ions seen in the mass spectra of benzothiete sulfone.[11e] The sultine shows an intense peak at *m/e* 308 (parent –SO) which is not very pronounced in the spectrum of sulfone **1** indicating that **1** does not decompose exclusively by rearrangement to sultine **6** before fragmentation in the spectrometer.

Reduction of the sultine with lithium aluminum hydride gave 1,4-diphenyl-3-hydroxymethyl-2-naphthalenethiol. The proton nmr spectrum of the naphthalenethiol was consistent with its structure. The chemical shift of the methylene protons is of the magnitude expected for methylene protons adjacent to oxygen rather than to sulfur.[12,25] At about −40° the nmr spectrum showed a broadened singlet at δ 4.66 (methylene protons) and a poorly resolved triplet at δ 2.12, the latter absorption indicating the slower exchange of the hydroxylic proton.



In the mass spectrum of the naphthalenethiol, the most abundant fragment was at *m/e* 324 corresponding to the parent ion minus water, a mode of decomposition characteristic of *o*-hydroxybenzyl alcohol.[26]

Pyrolysis of Sultine 6.—When the sultine was heated in the absence of 9,10-dihydroanthracene at 380–400° for 5 min in a nitrogen atmosphere, gases were evolved, and the mixture became dark red. The scarlet fluorenone **2** and fluorene **3** were obtained in yields of 21.2 and 7.8%, respectively. This result, in conjunction with the evidence from mass spectrometry, suggests that the sultine may have been an intermediate in the pyrolysis of naphthothiete sulfone **1**.

Pyrolysis of the thiete sulfone may involve initial scission of the sulfur–carbon bond to give an intermediate (dipolar or diradical in character) which may yield the sultine by formation of an oxygen–carbon bond (Scheme II). Loss of water and two hydrogen atoms

(19) The reduction of aromatic rings in Raney nickel desulfurization has been observed: W. Davies and Q. N. Porter, *J. Chem. Soc.*, 459 (1957).

(20) By analogy with the nomenclature of cyclic esters of sulfonic acids which are called sultones, we suggest that the cyclic esters of sulfinic acids be called sultines. The word "sultine" is derived by replacing the "o" in sultone with an "i" to indicate that a sulfinic acid and not a sulfonic acid is involved. We are indebted to a luncheon conversation with C. S. Greene over soup and crackers for this suggestion about nomenclature.

(21) (a) R. M. Dodson, P. D. Hammen, and R. A. Davis, *Chem. Commun.*, 9 (1968). (b) K. S. Dhami, *Chem. Ind.* (London), 1004 (1968); E. N. Givens and L. A. Hamilton, *J. Org. Chem.*, **32**, 2857 (1967); E. Baumann and G. Walter, *Ber.*, **26**, 1124 (1893). A sultine structure proposed for anthraquinone-1-sulfenic acid is believed to be incorrect: H. Z. Lecher and E. M. Hardy, *J. Org. Chem.*, **20**, 475 (1955); J. A. Barltrop and K. J. Morgan, *J. Chem. Soc.*, 4245 (1956); T. C. Bruice and A. B. Sayigh, *J. Amer. Chem. Soc.*, **81**, 3416 (1959). Sultones and other ring systems containing sulfur and oxygen have been reviewed recently: D. S. Breslow and H. Skolnik, "Multisulfur and Sulfur and Oxygen Five- and Six-membered Heterocycles," parts I and II, Interscience Publishers, New York, N. Y., 1966.

(22) (a) J. Kenyon and H. Phillips, *J. Chem. Soc.*, 1676 (1930); C. L. Arcus, M. P. Balfe, and J. Kenyon, *ibid.*, 485 (1938); A. C. Cope, D. E. Morrison, and L. Field, *J. Amer. Chem. Soc.*, **72**, 59 (1950); A. H. Wragg, J. S. McFadyen, and T. S. Stevens, *J. Chem. Soc.*, 3603 (1958); D. Darwish and R. McLaren, *Tetrahedron Lett.*, 1231 (1962); D. Darwish and E. A. Preston, *ibid.*, 113 (1964); E. Ciuffarin, M. Isola, and A. Fava, *J. Amer. Chem. Soc.*, **90**, 3595 (1968). (b) D. R. Rayner, E. G. Miller, P. Bickart, A. J. Gordon, and K. Mislow, *ibid.*, **88**, 3138 (1966); E. G. Miller, D. R. Rayner, and K. Mislow, *ibid.*, 3139.

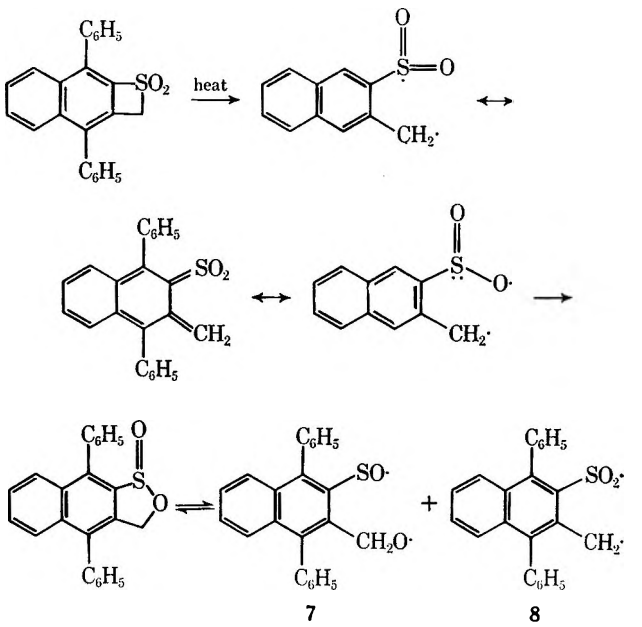
(23) M. Kobayashi and N. Koga, *Bull. Chem. Soc. Jap.*, **39**, 1788 (1966); B. Bonini, S. Ghersetti, and G. Modena, *Gazz. Chim. Ital.*, **93**, 1222 (1963); S. Detoni and D. Hadzi, *J. Chem. Soc.*, 3163 (1955).

(24) J. G. Pritchard and P. C. Lauterbur, *J. Amer. Chem. Soc.*, **83**, 2105 (1961); R. S. Edmundson, *Tetrahedron Lett.*, 1649 (1965).

(25) For comparisons of the chemical shifts of $-CH_2OH$ and CH_2SH groups, see "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., Vol. 1, No. 101, 102; "Sadtler Standard Nuclear Magnetic Resonance Spectra," Sadtler Research Laboratories, Inc., Philadelphia, Pa., No. 276.

(26) J. S. Shannon, *Aust. J. Chem.*, **15**, 265 (1962).

SCHEME II



7 8

from intermediate **7** or two hydroxyl groups from intermediate **8**, both losses accompanied by cyclizations, could give fluorenone **2** and fluorene **3**, respectively.[27] The loss of oxygen from the sulfur atom is analogous to the loss in the pyrolysis of sulfoxides to sulfides.[28] The carbon monoxide observed in the pyrolysis of thiete sulfone **1** may be formed by decarbonylation of fluorenone **2**. Thermal decomposition of sulfinic acids yields small amounts of carbon monoxide, carbon dioxide, and water.[29] Alternatively, sulfur dioxide may be evolved only to react subsequently with intermediates derived from the naphthalene nucleus.

The role of 9,10-dihydroanthracene in preventing further decomposition of sultine **6** in pyrolysis is unclear. It apparently is not acting as a diluent because the pyrolysis proceeded normally to **2** and **3** when the 9,10-dihydroanthracene was replaced by anthracene or *p*-terphenyl. Various excited states of reactant or intermediates may be involved and the dihydroanthracene may interact with one of these to prevent extensive rearrangement. Further investigation into the mechanism of these transformations is in progress.

Experimental Section

Melting points were obtained on a Fisher-Johns melting point apparatus (uncorrected) or a Herschberg melting point apparatus using Anschütz precision thermometers (corrected). Infrared spectra were taken on either a Perkin-Elmer Model 137 infrared spectrophotometer or on a Perkin-Elmer Model 521 grating spectrophotometer. The infrared absorptions are reported as weak (w), medium (m), and strong (s). Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 ultraviolet spectrophotometer. The absorptions are reported in millimicrons and the intensity of the absorptions in ϵ; the actual absorbance value is given in cases where the molecular weight was not known or the sample was not weighed. Proton nuclear magnetic resonance (nmr) spectra were obtained on a Varian Model A-60 nmr spectrometer. Nmr absorptions are reported as δ values and tetramethylsilane was used as an internal standard unless stated otherwise. Microanalyses were performed at Galbraith Laboratories, Knoxville, Tenn., or at Alfred Bernhardt Microanalytisches Laboratorium in Max-Planck Institut für Kohlenforschung, Mülheim, West Germany. Molecular weight determinations were done by vapor pressure osmometry in an appropriate solvent, by the Rast method or by mass spectrometry. Mass spectra were performed by Morgan-Schaffer Corp., Montreal, Quebec, Canada, or at the Department of Chemistry, Syracuse University, Syracuse, N. Y. In all cases, a Perkin-Elmer Hitachi Model RMU-6D single focusing spectrometer was used at an ionizing voltage of 70 eV.

Pyrolysis of 3,8-Diphenyl-2H-naphtho[2,3-*b*]thiete 1,1-Dioxide.—A 100-ml, three-necked, round-bottomed flask was fitted with a gas inlet stopcock in each of the side necks and a standard taper stopper in the center neck. 3,8-Diphenyl-2H-naphtho[2,3-*b*]thiete 1,1-dioxide[12,30] (2.00 g, 5.62×10^{-3} mol) was placed in the flask which was flushed with Linde high-purity dry nitrogen for 5 min. The outlet may be connected to a gas bubbler or, if the gases are to be collected, to a 100-ml syringe. Heating of the flask is done with a metal bath (Wood's metal alloy or a mixture of tin and lead) which was heated with a Bunsen burner. The temperature of the bath was measured with a partial immersion (76 mm) thermometer. Nitrogen flow through the flask was maintained until the sulfone melted (259°), and then was reduced until there was a slight positive pressure. The sulfone was heated from about 180 to 360° in 4–6 min, and then for 5 min from 360 to 400°. Decomposition of the sulfone started at about 370–380° with the appearance of a red color in the flask. The flask was removed from the metal bath and cooled as a stream of nitrogen was passed through the flask.

The pyrolyzed mixture was dissolved in a minimum of chloroform and separated by column chromatography on a column of Woelm acidic alumina, activity grade I. A column 1.5 × 50 cm is sufficient to effect the separation. Elution with benzene gave, after recrystallization from benzene, white crystals of 14H-benzo[*b*]benzo[3,4]fluoreno[2,1-*d*]thiophene (**3**, 0.21 g, 6.52×10^{-4} mol, 11% yield), mp 233°. Changing the solvent to chloroform caused elution of a broad red-brown band, which when recrystallized from chloroform gave 14-H-benzo[*b*]benzo-[3,4]fluoreno[2,1-*d*]thiophen-14-one (**2**, 0.60 g, 1.78×10^{-3} mol, 31.5% yield), mp 265°.

Anal. Calcd for $C_{23}H_{12}OS$ (**2**): C, 82.13; H, 3.60; S, 9.52; mol wt, 336. Found: C, 81.88; H, 3.59; S, 9.33; mol wt, 336 (mass spectrometry).

Anal. Calcd for $C_{23}H_{14}S$ (**3**): C, 85.69; H, 4.38; S, 9.93; mol wt, 322. Found: C, 85.56; H, 4.41; S, 9.65; mol wt, 322 (mass spectrometry).

Fluorenone **2** has the following properties: infrared (KBr) 3050 w, 1705 s, 1600 m, 1540 m, 1460 m, 1445 w, 1390 m, 1325 m, 1290 w, 1195 m, 1090 m, 1080 w, 945 m, 890 m, 770 s, 725 s, 710 m, 660 cm^{-1} s; ultraviolet ($CHCl_3$) 253 mμ (sh) (ϵ 3.75×10^4), 271 (6.40×10^4), 305 (sh) (3.50×10^4), 314 (4.20×10^4), 333 (1.40×10^4), and 347 (9.53×10^3); mass spectrum[31] *m/e* 338 (8.34%, isotope peak), 337 (26.05%, isotope peak), 336 (100.00%, parent ion), 308 (16.24%, P − CO), 307 (7.52%), 306 (13.19%), 305 (2.44%), 291 (6.09%), 276 (5.28%, $C_{22}H_{12}^+$), 263 (5.39%, $C_{21}H_{11}^+$), 168 (12.39%, $C_{23}H_{12}OS^{2+}$), 154 (11.78%), 153 (10.15%).

Fluorene **3** has the following properties: infrared (KBr) 3015 w, 2870 w, 1548 m, 1520 m, 1467 s, 1460 s, 1446 m, 1435 m, 1419 w, 1395 m, 1375 m, 1335 m, 1305 m, 1300 m, 1115 s, 1070 w, 1040 w, 1025 w, 940 w, 850 m, 765 s, 715 s, 710 s, 665 m, 630 s; ultraviolet ($CHCl_3$) 251 mμ (ϵ 4.20×10^4), 259 (4.08×10^4), 277 (2.69×10^4), 298 (9.69×10^3), 311 (1.40×10^4), 334 (sh) (1.88×10^4), 348 (3.06×10^4), and 367 (3.17×10^4); mass spectrum *m/e* 324 (8.42%, isotope peak, 323 (26.65%), isotope peak), 322 (100.00%, parent ion), 321 (47.10%), 320 (7.38%), 319 (14.03%), 289 (6.68%), 161 (15.78%, $C_{23}H_{14}S^{2+}$), 160.5 (15.41%), 160 (7.04%), 159.5 (11.93%).

Because of the low solubility of **2** and **3** in common nmr solvents (such as $CDCl_3$, dimethyl-d_6 sulfoxide, and benzene-d_6) no nmr spectra of good quality were obtained for either of these compounds.

(27) Speculative mechanisms can be written for these transformations.

(28) I. D. Entwistle and R. A. W. Johnstone, *Chem. Commun.*, 29 (1965); D. G. Barnard-Smith and J. F. Ford, *ibid.*, 120 (1965); W. Carruthers, I. D. Entwistle, R. A. W. Johnstone, and B. J. Millard, *Chem. Ind.* (London), 342 (1966).

(29) E. Wellisch, E. Gipstein, and O. J. Sweeting, *J. Org. Chem.*, **27**, 1810 (1962).

(30) L. A. Paquette, *ibid.*, **30**, 629 (1965).

(31) Only fragments which were 5% of the base peak or greater are included in this tabulation and in others, except for *m/e* 305. Percentages are relative to the intensity of the base peak.

The mass spectrum of 5-phenyl-7H-benzo[c]fluorenone[16] (5) was obtained for the purpose of comparison with that of fluorenone 2: *m/e* 307 (24.75%, isotope peak), 306 (100.00%, parent ion), 305 (15.00%), 278 (7.19%, P − CO), 277 (20.60%), 276 (34.70%), 275 (5.46%), 274 (9.29%), 153 (7.02%, $C_{23}H_{14}O^{2+}$), 138.5 (10.40%), 138 (35.90%), 137 (10.30%), 126 (7.38%), 125 (8.56%).

Analysis of the Gases.—The analysis of the gases obtained in the pyrolysis was done by mass spectrometry. The samples of naphthothiete sulfone 1 were pyrolyzed in evacuated Pyrex bulbs (volume 65 ± 1 cm³). Weighed samples of 1 were transferred into the bulbs which were then evacuated to less than 0.03 mm and sealed. The samples (each about 1.40×10^{-3} mol) were pyrolyzed and the composition and quantities (mole per cent) of the components in the gas mixture are given in Table I.

TABLE I

MASS SPECTRAL ANALYSIS DATA OF VOLATILE PRODUCTS FROM PYROLYSIS OF NAPHTHOTHIETE SULFONE 1

	Mole per cent of total gases			
Product	Run 1[a] (heated 5 min at 380–400°)	Run 2[b] (heated 5 min at 380–400°)	Run 3[a] (heated 0.5 min at 350–360°)	Run 4[c] (heated 5 min at 295–305°)
H_2O	1.4	6.4	18.4	43.6
CO	59.1	40.9	48.8	5.9
H_2S	3.9	12.3	0.2	0
CO_2	29.1	36.8	20.9	0.9
COS	1.2	1.8	1.2	0
SO_2	0.5	0.1	5.3	15.3

[a] Bulb pressure after pyrolysis was 110 mm. [b] Bulb pressure after pyrolysis was 190 mm. [c] Bulb pressure after pyrolysis was 22 mm.

Reduction of 14H-Benzo[b]benzo[3,4]fluoreno[2,1-d]thiophen-14-one (2) with Hydrogen-Poor Raney Nickel.—A suspension of W-5 Raney nickel[32] (5–6 g) was degassed slightly by refluxing it for 15 min in absolute ethanol. Solid 2 (0.213 g, 6.34×10^{-4} mol) was added and refluxed with the degassed nickel for 0.5 hr. The hot mixture was filtered and the residual nickel washed on the filter with hot chloroform (300 ml). The dry nickel residue was not pyrophoric. The orange filtrate was evaporated to dryness on a steam bath under a stream of air. The residue was dissolved partially in chloroform and the solid inorganic compounds were removed by filtration. Recrystallization from chloroform and a few milliliters of 95% ethanol gave 83 mg of an impure orange solid. The third crop of crystals was sublimed at 95° (0.03 mm) to give an impure sublimate (5.1 mg) and a residue of impure fluorene 3 (34.9 mg). The residue was recrystallized from methanol–chloroform (4:1) to give pure 3 (15.4 mg), mp 237–238° uncor. This sample of 3 had infrared and ultraviolet spectra identical with those of the fluorene obtained in the pyrolysis of naphthothiete sulfone 1. The first and second crops of crystals were chromatographed on a column (35 × 1 cm) of Woelm neutral alumina, activity grade I. Elution with benzene gave fluorene 3, which was recrystallized from methanol–chloroform (4:1) to give orange crystals (27 mg). The total yield of crude 3 was 30.4%. Although 3 is white when pure, the slight orange color here is due to a slight trace of fluorenone 2, which was detected by mass spectrometry.

Elution with chloroform gave a red band of impure 2 (14.9 mg). Recrystallization gave pure 2 (8.2 mg), mp 264–68° uncor. The sample of 2 recovered was compared with the starting material and found to have identical infrared and ultraviolet spectra. Further elution of compounds from the column with chloroform or chloroform–ethanol (3:1) gave only 19.4 mg of an unidentified oil.

Desulfurization of 14H-Benzo[b]benzo[3,4]fluoreno[2,1-d]thiophen-14-one (2) with Hydrogen-Rich Raney Nickel.—Fluorenone 2 (0.204 g, 6.08×10^{-4} mol) was refluxed with 10–12 g of W-5 Raney nickel[32] in 95% ethanol (100 ml) for 5 hr. The hot mixture was cooled slightly, then filtered under vacuum and the residual nickel washed with 250 ml of hot chloroform. The nickel was still pyrophoric. The filtrate was evaporated to dryness, and the residue taken up in chloroform to yield 183 mg of an oil. The chloroform-insoluble material was taken up in 95% ethanol to yield 26 mg of a crude solid. The oil gave more of the solid on cooling, which when combined with the crude solid above (26 mg) and recrystallized from chloroform–ethanol gave 13.4 mg of an unknown compound, mp 210–220°.

The oil was chromatographed on Woelm acidic alumina, activity grade I, on a 45 × 1 cm column. Elution with petroleum ether (bp 30–60°) and benzene gave a yellow oil (75 mg) and elution with chloroform gave a red oil (90 mg). The yellow oil gave the following analysis.

Anal. Calcd for $C_{23}H_{26}$: C, 91.33; H, 8.67; mol wt, 302. Found: C, 91.18; H, 8.50; mol wt, 304.

It had the following properties: infrared (KBr) 3045 m, 3010 m, 2915 s, 2845 s, 1600 m, 1515 m, 1460 m, 1440 s, 1400 m, 1335 w, 1260 m, 1085 m, 1070 m, 1025 m, 945 w, 870 w, 850 m, 765 s, 730 s, 700 cm^{-1} s; ultraviolet spectrum ($CHCl_3$) 254, 278 (weak), 290 (sh), 331 (sh), and 345 mμ (sh) (the two weak bands at 345 and 331 mμ may be due to impurities originating with starting material 2); nmr ($CDCl_3$) δ 0.89 (complex), 1.25 (singlet), 1.82 (complex), 2.72 (complex), 3.34 (complex), 3.82 (complex), 7.38 (complex), and 7.88 (complex). The ratio of the hydrogens at δ 7.38 and 7.88 to the rest of the hydrogens is 33:58.

The impure red oil gave the following analysis.

Anal. Calcd for $C_{23}H_{24}O$: C, 87.30; H, 7.64; mol wt, 316.5. Found: C, 84.35, 84.55; H, 12.63, 12.64; mol wt, 510, 520.

The red oil had the following properties: infrared (KBr) 3055 w, 3010 w, 2925 s, 2850 m, 1710 s, 1600 m, 1495 w, 1445 m, 1395 m, 1200 m, 755 s, and 700 cm^{-1} s; ultraviolet ($CHCl_3$) 257, 293 (sh), and 345 mμ (broad sh).

Synthesis of 5-Phenylbenzo[b]naphtho[1,2-d]thiophene.—This compound was prepared in order to compare its spectra with those of 3. 1,4-Diphenylnaphthalene[16,33] (1.500 g, 5.35 mmol) and sulfur (177 mg, 5.5 mmol) were melted together at 178° for 0.5 hr. Anhydrous aluminum chloride (42 mg, 0.313 mmol) was added in 21-mg quantities at 15-min intervals. The reaction became quite dark when the aluminum chloride was added. Heating in the oil bath was continued for 3.5 hr with occasional shaking of the reaction mixture. After the reaction mixture had cooled, 50 ml of water was added and the aqueous mixture was extracted with three 50-ml portions of benzene, to yield a dark red solution. The solvent was evaporated and the red oil chromatographed on a column (2.5 × 90 cm) of Woelm acidic alumina, activity grade I. The compound can be eluted with either benzene or carbon tetrachloride. Only the colorless eluent was found to give the desired product. After recrystallization from chloroform–ethanol, a white compound, mp 195.2–196° cor (179 mg, 5.78×10^{-4} mol, 10.8% yield), was obtained.

Anal. Calcd for $C_{22}H_{14}S$: C, 85.13; H, 4.55; mol wt, 310. Found: C, 85.30; H, 4.67; mol wt, 310 (mass spectrometry).

The compound had the following properties: infrared (KBr), 3010 w, 1490 w, 1465 w, 1440 w, 1430 m, 1338 m, 1160 w, 1015 w, 985 w, 873 m, 778 m, 760 m, 745 s, 730 m, and 695 cm^{-1} s; ultraviolet ($CHCl_3$) 249 mμ (ε 5.08×10^4), 258 (5.78×10^4), 281 (4.67×10^4), 305 (2.18×10^4), 321 (sh) (8.48×10^3), and 353 (4.03×10^3); mass spectrum *m/e* 312 (7.00%, isotope peak), 311 (24.81%, isotope peak), 310 (100.00%, parent ion), 309 (24.7%), 308 (35.3%), 306 (5.4%), 280 (10.5%), 155 (11.6%, $C_{22}H_{14}S^{2+}$), 154.5 (10.5%), 154 (15.5%), 153 (7.4%).

Desulfurization of 14H-Benzo[b]benzo[3,4]fluoreno[2,1-d]thiophene (3) with Raney Nickel.—A mixture of 3 (150 mg, 4.66×10^{-4} mol) was refluxed in 95% ethanol (50 ml) with W-5 Raney nickel[32] (5–6 g) for 0.5 hr. The mixture was then filtered and the residual nickel washed with hot benzene (350 ml). The solvent was evaporated on a steam bath under a stream of air and the oily residue was recrystallized from methanol–ligroin (bp 40–60°) in two crops for a total of 95 mg of a compound, mp 128–130° cor (lit.[16] mp 128°). The melting point was not depressed when mixed with an authentic sample of 5-phenyl-7H-benzo[c]fluorene (4). It also had infrared and ultraviolet spectra identical with those of the authentic material. Fluorene 4 had the following properties: infrared (KBr) 3090 w, 3040 w, 2920 w, 1590 w, 1490 m, 1460 m, 1440 w, 1395 m, 1335 m, 1205 w, 1020 w, 945 m, 910 w, 872 m, 785 w, 769 s, 755 s, 745 m, 710 s, 698 s, and 640 cm^{-1} s; ultraviolet ($CHCl_3$) 247, 330, and 345 mμ.

Synthesis of 5-Phenyl-7H-benzo[c]fluorene (4).—A mixture of 5-phenyl-7H-benzo[c]fluorenone,[16] 5 (1.00 g, 3.27×10^{-3} mol), and 1,2-ethanedithiol (20 ml) was warmed on a steam bath until the ketone dissolved. Boron trifluoride–ethyl etherate (15 ml) was added to the warm solution and the mixture was allowed to stand for 15 min. Methanol (50 ml) was added

(32) H. R. Billica and H. Adkins, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 176.

(33) C. Dufraisse and R. Priou, *Bull. Soc. Chim. Fr.*, **5**, 502 (1938).

and the solution cooled to give white crystals of the dithioketal (1.25 g, crude). The crude product was recrystallized from ethanol–benzene (10:1) to give pure dithioketal (0.69 g, 55% yield), mp 219–222° uncor.

Anal. Calcd for $C_{25}H_{18}S_2$: C, 78.52; H, 4.74; mol wt, 382. Found: C, 78.37; H, 4.90; mol wt, 382 (mass spectrometry).

The dithioketal (0.500 g, 1.31×10^{-3} mol) and W-5 Raney nickel (10–11 g) were refluxed in absolute ethanol (200 ml) for 1 hr. The warm mixture was filtered and the nickel washed with hot chloroform (200 ml). The residual nickel was not pyrophoric. The solution was evaporated to dryness on a steam bath under a stream of air. The residue was taken up in chloroform (200 ml) and the insoluble inorganic compounds removed by filtration. The chloroform was evaporated and the residue recrystallized from methanol–chloroform (10:1) to give slightly off-white crystals (268 mg, 70% yield), mp 126–29° uncor (lit.[15] mp 128°).

Anal. Calcd for $C_{23}H_{16}$ (4): C, 94.48; H, 5.52; mol wt, 292. Found: C, 94.38; H, 5.51; mol wt, 280 (Rast), 292 (mass spectrometry).

Fluorene 4 had the following properties: nmr ($CDCl_3$) δ 7.15–8.55 (complex multiplet, aromatic protons), 3.97 (singlet, methylene protons); infrared (KBr) 3040 w, 1600 w, 1590 w, 1510 w, 1492 m, 1460 m, 1440 w, 1395 m, 1333 m, 1205 w, 1065 w, 1020 w, 998 w, 945 s, 910 w, 872 m, 855 w, 785 w, 769 s, 755 s, 745 m, 710 s, 695 s, and 635 m cm^{-1}; ultraviolet ($CHCl_3$) 246 mμ (ϵ 3.25×10^4), 330 (2.06×10^4), and 343.5 (2.09×10^4).

Pyrolysis of 3,8-Diphenyl-2H-naphtho[2,3-*b*]thiete 1,1-Dioxide (1) with 9,10-Dihydroanthracene.—A mixture of sulfone 1 (2.017 g, 5.66×10^{-3} mol) and 9,10-dihydroanthracene (2.321 g, 12.88×10^{-3} mol) (Aldrich Chemical Co., recrystallized once from 95% ethanol) was pyrolyzed as described previously for neat 1. The slightly orange solid which was obtained was dissolved in a minimum amount of carbon tetrachloride and chromatographed on a column (2 × 50 cm) of Woelm acidic alumina, activity grade I. A mixture of 9,10-dihydroanthracene (78–84%) and anthracene (22–16%) (total recovery of the combined compounds was 83%) was eluted with carbon tetrachloride. A yellow band was eluted with chloroform–ethanol (20:1), and recrystallized (with decolorization with activated carbon) from 95% ethanol to give the slightly yellow sultine (6) (78–81% yield), mp 202.4–203° cor.

Anal. Calcd for $C_{23}H_{16}O_2S$ (6): C, 77.50; H, 4.52; S, 8.99; mol wt, 356. Found: C, 77.40; H, 4.62; S, 8.84; mol wt, 356 (mass spectrometry).

Sultine 6 has the following properties: infrared (KBr) 3020 w, 2900 w, 1585 w, 1508 w, 1490 w, 1440 m, 1405 w, 1364 m, 1325 w, 1270 w, 1175 w, 1120 s, 1070 w, 1020 w, 995 w, 948 s, 920 m, 835 m, 765 s, 740 s, 700 s, 680 s, and 665 cm^{-1} s; nmr ($CDCl_3$) δ 7.00–8.00 (complex multiplet, aromatic protons), 5.98 (doublet), and 5.32 (doublet, J_{AB} = 14 Hz); ultraviolet (C_2H_5OH) 239 (ϵ 5.70×10^4), 300.5 (1.4×10^4), and 333 (5.98×10^3).

Lithium Aluminum Hydride Reduction of Sultine 6.—A suspension of the sultine (0.5 g, 1.4×10^{-3} mol) in anhydrous ethyl ether (30 ml) was added to a slurry of lithium aluminum hydride (0.53 g, 14 mmol) in anhydrous ethyl ether (50 ml) stirred with a magnetic stirring bar. The addition and reaction were done in a nitrogen atmosphere. After the addition (0.5 hr) the slurry was refluxed for 5 hr. Excess hydride was destroyed with water (30 ml) which contained about 1 ml of concentrated hydrochloric acid. The decomposed mixture was neutralized to pH 5–6 with aqueous sodium hydroxide and extracted with four 100-ml portions of benzene, and the benzene evaporated on a steam bath under a stream of air. The yellowish residue was taken up in methanol and filtered with decolorizing carbon, and water was added to the filtrate to the cloud point. Cooling of the solution gave a yellow solid (0.248 g, 60% yield), mp 234.4–236° cor.

Anal. Calcd for $C_{23}H_{18}OS$: C, 80.67; H, 5.30; S, 9.36; mol wt, 342. Found: C, 80.97; H, 5.47; S, 9.38; mol wt, 342 (mass spectrometry).

The reduction product had the following properties: infrared (KBr) 3520 w, 3400 m, 3050 w, 3020 w, 2930 w, 2870 w, 2550 w, 1595 w, 1540 w, 1500 w, 1490 m, 1440 m, 1365 m, 1320 w, 1270 w, 1170 w, 1042 m, 1020 w, 980 w, 915 w, 810 w, 760 m, 750 m, 735 m, and 695 cm^{-1} s; ultraviolet (C_2H_5OH) 231 mμ (ϵ 2.75×10^4), 253 (3.22×10^4), 278 (sh) (8.95×10^3), 292.5 (8.13×10^3), 304 (7.85×10^3), and 346 (sh) (1.79×10^3); nmr ($CDCl_3$) δ 7.16–7.76 (complex multiplet, aromatic protons), 4.66 (singlet, $-CH_2-$), 3.88 (singlet, –SH), and 2.12 (singlet, –OH); relative areas 14:2:1:1, respectively. The mass spectra of naphthothiete sulfone 1 and sultine 6 are compared in Table II.

TABLE II
MASS SPECTRAL DATA FOR NAPHTHOTHIETE SULFONE 1 AND SULTINE 6[a]

m/e	% of base peak 1	% of base peak 6	Possible ion formula	M⁺ – fragment
358		8.23	Isotope peak	
357	11.42	26.50	Isotope peak	
256	43.02	100.00	$C_{23}H_{16}O_2S^+$	M^+
339		6.32	$C_{23}H_{15}OS^+$	$M^+ - 17$
338		10.20	$C_{23}H_{14}OS^+$	$M^+ - 18$
337		6.32	$C_{23}H_{13}OS^+$	$M^+ - 19$
336		7.29	$C_{23}H_{12}OS^+$	$M^+ - 20$
321		6.32		$M^+ - 35$
311		6.32	$C_{22}H_{15}S^+$	$M^+ - 45$
310		9.71	$C_{22}H_{14}S^+$	$M^+ - 46$
309		19.89	$C_{22}H_{13}S^+$	$M^+ - 47$
308	10.05	53.85	$C_{23}H_{16}O^+$	$M^+ - 48$
307	5.44	29.10	$C_{23}H_{15}O^+$	$M^+ - 49$
293	13.85	10.70	$C_{22}H_{13}O^+$	$M^+ - 63$
292	66.97	45.60	$C_{23}H_{16}^+$	$M^+ - 64$
291	100.00	76.75	$C_{23}H_{15}^+$	$M^+ - 65$
290	29.13	21.84	$C_{23}H_{14}^+$	$M^+ - 66$
289	52.24	35.40	$C_{23}H_{13}^+$	$M^+ - 67$
288	5.98		$C_{23}H_{12}^+$	$M^+ - 68$
287	11.42	6.32	$C_{23}H_{11}^+$	$M^+ - 69$
281		7.77		$M^+ - 75$
280	5.71	28.64	$C_{22}H_{16}^+$	$M^+ - 76$
279		16.99	$C_{22}H_{15}^+$	$M^+ - 77$
278		9.71		$M^+ - 78$
277	10.60	15.52	$C_{22}H_{13}^+$	$M^+ - 79$
276	16.32	25.73	$C_{22}H_{12}^+$	$M^+ - 80$
274		7.29		$M^+ - 82$
265		6.80		$M^+ - 91$
263	7.62	8.25	$C_{21}H_{11}^+$	$M^+ - 93$
252		5.34		$M^+ - 104$
234		5.38		$M^+ - 122$
216		5.34		$M^+ - 140$
215	31.83	23.88	$C_{17}H_{11}^+$	$M^+ - 141$
213	8.16	6.32		$M^+ - 143$
203		10.70	$C_{16}H_{11}^+$	$M^+ - 153$
202		11.65	$C_{16}H_{10}^+$	$M^+ - 154$
200		5.34		$M^+ - 156$
189		5.83		$M^+ - 167$
154.5		5.83		
154		16.99	$C_{23}H_{16}O^{2+}$	
153		7.29	$C_{23}H_{14}O^{2+}$	
145.5	7.07	7.77	$C_{23}H_{16}^{2+}$	
145	20.92	22.32	$C_{23}H_{14}^{2+}$	
144.5	23.61	22.32	$C_{23}H_{13}^{2+}$	
144	6.54	6.80	$C_{23}H_{12}^{2+}$	
143.5	9.79	8.74	$C_{23}H_{11}^{2+}$	
138.5		10.70	$C_{22}H_{13}^{2+}$	
138	16.01	23.30	$C_{22}H_{12}^{2+}$	
137		7.29		$M^+ - 219$
132		5.34		$M^+ - 224$
131.5	9.25	12.12	$C_{21}H_{11}^{2+}$	
126		5.83		$M^+ - 230$
125		7.77		$M^+ - 231$
113		5.34		$M^+ - 243$
83	5.71			$M^+ - 263$
77		5.83		$M^+ - 279$
31		6.32		$M^+ - 325$
28		8.25	N_2^+, CO^+, or C_2H_4	
18		7.77	H_2O^+	

[a] Only those fragments which were 5% of the base peak or greater are included in this table.

Pyrolysis of Sultine 6.—Cyclic sulfinate 6 (0.61 g, 1.71×10^{-3} mol) was placed in a 100-ml, three-necked, round-bottomed flask with a gas inlet and outlet stopcock in the side necks of the flask, and a standard taper stopper in the center neck. The flask was flushed with Linde high-purity dry nitrogen as it was heated up to 360°. The nitrogen flow was reduced to a slight positive pressure (the outlet may be connected to a mercury-filled bubbler) and the metal bath heated to 360–400° for 5 min. At about 375–380° [temperature measured with a partial (76 mm) immersion thermometer] a sudden evolution of gas was observed, and the compound became dark red. An analysis of the gases was not done. The pyrolyzed compound was cooled in a nitrogen atmosphere, dissolved in a minimum amount of carbon tetrachloride, and separated on a column (2 × 47 cm) of Woelm acidic alumina, activity grade I. Elution with ethanol–carbon tetrachloride (1:9) and with carbon tetrachloride alone gave fluorenone 2 (122 mg, 3.63×10^{-4} mol, 21.2% yield) and fluorene 3 (43 mg, 1.34×10^{-4} mol, 7.8% yield), identified by comparison of their ultraviolet and infrared spectra with those of 2 and 3 produced in the normal pyrolysis of naphthothiete sulfone 1.

Registry No.—1, 979-37-3; 2, 19639-51-1; 3, 19639-52-2; 4, 19639-53-3; 4 (dithioketal), 19639-54-4; 6, 19639-55-5; reduction product of 6 ($C_{23}H_{16}OS$), 19639-56-6; 5-phenylbenzo[*b*]naphtho[1,2-*d*]thiophene, 19639-57-7.

The Reaction of Phenyllithium with 1-Halo-2-butenes[1]

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Phenyllithium reacted with *cis*- and *trans*-1-chloro-2-butene and *trans*-1-bromo-2-butene and gave a mixture of 3-phenyl-1-butene, *cis*- and *trans*-1-phenyl-2-butene, and *cis*- and *trans*-1-methyl-2-phenylcyclopropane. The ratio of the isomeric cyclopropanes was similar to that obtained from the addition of phenyllithium to 3-methylcyclopropene and confirmed the formation of this compound in the reaction. Phenylsodium and phenylmagnesium bromide in their reactions with the 1-halo-2-butenes gave only the three olefins.

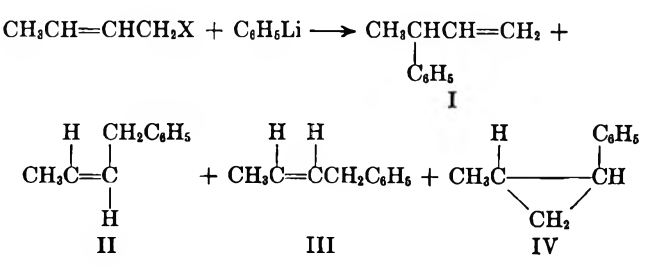
Two mechanisms have been offered for the formation of cyclopropanes in the reaction of phenyllithium with allylic halides. The first of these suggested an attack of the phenyl carbanion on the β-carbon atom of the halide followed by an intramolecular cyclization to the cyclopropane.[2] The second one suggested the formation of a carbene followed by cyclization to a cyclopropene which reacts with phenyllithium and forms the cyclopropane.[3] Results with deuterated allyl chloride and allyl-1-^{14}C chloride[4] have confirmed the second mechanism for the formation of the cyclopropane.

In this paper studies are reported on the course of the reaction between phenyllithium and 1-halo-2-butenes and the stereochemistry of the cyclopropane produced. The first mechanism would be expected to produce only *trans*-1-methyl-2-phenylcyclopropane and the second offers the possibility of a mixture of *cis* and *trans* isomers.

The results obtained for the reaction of phenyllithium with *cis*- and *trans*-1-chloro-2-butene and *trans*-1-bromo-2-butene, and of phenylsodium with *trans*-1-chloro-2-butene are listed in Table I.

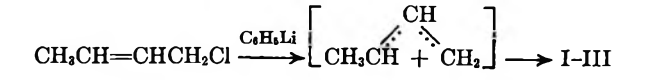
Examination of the results in Table I indicates that *cis*- and *trans*-1-methyl-2-phenylcyclopropane (IV) are formed together with 3-phenyl-1-butene (I), *trans*-1-phenyl-2-butene (II), and *cis*-1-phenyl-2-butene (III) in the reaction of phenyllithium with 1-halo-2-butenes (Scheme I). Phenylsodium in the same reaction did not form any detectable cyclopropane. The cyclopropane formed varied in yield with the conditions used and was by vpc analysis better than 93.9% *trans;* the *cis* compound was present in amounts of

SCHEME I



6.1% or less. The high ratio of *trans* to *cis* isomers would suggest that the first mechanism was operating but a study of the reaction of 3-methylcyclopropene with phenyllithium found the same ratio of isomeric cyclopropanes. The results therefore confirm the second mechanism for the formation of the cyclopropanes and are in agreement with the results of Magid and Welch.[4]

An interesting sidelight on the reaction was the formation of a small percentage of *cis*-1-phenyl-2-butene (III) in the reaction of phenyllithium with *trans*-1-chloro-2-butene and a small amount of the corresponding *trans* olefin in the reaction involving *cis*-1-chloro-2-butene. A similar behavior was found with phenylsodium and *trans*-1-chloro-2-butene. This isomerization is consistent with the ionization mechanism proposed for the reaction of phenyllithium and 1-chloro-2-butene.[5] The stereochemistry of the allylic



cation could be altered by an internal return of the halide ion to form the 3-halo-1-butene followed by ionization of this halide.

The effect of solvents on the ratio of the products obtained indicates that a complex between the phenyl-

(1) Abstracted in part from the Ph.D. Theses of B. J. Studnicka, 1966, and A. R. Zigman, 1968.

(2) (a) S. Wawzonek, B. J. Studnicka, H. J. Bluhm, and R. E. Kallio, *J. Amer. Chem. Soc.*, **87**, 2069 (1965); (b) S. Wawzonek, H. J. Bluhm, B. J. Studnicka, R. E. Kallio, and E. J. McKenna, *J. Org. Chem.*, **30**, 3028 (1965).

(3) (a) R. M. Magid and J. G. Welch, *J. Amer. Chem. Soc.*, **88**, 5681 (1966); (b) J. G. Welch and R. M. Magid, *ibid.*, **89**, 5300 (1967).

(4) R. M. Magid and J. G. Welch, *ibid.*, **90**, 5211 (1968).

(5) S. J. Cristol, W. C. Overhults, and J. S. Meek, *ibid.*, **73**, 813 (1951).

TABLE I

REACTION OF PHENYLLITHIUM AND PHENYLSODIUM WITH 1-HALO-2-BUTENES

$CH_3CH=CHCH_2X$	Solvent	Addn[b] temp, °C	Reaction time, hr	Total[c] yield, %	Isolated[d] yield, %	Product distribution[e] I	II	III	IV
				C_6H_5Li[a]					
trans chloride	Ether	Reflux	2.25	79	66	18	54	16	11 (0.54)
trans chloride[f]	Ether	Reflux	3.25	78	49	28	56	5	12 (0.67)
trans chloride	Benzene[g]	Reflux	2.5	98	64	49	31	8	2 (0.06)
trans chloride	THF[g]	10–15	2.5	61	44	2	77	17	3 (0.20)
cis chloride[h]	Ether	Reflux	2.25		40	23	7	67	3 (0.10)
trans bromide[i]	Ether	Reflux	2.25	43	14	11	79	8	2
				C_6H_5Na[j]					
trans chloride	Pentane	Reflux	2.25		39	10	70	20	0

[a] 1-Halo-2-butene (0.111 mol) was added to phenyllithium (0.222 mol) unless otherwise noted. [b] Initial addition temperature of the reaction. [c] The total yield of compounds I–IV was determined by vpc analysis. Thermal conductivity corrections were not made for the products. [d] Total yield of compounds I–IV by vpc analysis after distillation. [e] Product distribution of compounds I–IV was determined from the total isolated yield. The total amount of cyclopropanes is listed under IV. The amount of *cis*-1-methyl-2-phenylcyclopropane is given in parentheses. The yield from the *trans* bromide was too small to evaluate. [f] The phenyllithium solution was added to the ether solution of the halide. [g] The phenyllithium was first prepared in ether and the ether was replaced by benzene or tetrahydrofuran. [h] The reaction was carried out using 0.0308 mol of the chloride and 0.0555 mol of phenyllithium. [i] The reaction was carried out using 0.0667 mol of the bromide and 0.222 mol of phenyllithium. The bromide consisted of 23.7% 3-bromo-1-butene and 76.3% *trans*-1-bromo-2-butene. [j] Phenylsodium (0.2 mol) was coupled with the halide (0.111 mol).

TABLE II

REACTION OF PHENYLMAGNESIUM BROMIDE[a] WITH 1-HALO-2-BUTENES

$CH_3CH=CHCH_2X$	Solvent	Addn[b] temp, °C	Reaction time, hr	Total yield,[b] %	Isolated yield,[b] %	Product distribution[b] I	II	III
trans chloride	Ether	Reflux	8.25[c]	73	64	44	52	5
trans chloride[d]	Ether	Reflux	1.25[e]	96	81	39	54	7
trans chloride	Ether	0	2.5[f]	71	66	37	57	6
trans chloride	Benzene[b]	Reflux	8.25[c]	90	85	20	69	11
trans chloride	THF[b]	Reflux	3.5[g]	73	67	11	79	10
trans bromide[b]	Ether	Reflux	8.25[c]	68	50	55	41	4
cis chloride[h]	Ether	Reflux	8.25[c]		53	49	14	38

[a] Phenylmagnesium bromide (0.222 mol) was treated with 1-halo-2-butene (0.111 mol) unless noted otherwise. [b] Same as Table I. [c] The addition of the allylic halide required 15 min and the reaction was refluxed for an additional 8 hr. [d] The phenylmagnesium halide solution was added to the allylic halide. [e] The addition required 15 min and the solution was refluxed for 1 hr and allowed to stand at room temperature for 30 hr. [f] The addition process was completed in 30 min at 0° and the solution was stirred at 0° for 2 hr and allowed to stand at room temperature for 6 hr. [g] The addition process was completed in 30 min and the solution was stirred under reflux for an additional 3 hr. [h] *cis*-1-Chloro-2-butene (0.0308 mol) was added to phenylmagnesium bromide (0.0555 mol).

lithium and the halide, similar to that postulated in the metalation reaction of aromatic compounds,[6] is formed with a stability dependent upon the solvent involved. Further evidence for such a complex is the formation of similar olefinic products with the exception of the cyclopropene in the reaction of phenylmagnesium bromide with 1-halo-2-butenes. The results obtained under varying conditions are given in Table II.

The effects of the solvents on the ratio of the products using the Grignard reagent is the same as that with the phenyllithium with the exception of benzene. The most polar solvent, tetrahydrofuran, gives the smallest amount of the SN2′ product.

Experimental Section[7]

Coupling of Phenyllithium with *trans*-1-Chloro-2-butene.—To a stirred phenyllithium (0.222 mol) solution in ether (90 ml) under nitrogen was added dropwise *trans*-1-chloro-2-butene (10 g) in anhydrous ether (20 ml) over a period of 15 min at the reflux temperature of the solution. The reaction mixture was refluxed with stirring for an additional 2 hr. The resulting reaction mixture was cooled and treated with water and the ether layer obtained was washed with 2 *N* sodium hydroxide and water, and dried over anhydrous potassium carbonate.

Removal of the ether gave an oil (15.9 g) which by vpc analysis on an 8 ft × 0.25 in. column (A) packed with Carbowax 20M (0.2 g) on Chromsorb P (19.8 g) contained the coupled products (79%). The retention times for bromobenzene, 3-phenyl-1-butene, *trans*-1-phenyl-2-butene, *cis*-1-phenyl-2-butene, *trans*-1-methyl-2-phenylcyclopropane, and biphenyl were 1.07, 1.24, 1.80, 1.80, 1.80, and 22.0 min, respectively.

The experimental conditions were as follows: detector temperature, 290°; injection port temperature, 330°; column temperature, 100°; helium pressure, 30 psi; helium flow rate, 150 ml/min.

The crude product was distilled through a zigzag column rated at six theoretical plates and a fraction distilling at 85–100° (50 mm) was collected. Vpc analysis using a 50 ft × 0.25 in. column (B) packed with XF-1150 (16.0 g) (nitrile silicon polymer liquid) on Chromosorb P (15.0 g) (35/80 mesh) showed a 65.5% yield of hydrocarbons with a relative product distribution of 3-phenyl-1-butene, *trans*-1-phenyl-2-butene, *cis*-1-methyl-2-phenylcyclopropane, *cis*-1-phenyl-2-butene, and *trans*-1-methyl-2-phenylcyclopropane of 18.0, 54.0, 0.54, 16.3, and 10.46%, respectively. Retention times for the above compounds were 62.7, 87.8, 90.1, 103.2, and 106.5 min, respectively.

For the examples containing 3.3% or less cyclopropanes the ratio of the cyclopropanes, was difficult to evaluate in the mixture directly by vpc. These mixtures were therefore oxidized with potassium permanganate in acetone as described under *trans*-1-methyl-2-phenylcyclopropane and the product was evaluated on column B.

Experimental conditions were as follows: detector temperature, 300°; injection port temperature, 295°; column temperature, 105°; helium pressure, 40 psi; helium flow rate, 67 ml/min.

(6) H. Gilman and J. W. Morton, Jr., *Org. Reactions*, **8**, 258 (1954).

(7) Boiling points are not corrected. Infrared spectra were obtained using films of undetermined thickness between sodium chloride windows and a Perkin-Elmer 21 double-beam recording spectrophotometer. Nmr spectra were measured with a Varian A-60 nuclear magnetic resonance spectrometer using tetramethylsilane as an internal standard. The samples were analyzed either neat or in carbon tetrachloride.

Preparative vpc on a 10 ft × 3/8 in. column (C) packed with polydiethanolamine succinate polyester (45.0 g) on Chromosorb P_1 (125 g) (80/100 mesh) gave pure samples of 3-phenyl-1-butene, *trans*-1-phenyl-2-butene, and a sample containing a mixture of *cis*-1-phenyl-2-butene and *trans*-1-methyl-2-phenylcyclopropane.

Experimental conditions were as follows: detector temperature, 200°; injection port temperature, 210°; column temperature, 150°; helium pressure, 30 psi; helium flow rate, 100 ml/min.

The infrared spectrum of 3-phenyl-1-butene was identical with Sadtler No. 1616; nmr (CCl_4) δ 1.37 doublet (CH_3), 3.44 multiplet (3-H), 5.00 multiplet (=CH_2), 6.00 multiplet (2-H), 7.17 singlet (aromatic); relative ratio 3:1:2:1:5.

The infrared spectrum of *trans*-1-phenyl-2-butene was identical with Sadtler No. 7852; nmr (CCl_4) δ 1.68 doublet (CH_3), 3.27 doublet (CH_2), 5.56 triplet (CH=CH), 7.11 singlet (aromatic); relative ratio of 3:2:2:5.

The nmr spectrum of the third fraction (CCl_4) was a composite of the spectra of *trans*-1-methyl-2-phenylcyclopropane and *cis*-1-phenyl-2-butene. The migration times of all the components of the reaction mixture agreed with those of authentic samples. Variation in conditions for other runs are given in Table I.

***trans*-1-Methyl-2-phenylcyclopropane.**—The mixture of coupling products (10.0 g) was refluxed in acetone (200 ml) with potassium permanganate (50 g) for 2 days. After this period an additional 50 g of permanganate was added and the refluxing continued for 2 days. Removal of the manganese dioxide was followed by the addition of more permanganate (30 g) and allowing the mixture to stand for 1 day at room temperature. Permanganate (20 g) was added and the solution was refluxed for an additional 3 days. Removal of the manganese dioxide and acetone gave an oil which was taken up in pentane and chromatographed through 8 in. × 0.75 in. alumina column. The product (0.8 g) when purified by preparative vpc on column C gave *trans*-1-methyl-2-phenylcyclopropane which agreed in properties with a sample prepared by the reaction of *trans*-1-phenyl-1-propene with methylene iodide and zinc-copper couple.[8]

Coupling of Phenylmagnesium Bromide with *trans*-1-Chloro-2-butene.—To a stirred and refluxing solution of phenylmagnesium bromide (0.222 mol) in ether (90 ml), *trans*-1-chloro-2-butene (10 g, 0.111 mol) was added over a period of 15 min and the resulting reaction mixture was refluxed for an additional 8 hr. The reaction mixture was treated with saturated ammonium chloride (40 ml) and the ether layer after washing with water and sodium hydroxide solution and drying gave 14.68 g of crude product. Analysis by vpc on column A indicated a 73% yield of coupled products.

Fractional distillation gave 9.43 g of product, bp 84–102° (50 mm). Vpc analysis on an 8 × 0.25 in. column (D) packed with diisodecyl phthalate (1.0 g) on Gas Chrom P (19.0 g) showed that the product consisted of 3-phenyl-1-butene, *trans*-1-phenyl-2-butene, and *cis*-1-phenyl-2-butene in a ratio of 43.6:51.5:4.9, respectively. The retention times were 13.8, 21.8, and 22.8 min, respectively.

Experimental conditions were as follows: detector temperature, 200°; injection port temperature, 215°; column temperature, 100°; helium pressure, 40 psi; helium flow rate, 105 ml/min. Vpc analysis of the distillate on column B indicated the absence of *cis*- and *trans*-1-methyl-2-phenylcyclopropane. Variations in this procedure are reported in Table II.

Addition of Phenyllithium to 3-Methyl-1-cyclopropene.—3-Methyl-1-cyclopropene was prepared by the addition of *trans*-1-chloro-2-butene (90 g) to a refluxing slurry of sodium amide (50 g) in tetrahydrofuran (250 ml). The 3-methyl-1-cyclopropene was displaced by a stream of nitrogen through a trap containing 2 *N* sulfuric acid, dried with Drierite, and collected in a Dry Ice trap. Four bulb-to-bulb distillations gave a liquid (3 g) which by nmr analysis[9] consisted of 3-methyl-1-cyclopropene (0.8 g) and tetrahydrofuran. This liquid in ether (10 ml) was treated with 25 ml of 1 *M* phenyllithium solution in ether in a Dry Ice bath. The resulting solution when treated with water gave 2.85 g of a liquid which by vpc analysis on a 10 ft × 0.25 in. column packed with Carbowax 20M (10%) on Gas Chrom P (100/120 mesh) contained 30.5% 1-methyl-2-phenylcyclopropane. Vpc analysis indicated a mixture of 94.5% *trans*- and 5.5% *cis*-1-methyl-2-phenylcyclopropane.

Experimental conditions were as follows: detector temperature, 300°; injection port temperature, 270°; column temperature, 150°; helium pressure, 30 psi; helium flow rate, 60 ml/min, retention time, 8.7 min.

Starting Materials and Authentic Samples.—*trans*-1-Chloro-2-butene (Aldrich) was used directly as purchased. Analysis by vpc using column D indicated that this compound was 98.6–99.1% pure. The impurity was probably 3-chloro-1-butene. Retention times were 3.3 and 1.7 min, respectively, using a column temperature of 60°; detector block, 150°; injection port temperature, 150°; helium pressure, 30 psi; helium flow rate, 133 ml/min.

***trans*-1-Bromo-2-butene.**—The commercial sample (Aldrich) was washed with cold water and 3% sodium carbonate solution and distilled at atmospheric pressure using a spinning-band column rated at 40 theoretical plates. The fraction boiling at 97–98°, $n^{20}D$ 1.4808 (lit.[10] $n^{25}D$ 1.4795), and corresponding to the primary bromide showed by vpc analysis on a 6-ft diisodecyl-phthalate column (F&M Scientific Corp.) a mixture of 23.7% 3-bromo-1-butene and 76.3% *trans*-1-bromo-2-butene with retention times of 3.9 and 8.3 min using a column temperature of 70°; detector block, 125°; injection port temperature, 105°; helium pressure, 30 psi; helium flow rate, 200 ml/min. The liquid did not change in composition after standing for 4 days at room temperature and was used as such in the reaction with phenyllithium and phenylmagnesium bromide.

Isomeric 1-Phenyl-2-butenes.—The coupling between 1-chloro-2-butyne and phenylmagnesium bromide was carried out using the directions given for the coupling with the bromo compound.[11] The yield of product distilling at 72–84° (16 mm) was 23.6% [lit.[11] bp 70–82° (13 mm)]. Vpc analysis on column C showed two components in the ratio of 31:69 with retention times of 36.0 and 48.1 min, respectively. Experimental conditions were as follows: detector temperature, 245°; injection port temperature, 255°; column temperature, 150°; helium pressure, 40 psi; helium flow rate, 158 ml/min.

The same reaction with phenyllithium in place of the Grignard reagent gave no volatile hydrocarbon.

The mixture of hydrocarbons from the Grignard reaction was not separated further but was hydrogenated in methanol using 5% palladium on barium sulfate as the catalyst at room temperature with a hydrogen pressure of 40 psi. The product obtained from vpc analysis on column C contained a mixture of *trans*- and *cis*-1-phenyl-2-butene (36%) with a distribution of 46–54% and retention times of 18.7 and 21.1 min, respectively. Experimental conditions were similar to the above.

Preparative vpc gave pure samples of the two isomers. The infrared spectrum of *cis*-1-phenyl-2-butene showed medium-to-strong bands at 3.32, 3.43, 6.03, 6.22, 6.68, 6.68, 6.87, 7.15, 7.31, 9.35, 9.72, 10.08, 10.62, 12.15, 12.43, 13.55, and 14.37 μ; nmr (CCl_4) δ 1.71 doublet (CH_3), 3.37 doublet (CH_2), 5.57 multiplet (CH=CH), 7.12 singlet (aromatic); relative ratios 3:2:2:2:5.

***cis*-1-Chloro-2-butene**[12] by vpc analysis on column D was 98% pure and had a retention time of 3 min using a column temperature of 60°; detector temperature, 150°; injection port temperature, 155°; helium pressure, 30 psi; helium flow rate, 133 ml/min. The nmr spectrum (heat) showed δ 1.68 multiplet (CH_3), 4.07 multiplet (CH_2), 5.63 multiplet (CH=CH); relative ratio of 3:2:2, respectively.

***cis*-1-Methyl-2-phenylcyclopropane** was prepared by the reaction of *cis*-1-phenyl-1-propene with methylene iodide and zinc copper couple.[8]

Registry No.—Phenyllithium, 591-51-5; I, 934-10-1; II, 935-00-2; III, 15324-90-0.

(8) S. Wawzonek, B. J. Studnicka, and A. R. Zigman, *Org. Prep. Proceed.*, **1**, 67 (1968).

(9) G. L. Closs, L. E. Closs, and W. A. Boil, *J. Amer. Chem. Soc.*, **85**, 3796 (1963).

(10) S. Winstein and W. G. Young, *ibid.*, **58**, 104 (1936).

(11) A. D. Petrov and E. P. Kaplan, *Zh. Obshch. Khim.*, **24**, 1355 (1954).

(12) L. F. Hatch and S. S. Nesbitt, *J. Amer. Chem. Soc.*, **72**, 727 (1950).

Solvent Effects and Nucleophile Competition in Reactions of 3-Chloro-3-methyl-1-butyne[1]

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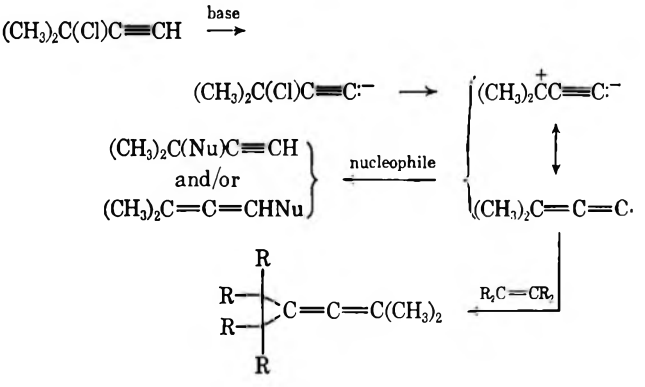
The title compound reacts at 25° with (aqueous) alcohols in the presence of base *via* second-order kinetics (first order each in halide and base) and with rates related to the dielectric constant (water content) of the solvent but only slightly affected by ordinary salt effects or by the nature of the alcohol used. The reactions produce *t*-propargylic ethers in satisfactory yield from methanol and ethanol. Use of aqueous isopropyl or *t*-butyl alcohol results in hydrolysis, elimination, and rearrangement to the carbinol, enyne, and chloroallene, respectively. Relative rates of ether formation from alcohols follow (approximate): methyl (standard), 100; ethyl, 45; isopropyl, 4; *t*-butyl, 0. Unlike alcohols, amines of all types are excellent nucleophiles and lead to amino products in good yield. The reactions with amines are catalyzed by traces of either copper powder or cuprous chloride and are notably insensitive to steric factors.

Aliphatic *t*-propargylic chlorides (and bromides), *e.g.*, 3-chloro-3-methyl-1-butyne (I) and homologs, successfully alkylate methanol, ethanol, ammonia, and amines of virtually all types to produce the corresponding propargylic ethers and amines.[3] All of these reactions proceed under very mild conditions in alkaline, partially aqueous media[4] and generally give good yields. The novelty and notable utility of these processes arise from the fact that they achieve nucleophilic substitution at tertiary aliphatic carbon, a reaction which is ordinarily unsatisfactory.

It is now generally accepted[3,5,6] that the successful *t*-propargylic halide reactions involve an intermediate (neutral) zwitterion–allenecarbene which is rather stable to proton elimination and notably electrophilic at the tertiary carbon. Nucleophiles employed in these reactions include not only solvents such as alcohols



(alkoxide ions?), and many amines as mentioned above, but also sodioacetoacetic ester,[7] sodiodiethyl malonate[8] and diethyl methylmalonate,[9] and thiophenoxide.[5c] It is obvious that the zwitterion–allenecarbene should be an ambident electrophile, capable of yielding both propargylic and allenic products as has been observed in particular cases.[3g,5c,9] Good evidence for the validity of the mechanism pictured above arises not only from kinetic studies[3a,3c,5,6] and reaction products, but also from the fact that the unique allenecarbene has been trapped by stereospecific reaction with olefins in the manner typical of ordinary carbenes.[10]

There remain, however, a variety of observations not readily reconcilable with the general zwitterion–allenecarbene mechanism. Methanol and ethanol give good yields of the propargylic ethers[3e] and the alkaline aqueous alcohols containing up to 40–50 mol % water produce much more ether than carbinol. The reactions follow second-order kinetics (first order each in *t*-propargylic halide and base) and the significance of this has already been discussed in considerable detail.[5,6] *t*-Butyl alcohol, however, gives no ether product,[3e] despite the fact that steric inhibition of *t*-butyl allenyl ether formation should not be serious. This is in sharp contrast to the reactions with *t*-alkyl and other sterically crowded amines which afford N-*t*-propargylic amines in reasonably good yields.[3d,3f,11] Furthermore, trialkylamines react typically and lead to *both* propargylic and allenic quaternary ammonium salts.[3g] It is also not clear why all of the reactions with amines are markedly catalyzed by trace amounts of cuprous salts.[3d] In our hands some good nucleophiles give no substitution products even though steric effects cannot explain the failure. Thus, for example, reaction of I with excess potassium cyanide in aqueous methanol yields only the solvent derived methyl ether (no nitriles). On the other hand, similar use of diethyl malonate and diethyl methylmalonate leads to the desired propargylic and/or allenic products[8,9] despite the seemingly unfavorable steric features of the reaction. Also significant is the fact that reaction with phenoxide[3e] results in competitive O and ring C alkylation. Enamines derived from cyclopentanone and cyclohexanone lead to C-*t*-propargylic derivatives, again despite anticipated steric difficulties.[12] In conclusion, no satisfactory correlation now exists between the basicity, nucleophilicity, polarizability, steric features of the nucleophilic reagent, solvent employed, and success, failure, or outcome of

(1) Paper No. 87 on substituted acetylenes; previous paper, G. F. Hennion and J. E. Reardon, *J. Org. Chem.*, **32**, 2819 (1967).

(2) Eli Lilly Co. Fellow, 1964–1967. Abstracted from a portion of the Ph.D. dissertation of J. F. M.

(3) (a) G. F. Hennion, *et al.*, *J. Amer. Chem. Soc.*, **73**, 4735 (1951); (b) *ibid.*, **75**, 1653 (1953); (c) *ibid.*, **79**, 2142 (1957); (d) *ibid.*, **82**, 4908 (1960); (e) G. F. Hennion, *et al.*, *J. Org. Chem.*, **26**, 2677 (1961); (f) *ibid.*, **30**, 2645 (1965); (g) *ibid.*, **31**, 1977 (1966); also references cited.

(4) Except in the case of ammonia where anhydrous liquid ammonia is needed.[3b,e,f]

(5) (a) V. J. Shiner, *et al.*, *J. Amer. Chem. Soc.*, **84**, 2402 (1962); (b) *ibid.*, **84**, 2408 (1962); (c) *ibid.*, **89**, 622 (1967).

(6) W. J. le Noble, *ibid.*, **87**, 2434 (1965).

(7) L. Crombie and K. Mackenzie, *J. Chem. Soc.*, 4417 (1958).

(8) N. R. Easton and R. D. Dillard, *J. Org. Chem.*, **27**, 3602 (1962).

(9) A. F. Bramwell, L. Crombie, and M. H. Knight, *Chem. Ind.* (London), 1265 (1965).

(10) (a) H. D. Hartzler, *J. Amer. Chem. Soc.*, **81**, 2024 (1959); (b) *ibid.*, **83**, 4990, 4997 (1961); (c) *ibid.*, **88**, 3155 (1966); (d) H. D. Hartzler, *J. Org. Chem.*, **29**, 1311 (1964).

(11) N. R. Easton, R. D. Dillard, W. J. Doran, M. Livezey, and D. W. Morrison, *ibid.*, **26**, 3772 (1961).

(12) Unpublished work with F. X. Quinn in progress.

the alkylation reaction. It must be noted, however, that all of the known reactions recited above occur in strongly basic media. 3-Chloro-3-methyl-1-butyne does not react with potassium acetate in acetic acid at temperatures up to 60°; use of silver acetate, however, leads to a mixture of propargylic and allenic esters.[13]

Kinetics.—We report now the results of a preliminary study of nucleophilic solvent variation, with respect to both kinetics and products formed, and nucleophile competition experiments. The findings are summarized in Tables I–IV. Most of the reactions showed clean second-order kinetics and the rates varied relatively little (only by a factor of about 7; Table I, entries 1 and 12). Rates in various alcohol

TABLE I

SECOND-ORDER RATE CONSTANTS FOR REACTION OF 3-CHLORO-3-METHYL-1-BUTYNE (I) WITH ALCOHOLS AND KOH[a] AT 25.0°

Entry	Solvent: Alcohol	Solvent: H_2O, % (v/v)	Added salt (equiv)	k_2[b]
1	EtOH	5	None[c]	0.48, 0.48
2	EtOH	10	None[c]	0.71, 0.70
3	EtOH	15	None[c]	0.96, 0.94
4	EtOH	20	None	1.35, 1.35[d]
5	EtOH	20	KCl (1)[c]	1.47
6	EtOH	20	KBr (1)	1.42
7	EtOH	20	KI (1)	0.9 → 0.7
8	EtOH	20	KNO_3 (1)[e]	1.41
9	EtOH	25	None	2.02, 1.98
10	EtOH	30	None	2.31, 2.30
11	EtOH	35	None	2.95
12	EtOH	40	None	3.64, 3.60
13	*i*-PrOH	25	None[c]	2.19
14	*i*-PrOH	30	None	2.66
15	*i*-PrOH	35	None	3.03
16	*i*-PrOH	40	None	3.37
17	*t*-BuOH	35	None	1.99
18	*t*-BuOH	45	None	2.61

[a] $c_0(I) = c_0(KOH) = 0.1\ M$. [b] In l. mol^{-1} hr^{-1}; multiple entries are for duplicate runs. [c] KCl crystallizes as the reaction proceeds. [d] Previously reported to be 1.40 (ref 3a) and 1.27 (ref 3c) using NaOH. [e] Only partially soluble.

TABLE II

SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF 3-CHLORO-3-METHYL-1-BUTYNE (I) WITH MIXED ALCOHOLS AND KOH[a] AT 25.0°

Entry	Solvent, 20% water (v/v): ROH (%)	R'OH (%)	k_2[b]
1	EtOH (60)	MeOH(20)	0.78
2	EtOH (40)	MeOH (40)	0.62
3	EtOH (20)	MeOH (60)	0.47
4	EtOH (60)	*i*-PrOH (20)	1.55
5	EtOH (40)	*i*-PrOH (40)	1.80
6	EtOH (20)	*i*-PrOH (60)	2.12
7	EtOH (60)	*t*-BuOH (20)	1.62
8	EtOH (40)	*t*-BuOH (40)	1.77

[a] $c_0(I) = c_0(KOH) = 0.1\ M$. [b] In l. mol^{-1} hr^{-1}

mixtures were similar to those in individual alcohols so long as other solvent features were comparable (Table II). Increase in solvent dielectric constant resulting from increase in water concentration resulted in rate acceleration as expected.[14]

(13) A. I. Zakharova, *J. Gen. Chem. USSR*, **15**, 429 (1945); *Chem. Abstr.*, **40**, 4654 (1946). See also ref 5a, p 2405.

Salt Effects.—Except for potassium iodide, the effect of salts in concentrations (0.1 *M*) equivalent to substrate halide (Table I, entries 4–8) appeared too small to assess with confidence. The limited solubility of potassium salts in our solvent systems (potassium hydroxide used as base) did not permit a critical study of the type Shiner and Wilson reported[5a] for 3-bromo-3-methyl-1-butyne, using sodium hydroxide as the base along with various sodium salts. These investigators noted large rate depressions (40% in the presence of 0.22 *M* NaBr and 18% for either $NaNO_3$ or $NaClO_4$) using 80% ethanol as the solvent. Our findings suggest that rate enhancement (in the case of the *t*-chloride) arises both from increase in dielectric constant of the solvent medium and (slightly) from increase in ionic strength of the solution. We interpret the observed iodide effect (Table I, entry 7; rate depression with drifting rate constant) as indicative of a competing S_N2' reaction leading to the allenyl iodide[15] which then forms the zwitterion–allenecarbene at a slower rate.

$$I^- + (CH_3)_2C(Cl)C{\equiv}CH \longrightarrow (CH_3)_2C{=}C{=}CHI + Cl^-$$
$$-HCl \downarrow \text{(fast)} \qquad -HI \downarrow \text{(slow)}$$
$$(CH_3)_2{}^+CC{\equiv}C{:}^- \longleftrightarrow (CH_3)_2C{=}C{=}C{:}$$

Reaction Products.—The reaction of halide I with aqueous alcohols in the presence of base takes the course given in Scheme I with respect to the major

SCHEME I

$$\underset{\text{I}}{(CH_3)_2C(Cl)C{\equiv}CH} + ROH + H_2O + KOH \xrightarrow{25^\circ}$$
$$\underset{\text{II}}{(CH_3)_2C(OR)C{\equiv}CH} + \underset{\text{III}}{(CH_3)_2C(OH)C{\equiv}CH} +$$
$$\underset{\text{IV}}{CH_2{=}C(CH_3)C{\equiv}CH} + \underset{\text{V}}{(CH_3)_2C{=}C{=}CHCl}$$

products. The relative amounts of these varied widely even though the reaction rates did not. The previous report[3e] that isopropyl ethers form only in low yield while *t*-butyl ethers cannot be made in this way was confirmed. Whether or not this relates to steric features or to the acidity (k_a) of the alcohol used remains obscure. It may well be that both aspects are critical so that ethers arise only from sterically suitable lyate ions and not from alcohols *per se*. While the rates of ether formation (as distinct from other products) have not been determined, Table III provides information for the estimation of relative rates. Thus entries 1 and 2 show $k_{ROMe}/k_{ROEt} \approx 2.3$; from entry 4, $k_{ROMe}/k_{RO\text{-}t\text{-}Pr} \approx 24$; from entries 7 and 8 $k_{ROEt}/k_{RO\text{-}t\text{-}Pr} \approx 11.4$. The latter figure is in fair agreement with the expected ratio 10.4 (=24/2.3).[16] The yields listed in Table III account for 65–85% of the *t*-chloride used. Competitive formation of carbinol III was established

(14) Analysis of the solvent effect data presented in Table I, entries 1–4 and 9–12, and earlier solvolysis data[3a] in the manner of J. G. Kirkwood [*J. Chem. Phys.*, **2**, 351 (1934)] and E. Grunwald and S. Winstein [*J. Amer. Chem. Soc.*, **70**, 846 (1948)] results in typical straight-line plots, except for low water concentrations. The Grunwald–Winstein substrate susceptibility constant in ethanol, m_{EtOH}, was found to be about 0.66 for S_N1 ionization of I and 0.52 for reaction in the presence of base.

(15) T. L. Jacobs and W. L. Petty, *J. Org. Chem.*, **28**, 1360 (1963).

(16) It was established experimentally that the ethers do not react with alcohols, water, or other nucleophiles present under the reaction conditions and are therefore products of kinetic control. The relative reactivities of the alcohols used are therefore approximately as follows: methyl, 100; ethyl, 45; isopropyl, 4; *t*-butyl, 0.

Table III

Products from Reaction of 3-Chloro-3-methyl-1-butyne (50 mmol) with Mixed Aqueous Alcohols and KOH (55 mmol) at 25°

	Solvent, 20% water (v/v)			Yields of products, %			
	Alcohols (mmol)		Water,	Ethers[a]			
Entry	ROH	R'OH	mol %	R	R'	Enyne	Isomer[b]
1	Me(247)	Et (171)	40	55.0	15.9	12.9	0
2	Me (124)	Et (257)	42	38.4	37.2	13.3	0
3	Me (247)	*i*-Pr (131)	42	57.0	0.5	19.8	0
4	Me (124)	*i*-Pr (196)	47	54.3	3.6	22.9	0
5	Me (371)	*t*-Bu (50)	40	67.6	0	14.3	0
6[c]	Me (124)	*t*-Bu (150)	50	43.8	0	24.8	6.0
7	Et (171)	*i*-Pr (131)	48	55.1	3.9	19.1	0
8	Et (86)	*i*-Pr (196)	50	49.9	9.4	23.6	0
9	Et (257)	*t*-Bu (50)	48	55.9	0	17.4	0
10	Et (171)	*t*-Bu (100)	51	52.6	0	25.8	5.7
11[c]	Et (86)	*t*-Bu (150)	54	41.6	0	29.6	6.3
12[c]	*i*-Pr (196)	*t*-Bu (50)	53	18.6	0	34.1	9.4
13[c]	*i*-Pr (131)	*t*-Bu (100)	55	15.4	0	38.5	11.1

[a] Ether refers to 3-alkoxy-3-methyl-1-butyne. [b] 1-Chloro-3-methyl-1,2-butadiene. [c] Yields are corrected for unreacted 3-chloro-3-methyl-1-butyne (5%).

Table IV

Reaction of 3-Chloro-3-methyl-1-butyne (0.50 mol) with KOH (0.55 mol) in Alcohol–Amine Solvents at 25°

	Solvent		Yields of reaction products, %			
Entry	Alcohol[a]	Amine[a]	Ether[b]	Amine[c]	Enyne	Isomer[d]
1	MeOH	*t*-$BuNH_2$	24.1	36.7	16.1	9.5
2	EtOH	$EtNH_2$	12.1	52.3	14.8	8.6
3	*i*-PrOH	$MeNH_2$	2.6	60.1	12.9	12.1
4	EtOH	$PhNH_2$	52.4	2.7	15.1	9.1
5		$HOCH_2CH_2NH_2$[e]	9.5	33.4	Nd[f]	Nd
6		$HOCH_2CH_2NH_2$[e,g]	0.0	58.3	Nd	Nd
7[h]	MeOH[i]	*i*-$PrNH_2$[g]	4.8	59.8	Nd	Nd

[a] 0.75 mol used, except for entries 5 and 6 as noted. [b] Ether refers to 3-alkoxy-3-methyl-1-butyne. [c] Amine refers to 3-alkylamino-3-methyl-1-butyne. [d] 1-Chloro-3-methyl-1,2-butadiene. [e] Total amount of ethanolamine used was 2.0 mol. [f] Not determined. [g] Reaction catalyzed with copper (0.1 g); KOH was not used. [h] Only 0.25 mol of 3-chloro-3-methyl-1-butyne used. [i] 1.0 mol of MeOH used.

only qualitatively. Analyses for III could not be achieved satisfactorily due to its polarity, water solubility, and unfavorable glpc response in columns suitable for mixtures of I, II, IV, and V.[17]

Isopropenylacetylene (IV) was always a reaction product although relatively large amounts were formed only when ether formation was suppressed due to lack of sufficiently high methanol and/or ethanol concentrations in the solvent medium. It is particularly noteworthy that the allenyl chloride (V), isomeric with I, appears when solvent composition deters ether formation (Table III, entries 6 and 10–13). Since Sn1 ionization of I is extremely slow,[3a,3c] V probably arises from external return.

Table IV, entries 1, 2, 3, and 5, show that highly basic amines are better nucleophiles than alcohols, even when the amine is sterically handicapped and the alcohol is not. The product ratios observed are understandable if ether formation results only from alkoxide ion, present in low concentration, competing with amine in high concentration. Entry 4 of Table IV shows, however, that only highly basic amines are sufficiently nucleophilic to react preferentially in competition with alcohols. Entries 5 and 6 both refer to use of ethanolamine as the nucleophile but under very different conditions. In the presence of potassium hydroxide (entry 5) N alkylation predominates (3.5:1) over ether formation much as expected. In the absence of hydroxide, using copper powder as a catalyst (entry 6) only N alkylation occurred. This supports the view that ethers arise only from alkoxide ion. It was thus expected that in competition between methanol and isopropylamine, using copper powder as a catalyst and in the absence of hydroxide (entry 7), no methyl ether would be produced. A low yield (4.8%) was realized, however, suggesting that the solution was near the borderline of basicity required for ether formation. In all of these experiments (Table IV) solvent components were not in notably high concentration and so formation of some enyne (III) and allenyl chloride (V) was observed as expected.

Formation of allenyl products other than V was never encountered although trace amounts may have escaped detection. It appears from other studies[3g,10c,18] that allenyl amines and ethers form only when steric effects strongly disfavor the propargylic isomer.

Correlation of the present findings with the literature cited emphasizes that second-order rate constants, such as reported here, measure only rates of the intermediate zwitterion–allenecarbene formation, loss of halide ion being rate determining, and bear no significant relation to the reaction end products. Clearly the dipolar ion–carbene is a discriminating electrophile often

(17) Reaction products were extracted into pentane and III was removed by washing with water. The dried pentane solutions were analyzed by glpc.

(18) T. L. Jacobs and S. Hoff, *J. Org. Chem.* **33**, 2986 (1968).

uniquely useful in synthetic work and deserving of further study.

Experimental Section

3-Chloro-3-methyl-1-butyne (I), triply distilled, bp 75.3–75.4°, $n^{25}D$ 1.4142, was prepared from the carbinol as previously reported.[3c,19]

***t*-Propargylic ethers, $(CH_3)_2C(OR)C{\equiv}CH$,[3c] isopropenylacetylene,[20] and 1-chloro-3-methyl-1,2-butadiene,[19]** needed as pure standards for glpc, ir, and nmr comparison with reaction products, were prepared by literature methods cited.

Reaction rate measurements were made as previously described[3a,c] except that the rate constants were calculated from the integrated second-order rate expression on the University of Notre Dame UNIVAC 1107 computer.

Alcohol Competition Reactions.—In a typical experiment 4.6 g (55 mmol) of potassium hydroxide (86% assay) was dissolved in 5.0 ml of distilled water and the appropriate amounts of the respective alcohols (Table III). Then 5.12 g (50 mmol) of I was added dropwise over the period of 1 hr while the temperature was maintained at 25 ± 3°. After 48 hr at room temperature, the reaction mixture was chilled and filtered to remove potassium chloride. Two 10-ml portions of pentane were used to wash the residue and were combined with the filtrate. The layers were separated. The aqueous layer was extracted with two 7-ml portions of pentane. The combined pentane extracts were washed with two 20-ml portions of water and dried over calcium chloride. The filtered pentane solutions were analyzed by glpc using a 10-ft stainless steel column packed with 20% Octoil-S on firebrick employing isothermal operation at 78° with a He flow of 60 cc/min. The actual presence of 1-chloro-3-methyl-1,2-butadiene (V) in some cases was further established by preparative glpc isolation and comparison of the ir and nmr spectra with those of an authentic sample.

Reaction of I with Ethanolamine—Copper Catalysis.—To a mixture of 48.8 g (0.8 mol) of ethanolamine, 12.3 g of water (80% amine solution), and *ca.* 0.1 g of copper powder was added dropwise with vigorous stirring 20.5 g (0.2 mol) of I while the temperature was maintained at 25 ± 5°. After 6 hr of stirring at 30°, the reaction mixture was allowed to stand overnight at room temperature. The dark syrupy mixture was diluted with 50 ml of saturated brine and extracted thrice with 50-ml portions of benzene and once with 50 ml of ether. The combined organic extracts were washed thrice with 50-ml portions of saturated brine. The organic layer was then treated with 100 ml of 4 *N* HCl. The acidic layer was separated and extracted twice with 25 ml of ether (discarded). The aqueous solution was adjusted to pH 12 with 40% sodium hydroxide, saturated with sodium chloride, and then extracted with three 50-ml portions of benzene. Distillation through a 20-cm Vigreaux column yielded 14.8 g (58.3%) of 3-(2-hydroxyethylamino)-3-methyl-1-butyne: bp 82.0–82.8° (4.1 mm); $n^{25}D$ 1.4633; ir (neat) 3.05 μ (≡CH), 3.12 (associated –NH and –OH), 4.8 (C≡C), 7.28 (doublet, CeM_2). The hydrochloride salt had mp 101–103° (lit.[21] mp 84–86°).

Anal. Calcd for $C_7H_{14}ClNO$: C, 51.37; H, 8.62; Cl, 21.67; N, 8.56. Found: C, 51.37; H, 8.83; Cl, 21.60; N, 8.56.

Reaction of I with Ethanolamine and Potassium Hydroxide.—To 122 g (2.0 mol) of ethanolamine was added with stirring one-half of a 120-ml solution of 97.9 g (1.5 mol) of potassium hydroxide (86% assay) in 75 ml of water. At 5 ± 5°, 51.3 g (0.5 mol) of I and the remaining 60 ml of the base solution were added dropwise (simultaneously) to the amine solution over a period of 3 hr. After the yellow syrupy mixture (KCl precipitate) had been stirred for 3 more hr at 5 ± 5°, the mixture warmed to room temperature overnight and was then stirred vigorously with 100 ml of ether plus 100 ml of water for 1 hr. After separation, the aqueous layer was extracted twice with 100-ml portions of ether. The combined ether extracts were washed with three 50-ml portions of saturated brine. The aqueous layer from above, together with the brine washes, was extracted thrice with 100-ml portions of benzene. The combined organic extracts (ether plus benzene) were stripped of solvents at reduced pressure. Distillation of the residue through a micro spinning band column gave two distinct fractions. The lower boiling hygroscopic liquid, 3-(2-aminoethoxy)-3-methyl-1-butyne, was recoverd in 9.5% yield: bp 57–58° (14.5 mm); $n^{25}D$ 1.4433; ir (neat) 3.05 μ (≡CH), 3.18 (NH_2), 3.40 ($-CH_2$), 3.45 ($-CH_3$), 4.8 (C≡C), 7.25 (doublet, CMe_2), and 9.70 (COC); nmr ($CDCl_3$) δ 1.45 (s, 6, CMe_2), 1.62 (s, 2, NH_2), 2.42 (s, 1, ≡CH), 2.84 (t, 2, CH_2N), 3.48 (t, 2, CH_2O).

Anal. Calcd for $C_7H_{13}NO$ + 3% H_2O: C, 64.12; H, 10.30. Found: C, 64.38; H, 10.42.

The hydrochloride salt had mp 123–125° after four crystallizations from ethanol plus ethyl acetate.

Anal. Calcd for $C_7H_{14}ClNO$ + 4.1% $HOCH_2CH_2NH_2 \cdot HCl$: C, 50.24; H, 8.60; N, 8.79. Found: C, 50.24; H, 8.51; N, 8.64.

The higher boiling liquid, 3-(2-hydroxyethylamino)-3-methyl-1-butyne, produced in 33.4% yield, had bp 79° (3.2 mm), $n^{25}D$ 1.4628, and gave a hydrochloride, mp 101–103°, not depressed by mixture with the sample described above.

Nucleophile Competition between *t*-Butylamine and Methanol.—To a stirred solution of 54.9 g (0.75 mol) of *t*-butylamine and 24.0 g (0.75 mol) of methanol was added with stirring 51.3 g (0.50 mol) of I. No indication of reaction was apparent. The temperature was adjusted to 25° and 35.9 g (0.55 mol) of potassium hydroxide dissolved in 35.9 g of water was added dropwise over a period of 2 hr. The temperature was maintained at 25 ± 3°. After the addition, the mixture was stirred for 6 more hr at 25° and then was allowed to stand overnight at room temperature.

The reaction mixture was transferred to a separatory funnel containing 100 ml of ether. The layers were separated and the aqueous layer was extracted with an additional 100-ml portion of ether. The combined ether extracts were washed four times with 100-ml portions of water (discarded), and then treated with a 100-ml portion of 4 *N* HCl. The acidic aqueous layer was saved and combined with an additional 50-ml portion of water used to wash the ether layer. The ether layer was dried over calcium chloride. Analysis by glpc showed 3.3 g (10.1% yield) of isopropenylacetylene and 11.6 g (24.1% yield) of 3-methoxy-3-methyl-1-butyne.

The acidic aqueous layer was adjusted to pH 12 by the addition of 40% potassium hydroxide solution and then extracted with two 75-ml portions of ether. The combined ether extracts were washed with 100 ml of saturated brine solution and dried over potassium carbonate. Distillation through a small Vigreaux column yielded 25.3 g (36% yield) of 3-*t*-butylamino-3-methyl-1-butyne: bp 131–135°; $n^{25}D$ 1.4285 (lit.[22] bp 135–136°; $n^{25}D$ 1.4292).

Nucleophile Competition between Isopropylamine and Methanol *via* Copper Catalysis.—To a stirred mixture of 29.5 g (0.5 mol) of isopropylamine, 32.0 g (1.0 mol) of methanol, and 0.1 g of copper powder was added dropwise with cooling 25.6 g (0.25 mol) of I. The temperature was maintained at 25 ± 3° over the 2 hr required for the addition. After standing overnight, the reaction mixture was cooled and added to 150 ml of cold 3 *N* HCl with vigorous stirring. The chilled acidic mixture was extracted with two 50-ml portions of ether. The combined ether extracts were washed four times with water and then dried over calcium chloride. Analysis by glpc as described above showed 1.18 g (4.8% yield) of 3-methoxy-3-methyl-1-butyne. The acidic aqueous layer was adjusted to pH 12 by the addition of 40% KOH solution and then extracted with two 50-ml portions of ether. The combined ether extract was washed with three 50-ml portions of water and then dried over anhydrous potassium carbonate. Distillation yielded 19.3 g (59.8% yield) of 3-isopropylamino-3-methyl-1-butyne: bp 113–118°; $n^{25}D$ 1.4172 (lit.[22] bp 117°; $n^{25}D$ 1.4179).

Registry No.—I, 1111-97-3; 3-(2-hydroxyethylamino)-3-methyl-1-butyne, 4067-36-1; 3-(2-aminoethoxy)-3-methyl-1-butyne, 19766-40-6; 3-(2-aminoethoxy)-3-methyl-1-butyne (HCl salt), 19766-41-7.

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(21) N. R. Easton, D. R. Cassady, and R. D. Dillard, *J. Org. Chem.*, **28**, 448 (1963).

(22) G. F. Hennion and R. S. Hanzel, *J. Amer. Chem. Soc.*, **82**, 4908 (1960).

The Lilly Research Laboratories for elemental analyses; also to the Notre Dame Computing Center for donation of computer time and to Michael Moore for assistance in writing the computer program. The A-60A nmr instrument used in this investigation was acquired under NSF Equipment Grant GP-6875.

Halogenation of Diazopropane with *t*-Butyl Hypobromite. Evidence for the Formation of α-Bromopropylidene[1]

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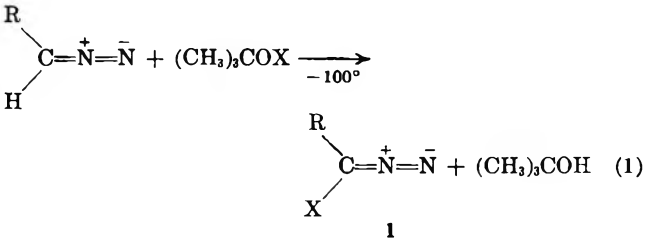
Reaction of diazopropane and *t*-butyl hypobromite at −100° and subsequent warming of the reaction mixture to room temperature leads to the formation of *cis*- and *trans*-1-bromopropene, 1-bromopropane, 1,1-dibromopropane, 1,1-dibromopropene, and *cis*- and *trans*-3-bromo-3-hexene. The effect of reaction conditions on the product distribution and other observations have been interpreted on the basis of the formation of α-bromodiazopropane and its thermal or photochemical decomposition to give α-bromopropylidene.

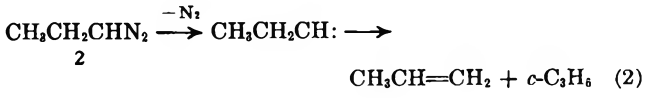
The syntheses of α-bromo- and α-chlorodiazomethane (**1**, R = H; X = Br or Cl) by reaction of the corresponding *t*-butyl hypohalite with diazomethane (eq 1)



have permitted a comparison of the reactivities of the free α-halomethylenes arising from compounds **1** with unsubstituted methylene and the formally analogous halocarbenoid species.[3] The results indicate that halogen substitution increases the selectivity of methylene,[4] but that the free halomethylene intermediates are significantly more reactive than chloromethylene transfer reagents generated by α-elimination reactions.[3,5]

Methylene and α-halomethylenes are restricted to intermolecular reactions such as C–H insertion, addition to multiple bonds, and reaction with the diazo precursor to produce the corresponding dimeric ethylenes.[5] However, alkyl-substituted methylenes (alkylidenes) react virtually exclusively by intramolecular rearrangements giving olefins and cyclopropanes.[5] For example, diazopropane (**2**) yields propylene and cyclopropane in the ratio of approximately 9:1 (reaction 2).[6] Studies have been carried out to determine the effect of varying β and γ substitution, and α-alkyl or α-aryl substitution, on the reactivity of such alkylidenes,[5-7] but no information is available concerning α-halogen substitution. The available data for α-halomethylenes[3] suggest that α halogenation of alkylidenes would increase their stability and possibly enable them to participate in intermolecular reactions.

The particular haloalkylidene precursor chosen for study was α-bromodiazopropane (**3**) and the products which were anticipated from intramolecular reactions of the intermediate α-bromopropylidene were *cis*- and *trans*-1-bromopropene (**4** and **5**) and bromocyclopropane (**6**). In view of the 9:1 propylene/cyclopropane ratio found from the intramolecular reactions of propylidene (eq 2), an increased selectivity due to α halogenation would lead to the prediction of a larger ratio for (**4** + **5**)/**6**. The low-temperature halogenation of diazopropane with *t*-butyl hypobromite was investigated as the potential source of α-bromodiazopropane.



This study has proven to be complex; however, evidence will be presented to support the formation of α-bromodiazopropane, and the thermal and photochemical decomposition of this diazo compound to yield α-bromopropylidene.

Results

Slow addition of trichlorofluoromethane (Freon 11) solutions of *t*-butyl hypobromite (*ca.* 0.5–0.6 *M*) to cold (−100°), stirred, pentane solutions containing *ca.* 40 mol % excess diazopropane (*ca.* 0.1 *M*) in the absence of light led to gas evolution and the formation of maroon solutions. Gas evolution was monitored in one experiment and it appeared that about 30–40% of the theoretical nitrogen yield (based on *t*-BuOBr) occurred during mixing of the reagents at −100°. The solutions underwent no subsequent gas evolution or further color change under the same conditions for periods up to 5 hr. However, on warming to −30° in the absence of

(1) (a) Support by the National Science Foundation (GP-4287 and GP-7349) is gratefully acknowledged. (b) Presented at the Pacific Conference on Chemistry and Spectroscopy, Anaheim, Calif., Oct 30–Nov 1, 1967.

(2) University Predoctoral Fellow, 1965–1966.

(3) G. L. Closs and J. J. Coyle, *J. Amer. Chem. Soc.*, **87**, 4270 (1965).

(4) (a) Available evidence indicates that both fluoro- and chloromethylene have ground singlet states.[4b] (b) A. J. Mercer and D. N. Travis, *Can. J. Phys.*, **44**, 525, 1541 (1966).

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(6) L. Friedman and H. Schechter, *J. Amer. Chem. Soc.*, **81**, 5512 (1959).

(7) (a) W. Kirmse, H. J. Schladetsch, and H.-W. Bücking, *Chem. Ber.*, **99**, 2579 (1966); (b) W. Kirmse and D. Grassmann, *ibid.*, **99**, 1746 (1966); (c) W. Kirmse and G. Wächtershauser, *Tetrahedron*, **22**, 63 (1966); (d) W. Kirmse and K. Horn, *Chem. Ber.*, **100**, 2698 (1967).

TABLE I

PRODUCT RATIOS FOR REACTION OF *t*-BUTYL HYPOBROMITE AND DIAZOPROPANE[a,b]

	Relative molar ratios[c]								
	Expt no.[c]								
	1	2	3	4	5	6	7	8	9
	Atmosphere								
	Air	Air	O_2	N_2	N_2	N_2	Air	N_2	N_2
	Special conditions[d]								
Products	...	...	...	...	...	EM	BzOH	MTHF	$h\nu$
cis-1-Bromopropene	3.2 ± 0.1	3.3	4.0 ± 0.2	3.4 ± 0.4	3.5 ± 0.1	2.9	3.4	3.4 ± 0.2	3.5
trans-1-Bromopropene	6.8 ± 0.1	6.7	6.0 ± 0.2	6.6 ± 0.4	6.5 ± 0.1	7.1	6.6	6.6 ± 0.2	6.5
1-Bromopropane	11.1 ± 0.6	12.4	11.4 ± 0.4	12.9 ± 0.1	16.3 ± 1.0	0.5	0.5	20.4 ± 0.1	10.0
1,1-Dibromopropane	5.9 ± 0.2	10.2	6.9 ± 0.5	6.5 ± 0.1	9.4 ± 1.1	10.1	7.7	9.3 ± 0.2	4.5
1,1-Dibromopropene	2.7	3.2	4.4 ± 0.4	2.7	2.1	6.5	2.9	3.6 ± 0.2	2.6
cis-3-Bromo-3-hexene	1.0	1.2	0.6 ± 0.1	0.7	1.3	<0.1	<0.1	1.5 ± 0.1	0.6
trans-3-Bromo-3-hexene	2.2	3.3	0.8 ± 0.2	1.5	2.9	<0.1	<0.1	4.0 ± 0.2	1.5
Over-all % yield[f]	89	84	60, 74	76	75	52	58	65, 71	69

[a] For detailed experimental conditions see Experimental Section. Product yields determined by glpc analyses. [b] Error limits indicate that the data represent a combination of two experiments conducted within a day of each other. [c] The chronological order of the experiments was 4, 1, 3, 5, 8, 9, 7, 6, and 2. One batch of *t*-BuOBr was used for the first five and a second batch was used for the last four experiments. [d] EM = equimolar *t*-BuOBr and diazopropane (the ratio *t*-BuOBr/diazopropane was *ca.* 0.67 in all other experiments); BzOH = excess benzoic acid added; MTHF = 2-methyltetrahydrofuran added to pentane in concentrations of 0.2 and 0.4 *M* (two experiments combined); $h\nu$ = photolysis rather than thermolysis. [e] Based on a normalized value of 10.0 for the combined yield of *cis*- and *trans*-1-bromopropene. [f] True per cent yield based on limiting reagent (*t*-BuOBr).

light, or on photolysis at −65° with visible light, further gas evolution occurred with simultaneous decolorization. Isolation of the products arising from the final reaction mixtures and characterization by spectral comparison with authentic samples demonstrated the presence of *cis*- and *trans*-1-bromopropene (**4** and **5**), 1-bromopropane (**7**), 1,1-dibromopropane (**8**), 1,1-dibromopropene (**9**), and *cis*- and *trans*-3-bromo-3-hexene (**10** and **11**). An additional major product was *t*-butyl alcohol. The glpc retention times for authentic samples of 1-bromopropane (**7**) and bromocyclopropane (**6**) were identical; however, no detectable quantity (>1% based on 1-bromopropane) of the latter could be seen by infrared analyses of the fraction whose retention time corresponded to these two compounds. No allyl bromide was found in the reaction mixture.

In a typical experiment as described above, with no precautions taken to exclude oxygen from the system by degassing or other methods, the brominated products (*vide infra*) accounted for up to 85% of the starting *t*-butyl hypobromite (limiting reagent). Procedures to remove oxygen did not improve the product balance. While control experiments demonstrated the complete absence of solvent bromination products (1-, 2-, and 3-bromopentane),[8] there were several minor peaks visible in the glpc traces both at longer and shorter retention times than the longest retention-time compound identified (*cis*-3-bromo-3-hexene). We have been unsuccessful in identifying these components, but mass spectral analyses indicated that they do not contain bromine.

The product distribution arising from the reaction of *t*-butyl hypobromite and diazopropane has been examined for several variations of reaction conditions including atmospheres of air, pure nitrogen, and pure oxygen; addition of free-radical hydrogen donors; addition of carboxylic acids; variation of the ratios of reactants and the addition rate of *t*-butyl hypobromite; photolysis rather than thermolysis; and the use of different sources of diazopropane. Some of the pertinent results are included in Table I.[9]

The molar product ratios from the various experiments included in Table I are based on a normalized value of 10.0 for the combined absolute percentage yields of *cis*- and *trans*-1-bromopropene in each experiment. The over-all percentage yields of detectable products are also given so that the absolute percentage yield of each product may be calculated. We believe that this method of data presentation is more significant than giving the absolute percentage yields, or giving the percentage yields based on a normalized over-all yield of 100%, since it appears that mechanical loss of both reactants occurred in experiments involving degassing procedures, while reactions leading to other products may have occurred in experiments involving additives.

Diazopropane was prepared and distilled prior to its use in each of these experiments. Various control experiments indicated that the source (N-propyl-N-nitrosourea[10] or propionaldehyde tosylhydrazone[11]) did not influence the product ratios.[9] All of the data in Table I were derived from experiments utilizing the nitrosourea precursor. Photolysis of diazopropane at −65° (in the absence of *t*-butyl hypobromite) under the same conditions as those for expt 9 led to the formation of propylene (80%) and cyclopropane (23%). No 3-hexene was detected from this reaction.

Mass spectral analysis of a *t*-butyl hypobromite sample used in these experiments indicated contamination with molecular bromine and also showed the presence of *t*-butyl alcohol. There is some indication that the molecular bromine contamination increased with the age of the *t*-butyl hypobromite samples (*vide infra*). The data in Table I represent the results

(8) Photolysis of *t*-butyl hypobromite under the same reaction conditions, but in the absence of diazopropane, gave 1-, 2-, and 3-bromopentane. These products could have been detected in yields of >0.4% by the glpc analyses.

(9) (a) The addition rate of *t*-butyl hypobromite and the source of diazopropane had no apparent effect on the product distribution and these data have not been included in Table I. Comparison of expt 9 (photolysis) with expt 1–5 (thermolysis) shows no differences. (b) The data presented in Table I represent only the most recent experiments. Earlier experiments, while giving qualitatively similar results, were not included because the experimental techniques were less well refined.

(10) R. C. Neuman, Jr., and M. L. Rahm, *J. Org. Chem.*, **31**, 1857 (1966), and references therein.

(11) G. M. Kaufman, J. A. Smith, G. G. Vander Stouw, and H. Shechter, *J. Amer. Chem. Soc.*, **87**, 935 (1965).

derived from two different batches of hypobromite; expt 1, 3–5, and 8 represent one preparation and expt 2, 6, 7, and 9 represent a second preparation.

In order to ascertain the products arising from reaction of molecular bromine with diazopropane, a control reaction was carried out under the same conditions as those used for the *t*-butyl hypobromite experiments. The maroon color observed in the hypobromite reactions did not develop on addition of bromine. Analysis of the final reaction mixture showed the quantitative formation (based on Br_2) of 1,1-dibromopropane (65%), 1-bromopropane (32%), *cis*-1-bromopropene (4%), and *trans*-1-bromopropene (3%).

Qualitative experiments were conducted in which diazoethane and diazoneopentane were treated with *t*-butyl hypobromite. In the former case, the reaction characteristics were similar to those for diazopropane and *t*-butyl hypobromite including maroon color formation; however, thermal decomposition and decolorization occurred at a lower temperature (*ca.* −60°). In the latter case, addition of *t*-butyl hypobromite led to no obvious reaction or color change at −100°.

Discussion

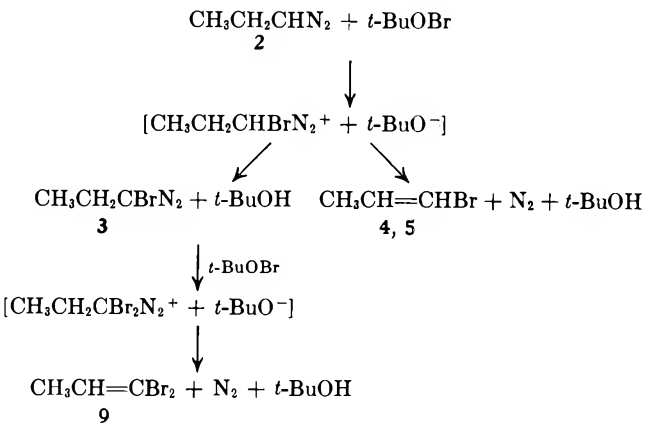
The experimental results indicate two separate reaction sequences: one which occurred at −100° on addition of *t*-BuOBr to diazopropane (Scheme I), and the other which occurred during warm-up (−40 to −30°) or photolysis of the reaction mixture (Scheme II). The formation of α-bromodiazopropane (**3**, Scheme I) is supported by the maroon coloration at −100° and subsequent decoloration of the solution with gas evolution on warm-up or photolysis. These observations directly parallel those of Closs and Coyle for α-chloro- and α-bromodiazomethane.[12,13] The ion-pair intermediate in the reaction sequence **2** → → **3** is proposed in direct analogy to this latter work.[3]

The formation of 1,1-dibromopropene (**9**) is also taken as evidence for the intermediacy of α-bromodiazopropane (**3**). It is anticipated that addition of benzoic acid to the reaction mixture *after* mixing *t*-BuOBr and diazopropane, but *before* warm-up of the reaction mixture, would destroy excess diazopropane (**2**) and possibly α-bromodiazopropane (**3**). This experiment (Table I, no. 7) was performed and the yield of **9** was unaffected (compare with expt 1–5) indicating its rapid formation during addition of *t*-BuOBr to diazopropane at −100°. Further support for the intermediacy of **3** and the sequence **3** → → **9** is provided by the significantly increased yield of **9** when a larger relative amount of *t*-BuOBr to diazopropane was utilized (compare expt 6 with expt 1–5 and 7, Table I).[14]

Decoloration and gas evolution during warm-up or photolysis have been offered as evidence for the existence of **3** (*vide supra*) and its most probable thermal or photochemical decomposition pathway is that giving

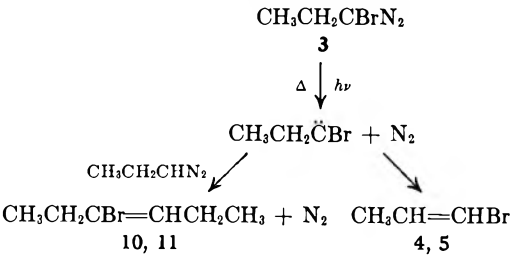
Scheme I

−100° Reaction Sequence



Scheme II

Warm-Up or Photolysis Sequence



α-bromopropylidene (Scheme II). The formation of *cis*- and *trans*-3-bromo-3-hexene (**10** and **11**) by reaction of α-bromopropylidene with excess diazopropane remaining after the initial chemistry at −100° has direct analogies in reactions of other methylenes with their diazo precursors.[5] When benzoic acid was added *before* warm-up (expt 7, Table I), presumably leading at least to the destruction of any unreacted diazopropane, or when little unreacted diazopropane remained because equimolar amounts of *t*-BuOBr and diazopropane were employed (expt 6, Table I), the yields of **10** and **11** were significantly reduced supporting the sequence **3** → → **10** + **11** (Scheme II).

The relative yields of the 1-bromopropenes (**4** and **5**) and bromocyclopropane (**6**) were suggested as diagnostic of the comparative stabilities of propylidene and α-bromopropylidene (*vide supra*). Thus, the apparent absence of **6** could be taken as supporting evidence of increased stability of alkylidenes due to α halogenation and would offer a rationale for the intermolecular reaction of α-bromopropylidene with diazopropane, a reaction *not* observed for propylidene itself.[6] However, the 1-bromopropenes (**4** and **5**) might also have arisen in part in the reaction sequence **2** → → **4** + **5** (Scheme I). The data in Table I do not permit a determination of the relative importance of this pathway compared to **3** → → **4** + **5** (Scheme II). While it might be argued that the formation of **4** and **5** in the presence of benzoic acid (expt 7) support the former pathway (Scheme I) it is not clear that carboxylic acids readily react with α-halodiazoalkanes.[15] Even if they do, such a reaction could lead to both **4** and **5**

(12) Closs and Coyle[3] report that the addition of *t*-butyl hypochlorite or *t*-butyl hypobromite to diazomethane at −100° gave dark red solutions which were stable until warmed to −40°.

(13) Additional evidence supporting the maroon coloration as indicative of the formation of α-bromodiazoalkanes is derived from the comparative behavior of diazoethene, diazopropane, and diazoneopentane. The latter diazo compound, expected to be relatively unreactive toward *t*-butyl hypobromite owing to steric hindrance, gave no color change on reaction with *t*-butyl hypobromite under the normal experimental conditions, while diazoethane gave the color change found for diazopropane reactions (Results).

(14) α-Halodiazomethanes react with a second mole of *t*-butyl hypohalite; however, this reaction may be slower than the first halogenation step.[3]

(15) Just as α-halodiazomethanes are less reactive than diazomethane toward *t*-butyl hypohalites, their comparative reactivities toward carboxylic acids show the same trend.[3] An attempt to isolate a bromopropyl ester was unsuccessful (see Experimental Section).

since it has been observed that reactions of carboxylic acids with diazoalkanes yield in part the corresponding olefins.[16] Appropriate deuterium labeling of diazopropane might define the relative importance of the alternate pathways to **4** and **5** in Schemes I and II; however, these experiments have not been undertaken.[17]

The origins of 1-bromopropane (**7**) and 1,1-dibromopropane (**8**) have not been included in Schemes I or II. The apparent insensitivity of the latter to the addition of benzoic acid (Table I) indicates that it was formed during the initial reaction sequence at −100° and molecular bromine contamination of the *t*-BuOBr samples (*vide supra*) suggests that its source was reaction 4. The control experiment using molecular bro-

$$\underset{\mathbf{2}}{CH_3CH_2CHN_2} + Br_2 \longrightarrow \underset{\mathbf{8}}{CH_3CH_2CHBr_2} + N_2 \qquad (4)$$

mine in place of *t*-butyl hypobromite showed that **8**, as expected, was the major reaction product. While the exact percentage contamination of the *t*-BuOBr samples by molecular bromine could not be determined, it appeared to be consistent with the observed yields of 1,1-dibromopropane (Table I). This proposal is further supported by the observation that the yield of 1,1-dibromopropane appeared to increase with the age of the *t*-BuOBr preparations indicative of increasing contamination by molecular bromine.[18]

It is tempting to argue that the formation of 1-bromopropane (**7**) can be explained by the simple direct-reaction of diazopropane and hydrogen bromide (reaction 5). However, it is unlikely that hydrogen bromide could have existed in the *t*-butyl hypobromite preparations in view of the expected facile reaction 6

$$\underset{\mathbf{2}}{CH_3CH_2CHN_2} + HBr \longrightarrow \underset{\mathbf{7}}{CH_3CH_2CH_2Br} + N_2 \qquad (5)$$

$$t\text{-BuOBr} + HBr \longrightarrow t\text{-BuOH} + Br_2 \qquad (6)$$

yielding *t*-butyl alcohol and bromine and we cannot offer an alternative source. The very large decreases in the yield of **7** in the benzoic acid experiment (Table I, no. 7), and when equimolar amounts of *t*-BuOBr and diazopropane were employed (Table I, no. 6), nonetheless clearly connect its origin to diazopropane and place its formation in the reaction sequence occurring during warm-up or photolysis. We have considered the possibility that 1-bromopropane may have been formed in a free-radical reaction involving hydrogen abstraction by an α-bromopropyl radical. Addition of 2-methyltetrahydrofuran caused a significant increase in the relative yield of 1-bromopropane (expt 8); however, there are inconsistencies in the comparative relative yields of **7** in the air, oxygen, and nitrogen atmosphere experiments based on what one would expect for an α-bromopropyl radical intermediate.[19,20]

Based on Schemes I and II, the combined yields of 1,1-dibromopropene (**9**) and *cis*- and *trans*-3-bromo-3-hexene in each of expt 1–5 give a range of 14–19% for the per cent yield of α-bromodiazopropane. This must represent a lower limit since the 1-bromopropenes (**4** and **5**) have not been included, and the yields of 1,1-dibromopropane (**8**) were included in the calculations even though **8** most likely did not arise from *t*-butyl hypobromite. Inclusion of the 1-bromopropenes raises this range to 40–48%.

Experimental Section

Solvents.—Reagent grade pentane (Mallinkrodt) was stirred over sulfuric acid for 24 hr and distilled. Reagent grade 2-methyltetrahydrofuran (MC and B) was refluxed over lithium aluminum hydride in a nitrogen atmosphere for 1 hr and distilled in a nitrogen atmosphere. Cumene was stirred over sulfuric acid and distilled in a nitrogen atmosphere. Research grade trichlorofluoromethane (Freon 11) was a gift of the E. I. du Pont de Nemours and Co. and was used without further purification.

***t*-Butyl Hypobromite.**—Reaction of hypobromous acid with *t*-butyl alcohol according to the procedure of Walling[22] gave *t*-butyl hypobromite in purities ranging from 88 to 93%.[23] Each preparation was stored in the dark at a temperature less than 0° and removed only prior to use in an experiment. Mass spectral analysis (80 eV) was consistent with that anticipated for *t*-butyl hypobromite, *m/e* 152 (P), 154 (P + 2), 57 [base peak, $(CH_3)_3C^+$], and additionally showed contamination by *t*-butyl alcohol, *m/e* 59 ($(CH_3)_2{}^+COH$), and molecular bromine, *m/e* 158, 160, 162.

1-Diazopropane. a.—Reaction of N-nitroso-N-propylurea with aqueous potassium hydroxide utilizing pentane as the organic phase, and subsequent codistillation of the resulting pentane–diazopropane layer, gave pentane solutions of diazopropane in 55–60% yields.[10] Diazopropane solutions were prepared and standardized with benzoic acid prior to each experiment.

b.—Preparation from the tosylhydrazone of propionaldehyde was carried out according to the procedure of Shechter.[11]

Diazoethane[14] **and diazoneopentane**[11] were prepared using procedures a and b, respectively.

Bromination of Diazopropane with *t*-Butyl Hypobromite.—A 5.0 ml solution of *t*-butyl hypobromite (2.5×10^{-3}) in trichlorofluoromethane (Freon 11) was added dropwise from an addition funnel (modified by the addition of a capillary tip to ensure slow, reproducible addition rates) to a stirred 40-ml pentane solution of diazopropane (3.6×10^{-3} mol) held at *ca.* −100° by an ether–liquid nitrogen cooling bath. Light was excluded during the addition and subsequent steps. After development of the maroon coloration (*ca.* 30 min) the bath was removed and the solution was allowed to warm slowly to room temperature. Vigorous gas evolution commenced at −40 to −30°.

In those cases in which the reactions were run under pure nitrogen or oxygen atmospheres the diazopropane and *t*-butyl hypobromite solutions were placed in the reaction apparatus and degassed using the freeze–thaw method. It is likely that a portion of each reactant was lost during the degassing procedure.

Photolysis experiments were set up in the same manner except that after mixing the reagents the reaction flask was immersed in a transparent Pyrex dewar containing Dry Ice–acetone and the solution was photolyzed at −65 to −70° using a 150-W tungsten bulb.

The reaction mixtures were analyzed by glpc using two types of columns: (A) 24 ft × 1/8 in. stainless steel column packed with 20% Apiezon-L on 60–80 firebrick (100°); (B) 21 ft × 1/8 in. stainless steel column packed with 20% SE-30 on 100–200

(16) H. Zollinger, "Azo and Diazo Chemistry," Interscience Publishers, Inc., New York, N. Y., 1961.

(17) (a) The *cis*-/*trans*-1-bromopropene ratio observed in all of the experiments (Table I) does not correspond to thermodynamic equilibrium:[17b-d] (b) K. E. Harwell and L. F. Hatch, *J. Amer. Chem. Soc.*, **77**, 1682 (1955); (c) J. W. Crump, *J. Org. Chem.*, **28**, 953 (1963); (d) R. C. Neuman, Jr., *ibid.*, **31**, 1852 (1966).

(18) The chronological order of the experiments using the first batch of *t*-butyl hypobromite was 4, 1, 3, 5, and 8, while that for the second batch of hypobromite was 9, 7, 6, and 2.

(19) Possible sources of the α-bromopropyl radical might include homolytic scission of the mixed azo compound $CH_3CH_2CHBrN{=}NOC(CH_3)_3$ (a potential product of the first ion pair in Scheme I)[20] or a hydrogen abstraction by α-bromopropylidene. The hydrogen donor to either the α-bromopropyl radical or α-bromopropylidene might have been diazopropane.

(20) Ion-destroying reactions of the diazonium ion–*t*-butoxide ion pairs (Scheme I) and possible coupling to give the azo compound would seem to be much more favorable than carbonium ion formation in view of the very low reaction temperature and nonpolar reaction medium. Even at much higher temperatures and in more polar media diazonium ions are sufficiently stable to undergo similar reactions in competition with carbonium ion formation.[21]

(21) See, for example, J. H. Bayless and L. Friedman, *J. Amer. Chem. Soc.*, **89**, 147 (1967).

(22) C. Walling and A. Padwa, *J. Org. Chem.*, **27**, 2976 (1962).

(23) C. Walling and B. B. Jacknow, *J. Amer. Chem. Soc.*, **82**, 6108 (1960).

Chromosorb W DMCS-AW (100°). The retention times (minutes) for each compound are given in the brackets following each compound in the order (A, B): *cis*-1-bromopropene (8.3, ...), *trans*-1-bromopropene (9.0, ...), 1-bromopropane (9.7, ...), 1,1-dibromopropane (41.7, 34.3), 1,1-dibromopropane (44.7, 36.5), *cis*-3-bromo-3-hexene (47.2, 40.3), *trans*-3-bromo-3-hexene (41.7, 44.8).

Product Identification.—All of the products were collected by preparative glpc. *cis*- and *trans*-1-bromopropene were identified by infrared spectral comparison with authentic samples synthesized from 1,2-dibromopropane.[24] 1-Bromopropane was identified by infrared spectral comparison with commercial 1-bromopropane (MC and B). Infrared analysis of authentic bromocyclopropane[25] demonstrated that it was not present in the 1-bromopropane fraction although the retention times of these compounds were identical. Bromocyclopropane in a yield of >1% of the total 1-bromopropane would have been detected. 1,1-Dibromopropene was characterized from its spectral data: infrared, 6.15 μ (C=C); nmr, δ 1.87 (doublet, 3 H, J = 7 cps), 6.17 (quartet, 1 H, J = 7 cps); mass spectrum (70 eV), m/e 198 (P), 200 (P + 2), 202 (P + 4); relative intensities to parent peak were 192 and 94%, respectively. 1,1-Dibromopropane was characterized by infrared spectral comparison with an authentic sample obtained from the reaction of bromine with diazopropane; nmr δ 1.41 (triplet, 3 H, J = 7 cps), 2.72 (multiplet, 2 H), 6.13 (triplet, 1 H, J = 6 cps). *cis*-3-Bromo-3-hexene was identified by infrared spectral comparison with an authentic sample.[26] *trans*-3-Bromo-3-hexene was identified by its infrared, nmr, and mass spectral data: infrared, 6.05 μ (C=C); nmr, δ 0.91 (multiplet, 6 H), 2.17 (multiplet, 4 H), 5.55 (triplet, 1 H, J = 6.5 cps); mass spectrum (70 eV), m/e 162 (P), 164 (P + 2), intensity of P + 2 relative to P was 96.5%. The nmr spectrum was very similar to that of *trans*-3-iodo-3-hexene.[26]

Attempted Trapping of α-Bromodiazopropane with Acetic Acid.—The reaction of *t*-butyl hypobromite (2.5×10^{-2} mol) with diazopropane (3.9×10^{-1} mol) at −100° was carried out in the usual manner. A solution of acetic acid (4.3×10^{-1} mol) in Freon 11 was then added dropwise at −100°. The solution became colorless near the end of the addition. Removal of solvent using a rotary evaporator left a red-brown oil possessing the odor of bromine and acetic acid. An nmr of this oil showed the presence of acetic acid and *n*-propyl acetate. A very weak resonance signal at δ 5.75 indicated the possible presence of α-bromopropyl acetate. The chloromethylene protons of chloromethyl acetate give a signal at δ 5.63. Attempts to distil this oil at reduced pressure resulted in decomposition.

Registry No.—*t*-Butyl hypobromite, 1611-82-1; 2, 764-02-3; α-bromopropylidene, 19807-22-8.

(24) (a) M. S. Kharasch and C. F. Fuchs, *J. Amer. Chem. Soc.*, **65**, 504 (1943); (b) R. C. Neuman, Jr., and D. N. Roark, *J. Mol. Spectrosc.*, **19**, 421 (1966).

(25) E. Renk, R. R. Shafer, W. H. Graham, R. H. Mazur, and J. D. Roberts, *J. Amer. Chem. Soc.*, **83**, 1987 (1961).

(26) (a) Spectral data kindly furnished by Professor G. Zweifel; (b) G. Zweifel and C. C. Whitney, *ibid.*, **89**, 2753 (1967).

Conformations of 1,2-Disubstituted Indans. Electronegativity Corrections to Nuclear Magnetic Resonance Coupling Constants

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Nmr spectra of hydrogens on the cyclopentene rings of 23 1,2-disubstituted indans of known stereochemistry have been analyzed completely. Constants in the Karplus equation that relates vicinal coupling constants to substituent electronegativity have been evaluated using data from the bicyclo[2.2.1]heptene system, and the resulting equations were used to correct the indan vicinal coupling constants for electronegativity effects. The corrected coupling constants (J^u values), which should be a function of dihedral angle only, show that 1,2-disubstituted indans exist as a mixture of two puckered conformations. For both *cis* and *trans* compounds the degree of pucker is controlled by substituent size and not by dipole–dipole forces. In the *trans* compounds the population of the diaxial conformation increases relative to that of the diequatorial conformation as the size of the substituents increases. *trans* compounds bearing a hydroxy group at C_1 or C_2 shown an unusually strong preference for the diequatorial conformation. Analysis of data in the literature shows that 1-haloindans prefer the conformation in which the halogen atom is axial.

Recently conformations of five-membered rings, especially cyclopentanes, have been the subject of a number of studies.[1] Cyclopentene and its derivatives have received less attention. Rathjens, using microwave spectroscopy, concluded that cyclopentene is puckered with an angle of 22° between the skeletal planes,[2] and Jakobsen[3] has interpreted the nmr spectrum of *cis*-3,5-dibromocyclopentene in terms of a ring puckered in the vicinity of 20°. Sable, *et al.*, have also studied substituted cyclopentenes by nmr spectroscopy.[1b] Jackson, *et al.*,[4] have studied some 2-substituted indans and their chromium tricarbonyl complexes, while Rosen, *et al.*,[5] investigated a series of 1,2-disubstituted and 2-substituted indans. Both of the latter groups interpreted their results in terms of a nonplanar cyclopentene ring, but Merritt and Johnson[6] have suggested nearly planar conformations for some fluorinated indans. Vicinal coupling constants in 1,2-disubstituted indans varied erratically with substituent changes and were not reliable indicators of stereochemistry. This work is an effort to identify the factors which determine conformation in 1,2-disubstituted indans and to make a start on the problem of separation of conformational and electronegativity influences on vicinal nmr coupling constants in flexible systems.

Synthesis.—Most 1,2-disubstituted indans used in this work were of well-established stereochemistry or

(1) (a) H. R. Buys, C. Altona, and E. Havinga, *Rec. Trav. Chim. Pays-Bas*, **87**, 53 (1968), and previous papers in this series; (b) H. Z. Sable, W. M. Ritchey, and J. E. Nordlander, *Carbohyd. Res.*, **1**, 10 (1965); *J. Org. Chem.*, **31**, 3771 (1966); (c) L. E. Erickson, *J. Amer. Chem. Soc.*, **87**, 1867 (1965); (d) D. J. Pasto, F. M. Klein, and T. W. Doyle, *ibid.*, **89**, 4369 (1967).

(2) G. W. Rathjens, Jr., *J. Chem. Phys.*, **36**, 2401 (1962); see also F. V. Brutcher and E. L. James, *Dissertation Absts.*, **24**, 1398 (1963).

(3) H. J. Jakobsen, *Tetrahedron Lett.*, 1991 (1967).

(4) W. R. Jackson, C. H. McMullen, R. Spratt, and P. Blandon, *J. Organometal. Chem.*, **4**, 392 (1965).

(5) W. E. Rosen, L. Dorfman, and M. R. Linfield, *J. Org. Chem.*, **29**, 1723 (1964).

(6) R. F. Merritt and F. A. Johnson, *ibid.*, **31**, 1859 (1966).

TABLE I

CHEMICAL SHIFTS AND COUPLING CONSTANTS OF *cis*-1,2-DISUBSTITUTED INDANS[a,b,o]

			Hz								RMS[q]	
Compd	R_1	R_2	J_{12}	J_{23}	J_{24}	H_1	H_2	H_3	H_4	Other	error	Solvent
1	OH	OH	5.1	(7.4)	2.0[p]	294.2	236.2	177.9	173.4	*g*	0.09	*c*
2	OCH_3	OCH_3	4.9	7.3	6.6	269.0	233.9	178.3	173.1	*h*	0.05	*d*
3	$OCOCH_3$	$OCOCH_3$	5.4	(6.8)	5.6	364.9	323.5	185.9	180.9	*i*	0.05	*c*
4	Acetonide		5.6	6.5	0.5	329.0	296.4	187.2	181.9	*j*	0.07	*c*
5	Carbonate		6.7	6.4	1.2	362.5	329.4	203.0	194.2		0.03	*c*
6	OH	OCHO	4.9			325	338	191	186	*k, l*		*e*
7	$OCOCH_3$	OCHO	5.4	7.4	4.4[p]	372.2	331.1	193.2	187.4	*m*	0.08	*d*
8	OH	Cl	5.1	(5.5)	3.5[p]	307.2	283.3	197.5	188.0	*k*	0.10	*c*
9	$OCOCH_3$	Cl	5.2	6.8	4.5[p]	359.8	279.7	191.7	190.1	*n*	0.05	*d*
10	Cl	Cl	5.1	(8.8)	5.1[p]	303.1	257.2	182.3	180.9		0.10	*f*
11	Br	Br	5.0			311						*f*

[a] Chemical shifts are in hertz downfield from internal tetramethylsilane at 60 MHz and coupling constants and root mean square error are in hertz. [b] All compounds gave a complex multiplet at 420 to 450 Hz for the aromatic hydrogens. [c] Acetone-d_6. [d] Carbon tetrachloride. [e] Pyridine. [f] Neat liquid. [g] OH at 240 Hz. [h] Methoxys singlet at 197 Hz. [i] Acetoxy methyls at 117 and 118 Hz. [j] Methyl singlets at 66 and 80 Hz. [k] Trace of HCl gas added, OH signal not determined. [l] Aldehyde hydrogen singlet at 505 Hz. [m] Acetoxy methyl 124 Hz, aldehyde hydrogen 487 Hz. [n] Acetoxy methyl 122 Hz. [o] Values in parentheses have probable errors greater than 1 Hz. [p] 0.3 < probable error ≤ 0.2 Hz. [q] Root mean square.

TABLE II

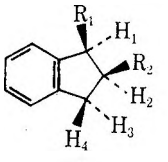
CHEMICAL SHIFTS AND COUPLING CONSTANTS OF *trans*-1,2-DISUBSTITUTED INDANS[a,b]

			Hz									RMS[n]	
Compd	R_1	R_2	J_{12}	J_{23}	J_{24}	J_{34}	H_1	H_2	H_3	H_4	Other	error	Solvent
12	OH	OH	5.5	7.2	7.0	−15.7	292.3	255.6	189.2	162.0	*g*	0.07	*c*
13	OCH_3	OCH_3	4.6	6.9	5.4	−16.1	278.5	239.5	191.6	160.9	*h*	0.04	*d*
14	$OCOCH_3$	$OCOCH_3$	3.8	7.3	4.8	−16.6	368.6	321.5	205.7	168.8	*i*	0.02	*c*
15	OH	OCHO	4.6				303	313	165	203	*j*		*e*
16	$OCOCH_3$	OCHO	3.9	7.3	4.9	−16.7	371.0	327.4	204.9	168.8	*k*	0.02	*d*
17	OH	Cl	5.5	7.3	6.9	−16.1	305.4	256.8	208.8	179.1	*g*	0.03	*c*
18	OCH_3	Cl	4.1	7.0	5.4	−16.5	281.5	256.3	200.4	173.7	*l*	0.06	*d*
19	$OCOCH_3$	Cl	3.8	6.8	4.7	−16.6	371.4	265.7	209.0	181.8	*m*	0.05	*d*
20	OH	Br	5.4	7.2	6.8	−16.4	313.0	259.2	215.4	188.3	*g*	0.03	*c*
21	Cl	Cl	3.3	6.2	3.8	−16.7	311.5	266.7	204.5	176.1		0.04	*f*
22	Br	Br	1.3	5.0	1.2	−17.5	333.0	282.3	211.5	181.6		0.13	*f*
23	Cl	I	2.9	6.2	3.2	−17.5	326.2	266.8	207.4	182.1		0.05	*f*

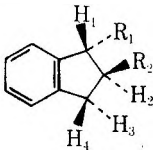
[a] Chemical shifts are in hertz downfield from internal tetramethylsilane at 60 MHz and coupling constants and root mean square error are in hertz. [b] All compounds gave a complex multiplet at 420 to 450 Hz for the aromatic hydrogens. [c] Acetone-d_6. [d] Carbon tetrachloride. [e] DMSO-d_6. [f] Neat liquid. [g] HCl gas added, OH absorption not measured. [h] Methoxy singlets at 203 and 209 Hz. [i] Acetoxy methyl singlets at 115 and 118 Hz. [j] Hydroxyl hydrogen singlet at 342 Hz, aldehyde hydrogen singlet at 497 Hz. [k] Acetoxy methyl singlet at 117 Hz, aldehyde hydrogen singlet at 477 Hz. [l] Methoxy singlet at 204 Hz. [m] Acetoxy methyl at 120 Hz. [n] Root mean square.

were prepared from precursors of known stereochemistry in a stereospecific fashion as described in the Experimental Section. Chlorination of indene in carbon tetrachloride gives both *cis*- and *trans*-1,2-dichloroindans.[7] The stereochemistry of these isomers was proven by determination of their dipole moments, *cis* 2.9 D, *trans* 2.3 D. Addition of bromine to indene in nonpolar solvents produces *cis*- and *trans*-1,2-dibromoindans, but addition of iodine monochloride gives only *trans*-1-chloro-2-iodoindan. The stereochemistry of these last three compounds was deduced by means of nmr spectroscopy using values of vicinal coupling constants (Tables I and II) and the appearance of the signals of the geminal hydrogens at C_3.[5,8]

Nmr Data.—Spectral parameters are listed in Tables I and II; the numbering scheme used is that shown.



cis



trans

Parameters were extracted from the spectra using the LAOCOON II computer program.[9] The hydrogens on the cyclopentene ring exhibited ABMX-type spectra where J_{AX} and J_{BX} are *ca.* 0. In all but compounds **6** and **15** H_1 appeared farthest downfield as a doublet, J_{12} = 1–7 Hz, while H_2 gave a sextet or octet at higher field. The geminal pair, H_3 and H_4, appeared at highest field. As noted by Rosen, *et al.*,[5] H_3 and H_4 have very similar chemical shifts in the *cis* isomers and give simple signals of two to four lines. The *trans* isomers have a larger chemical-shift difference and give the expected eight-line pattern with the inner four being most intense. In every case the hydrogen *cis* to the substituent at C_2 (H_4) was assigned at higher field than H_3. The shielding effect of a *cis* substituent on β hydrogens in rigid or semirigid rings has been observed by Wiberg[10] and has been discussed recently by

(7) C. M. Suter and G. A. Lutz [*J. Amer. Chem. Soc.*, **60**, 1360 (1938)] report the isolation of a single isomer, assumed to be *trans*, after distillation.

(8) Details of the electrophilic additions will be published elsewhere.

(9) S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964). We would like to thank Professor Bothner-By for sending us a copy of his program.

(10) K. B. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, **85**, 2788 (1963).

Andreatta, *et al.*[11,12] This assignment has the virtue of making J_{23} (*cis*) > J_{24} (*trans*) which is expected for a cyclopentene ring.[1,3-5,14]

Spectral parameters for the *trans* compounds could be determined with good accuracy. All probable errors[15] were less than 0.2 Hz except for dibromide **22**. Since no completely satisfactory set of parameters could be determined for **15**, we report only J_{12} which is determined uniquely by the separation between the lines of the H_1 doublet. In the *cis* compounds the small chemical shift between H_3 and H_4 makes the four outer lines of the H_3H_4 octet too weak to be detected. These simplified spectra do not permit accurate determination of all spectral parameters. A fixed J_{34} value of −16.7 Hz, typical of that observed for the *trans* compounds, was chosen.[16,17] Calculations showed that virtually no changes occurred in the other parameters as J_{34} was varied between −12 and −17 Hz. Probable errors for J_{12} and J_{24} are less than 0.2 Hz except in the few instances noted in Table I. Probable error values for J_{23} are all 0.34 Hz or greater, however.

Owing to the different solubilities of the compounds, spectra were obtained in several different solvents. Although Erickson has observed a large solvent effect on J_{vic} in *dl*-dibromosuccinic anhydride,[1c] normally solvent effects on vicinal H–H coupling constants are small.[18] *trans*-1,2-Dimethoxyindan has a J_{12} of 4.3 Hz in acetone-d_6 and 4.6 Hz in carbon tetrachloride, and J_{12} of *trans*-2-bromo-1-indanol (**20**) changes only 0.2 Hz on changing solvent from acetone-d_6 to pyridine. All samples were *ca.* 12 wt % in the solvent given. Variation of the concentration of **20** in acetone-d_6 from 6 to 21% caused no measurable change in J_{12}.

Electronegativity Corrections.—Karplus has pointed out that vicinal hydrogen coupling constants are functions of four major variables.[16,19] Bond lengths and angles should remain constant in our compounds except for carbonate **5** and acetonide **4**. However, the observed coupling constants will be a function of both dihedral angle[14,18] and effects of electronegative substituents.[13,18,20,21] Sable, *et al.*,[1b] noted that J_{vic} does not vary linearly with substituent electronegativity in tetrasubstituted cyclopentanes and Erickson[1c] observed that J_{trans} actually increases with increasing substituent electronegativity in substituted succinic anhydrides. Both authors attributed the deviation from expected behavior to superposition of conformational and electronegativity effects. Clearly, if they are to give reliable conformational information, our coupling constants must be corrected for electronegativity effects.

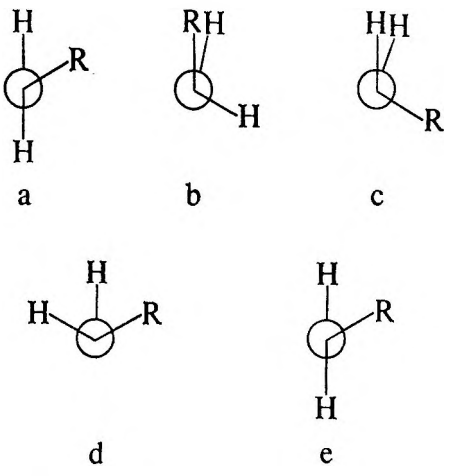


Figure 1.—Conformation of an electronegative substituent (R) and β hydrogen.

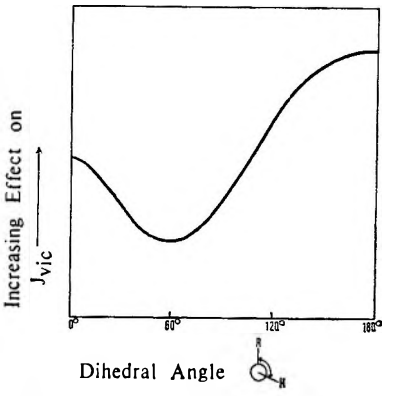


Figure 2.—Conformational dependence of the electronegativity effect on vicinal hydrogen–hydrogen coupling constants.

The diminution of vicinal coupling constants by electronegative substituents in saturated systems is well grounded theoretically[19] and has been verified experimentally.[13,20,21] Theory predicts[19] and experiments show[13,20,22,23] that the effect is conformation dependent. Williams and Bhacca[22] and Booth[23] have shown that the maximum effect obtains when the electronegative substituent is *trans* to the β hydrogen (Figure 1a) and Booth[23] has suggested that a second weaker maximum may exist when the substituent is *cis* to the β hydrogen (Figure 1b). Work on rigid bicyclo[2.2.1]heptenes[20,21] shows that sizable effects are obtained at dihedral angles of 0 (Figure 1b) and 120° (Figure 1c), with that at 120° being the greater. Work of Whitesides, *et al.*,[24] shows negligible effects for an angle of *ca.* 60° (Figures 1d and e). That the effect at 60° is minimal compared to that at 180° is dramatically illustrated by a series of α-halo steroidal ketones[25] in agreement with Williams and Bhacca[24] and Booth.[23] Thus available evidence suggests that the effect decreases with the dihedral angle between the substituent and the β hydrogen in the following order: 180° > 120° > 0° > 60°. This angular dependence is depicted in Figure 2.

(11) R. H. Andreatta, V. Nair, and A. V. Robertson, *Aust. J. Chem.*, **20**, 2701 (1967).

(12) Additional series of compounds which exhibit this effect are substituted ethylene oxides[13] and 1,1-dichlorocyclopropanes.[18] The carboxyl group does not follow this rule,[10,11] but all of our substituents are considered normal.[11]

(13) K. L. Williamson, C. A. Lanford, and C. R. Nicholson, *J. Amer. Chem. Soc.*, **86**, 762 (1964).

(14) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(15) Probable error is defined as the increment in a parameter necessary to double the root mean square error for all parameters.

(16) This is a reasonable value for an indan. *Cf.* A. A. Bothner-By in "Advances in Magnetic Resonance," Vol. I., J. S. Waugh, Ed., Academic Press, New York, N. Y., 1965, p 195.

(17) R. C. Cookson, T. A. Crabb, J. J. Frankel, and J. Hudec, *Tetrahedron Suppl.*, No. 7, 355 (1966).

(18) S. L. Smith and R. H. Cox, *J. Phys. Chem.*, **72**, 198 (1968).

(19) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(20) K. L. Williamson, *ibid.*, **85**, 516 (1963).

(21) P. Laszlo and P. von R. Schleyer, *ibid.*, **85**, 2709 (1963).

(22) D. H. Williams and N. S. Bhacca, *ibid.*, **86**, 2742 (1964).

(23) H. Booth, *Tetrahedron Lett.*, 411 (1965).

(24) G. M. Whitesides, J. P. Sevenair, and R. W. Goetz, *J. Amer. Chem. Soc.*, **89**, 1135 (1967).

(25) A. Nikon, M. A. Castle, R. Harada, C. E. Berkoff, and R. O. Williams, *ibid.*, **85**, 2185 (1963).

TABLE III

CORRECTED COUPLING CONSTANTS FOR *cis*-1,2-DISUBSTITUTED INDANS

Compd	R_1	R_2	J^u_{12}, Hz[a]	J^u_{24}, Hz	Sum of van der Waals radii,[b] Å	—Electronegativity[c]— R_1	R_2
5	Carbonate		11.2	2.6	3.0	3.72	3.72
3	$OCOCH_3$	$OCOCH_3$	9.0	12.0	3.0	3.72	3.72
7	$OCOCH_3$	OCHO	9.0	(9.4)[d]	3.0	3.72	3.72
4	Acetonide		8.2	0.8	3.0	3.31	3.31
9	$OCOCH_3$	Cl	8.0	(7.2)	3.25	3.72	3.25
1	OH	OH	7.9	3.6	3.0	3.43	3.43
6	OH	OCHO	7.9		3.0	3.43	3.72
8	OH	Cl	7.5	(5.6)	3.25	3.43	3.25
2	OCH_3	OCH_3	7.3	11.0	3.0	3.31	3.31
10	Cl	Cl	7.3	(8.2)	3.5	3.25	3.25
11	Br	Br	6.6		3.7	2.96	2.96

[a] The correction calculated by eq 3 was doubled to simulate the effect of the second substituent. The average electronegativity of the two substituents was used in the calculation. [b] Sum of the van der Waals radii for the substituent atoms bonded directly to C_1 and C_2. van der Waals radii from A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964). [c] Values from J. R. Cavanaugh and B. P. Dailey, *J. Chem. Phys.*, **34**, 1009 (1961), and ref 21. [d] Less reliable values in parentheses.

TABLE IV

CORRECTED COUPLING CONSTANTS FOR *trans*-1,2-DISUBSTITUTED INDANS

Compd	R_1	R_2	J^u_{12},[a] Hz	J^u_{23}, Hz	J^u_{24}, Hz	Sum of van der Waals radii,[b] Å	—Electronegativity[c]— R_1	R_2
12	OH	OH	11.9	12.8	12.5	3.0	3.43	3.43
17	OH	Cl	11.2	11.0	11.1	3.25	3.43	3.25
15	OH	OCHO	11.0			3.0	3.43	3.72
16	$OCOCH_3$	OCHO	10.6	15.7	10.5	3.0	3.72	3.72
14	$OCOCH_3$	$OCOCH_3$	10.4	15.7	10.3	3.0	3.72	3.72
20	OH	Br	10.4	10.0	9.5	3.35	3.43	2.96
13	OCH_3	OCH_3	9.2	11.5	9.0	3.0	3.31	3.31
19	$OCOCH_3$	Cl	8.6	11.0	7.6	3.25	3.72	3.25
18	OCH_3	Cl	8.0	11.3	8.7	3.25	3.31	3.25
21	Cl	Cl	6.3	10.0	6.1	3.5	3.25	3.25
23	Cl	I	5.0	7.6	4.0	3.75	3.25	2.66
22	Br	Br	2.0	7.0	1.7	3.7	2.96	2.96

[a] The correction increment calculated with eq 2 was increased by a factor of 1.5 to simulate the effect of the second substituent. The average electronegativity of R_1 and R_2 was used in the calculation. [b] Sum of the van der Waals radii for the substituent atoms bonded directly to C_1 and C_2. van der Waals radii from A. Bondi, *J. Phys. Chem.*, **68**, 441 (1964). [c] Values from J. R. Cavanaugh and B. P. Dailey, *J. Chem. Phys.*, **34**, 1009 (1961), and ref 21.

Karplus has derived equations that relate J_{vic} to substituent electronegativity of the form of eq 1 where J is the observed constant, J^u is an unperturbed constant, and ΔX is the electronegativity difference between the substituent and hydrogen.[19] The Karplus value of $m = 0.60$ for *cis* hydrogens (Figure 1c) predicts a much larger effect than that observed in norbornenes.[18,20,21] Use of data of Smith and Cox[18] from 2-substituted hexachloro-5-norbornenes to calculate values for m gives eq 2 and 3 which apply to con-

$$J = J^u(1 - m\Delta X) \quad (1)$$

$$J_{trans} = J^u_{trans}(1 - 0.330\Delta X) \quad (2)$$

$$J_{cis} = J_{cis}(1 - 0.157\Delta X) \quad (3)$$

formations b and c in Figure 1, respectively. The rigid norbornene molecule is not a perfect model for the more flexible indans. However, we expect that the conformations of the strained cyclopentene ring in indans will not differ grossly from the eclipsed conformation of the model. Thus eq 2 and 3 should apply, at least approximately, to indans. Neglect of the small effect of R_1 and J_{23} and J_{24} should not affect the accuracy of our method significantly.[26]

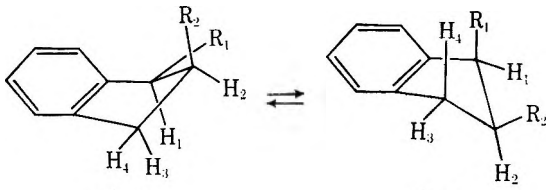
(26) A. D. Cohen and T. Schaffer, *Mol. Phys.*, **10**, 209 (1966).

Equations 2 and 3 were used to calculate J^u values. For *cis* compounds (Table III) the calculated correction to J_{12} was doubled to simulate the effect of a second substituent. The average electronegativity of R_1 and R_2 was used in each case. Owing to their large uncertainties, J_{23} values for *cis* compounds were not corrected. Table IV lists J^u values for *trans* compounds. Since J^u should be a function of conformation alone, the two *trans* coupling constants J^u_{12} and J^u_{24} should be equal for each compound, and the correction to J_{12} was adjusted accordingly. To make $J^u_{12} \sim J^u_{24}$ for these compounds the correction to J_{12} calculated by eq 2 had to be increased by a factor of 1.5. This suggests that the effects of two electronegative substituents on J_{12} are not additive in this case as we assumed for the *cis* compounds. Fortunately, our conclusions about conformation are not dependent on our assumptions regarding additivity of these effects.

Conformation.—Eclipsing and steric strain will make the planar conformation of indans a high-energy one,[27] and abundant evidence favors nonplanarity of cyclo-

(27) Calculations and experiment show that *trans*-1,2-dihalocyclopentanes exist as a mixture of diaxial and diequatorial conformers in which the halogen atoms occupy the most puckered part of the ring. *Cf.* (a) C. Altona, H. R. Buys, and E. Havinga, *Rec. Trav. Chim. Pays-Bas*, **85**, 973,993 (1966); (b) C. Altona, H. R. Buys, H. J. Hageman, and E. Havinga, *Tetrahedron*, **23**, 2265 (1967).

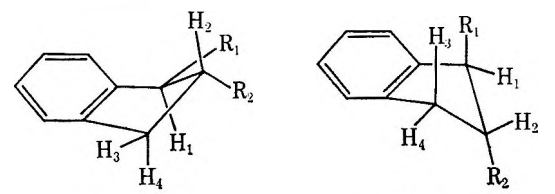
pentenes[2,3] and indans.[4,5] Our data support puckering strongly. For example, many J_{trans} in both series of compounds are too large to be consistent with a planar ring and a dihedral angle of 120°.[14] As for other flexible rings, no linear relationship between vicinal coupling constants and electronegativity is observed. Our data can be interpreted in terms of two puckered conformations shown for *cis* compounds.



cis-ea *cis*-ae

Distortion in either direction from the planar conformation should decrease J^u_{12};[14] so J^u_{12} will decrease as the average degree of puckering increases. The data in Table III reveal that puckering, as measured by J^u_{12}, increases as the combined size of R_1 and R_2, estimated by the sum of van der Waals radii for the atoms directly bonded to C_1 and C_2, increases.[28] However, as the electronegativities of R_1 and R_2 increase causing dipole–dipole repulsions to increase, the compounds become more planar. Clearly, the degree of puckering is controlled by steric rather than by dipole–dipole forces. J^u_{24} is small in the ea conformation but relatively large in the ae conformation.[14] Thus J^u_{24} should be a measure of the relative conformer populations. Scatter among J^u_{24} values in Table III suggests that factors other than R_1–R_2 repulsions control the relative populations. This is reasonable since the R_1–R_2 distance will be equal for the two conformations if they are equally puckered.

Conformations for *trans*-1,2-disubstituted indans are shown. The two *trans* coupling constants, J^u_{12} and

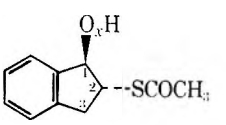


trans-ee *trans*-aa

J^u_{24}, should be principally a function of the relative populations of the two conformations as in the *cis* series. The decrease in the size of J^u_{12} and J^u_{24} as the sum of van der Waals radii for R_1 and R_2 increases can be attributed to a depopulation of the ee conformation in which the substituents approach one another closely.[28] As for the *cis* compounds, dipole–dipole repulsions predict the opposite trend. Again, the value of the *cis* coupling constant, J^u_{23}, should decrease with increasing puckering. The observed trend, which requires puckering to increase with substituent size, is reasonable; however some of the J^u_{23} values are unexpectedly large. This is particularly true for **14** and **16**, compounds with very electronegative substituents and J^u_{23} values which include large corrections. These two compounds exist primarily in the ee conformation in which the dihedral angle between R_2 and H_3 <120°. Reference to Figure 2 shows that eq 3, which is for an angle of 120°, should overestimate the electronegativity corrections in these cases.

None of the *cis* compounds seems to be far out of place in the substituent size *vs.* degree of pucker correlation. Compounds **8** and **9** should be more puckered relative to **1**, **2**, and **6**, but the coupling constant differences involved are probably too small to be significant. In the *trans* series chlorohydrin **17** and bromohydrin **20** appear to have unusually high ee populations. This may be a characteristic of hydroxy compounds since all compounds bearing a hydroxy group, **12**, **15**, **17**, and **20**, exhibit a marked preference for the ee conformation. It seems unlikely that this preference is caused by intramolecular hydrogen bonding since the more flexible *trans*-1,2-cyclopentanediol exhibits none.[29] Preference for the aa conformation by *trans*-1,2-dihaloindans in particularly striking, and is in agreement with data on *trans*-1,2-dihalocyclohexanes[30] and *trans*-1,2-dihalocyclopentanes.[27] *trans*-1,2-Dibromocyclopentane, for example, is about 80% diaxial conformer at 25° in acetonitrile.[27a]

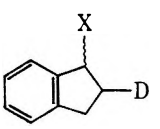
The stereochemistry of some previously reported indans can be clarified by reference to our data. The 1,3-*cis*-diacetoxy-2-nitroindan of Baer and Achmatowicz[31] is almost certainly the all-*cis* isomer. Because of the high electronegativity of the acetoxy and nitro substituents, the coupling constant values, J_{12} = J_{23} = 5–6 Hz, are consistent only with *cis* stereochemistry. Suitable *trans* model compounds **14**, **16**, and **19** have J_{12} values of 3.8 or 3.9 Hz (Table II) while for the corresponding *cis* derivatives **3**, **7**, and **9**, J_{12} = 5.2–5.4 Hz. Oswald, *et al.*,[32] have reported 1-hydroxy- and 1-peroxy-2-thiolacetates **23** and **24**. The ap-



23, $x = 1$, $J_{12} = 6$Hz
24, $x = 2$, $J_{12} = 4.5$Hz

pearance of the signals for the hydrogens at C_3 shows that these are indeed *trans* compounds, though this could hardly have been deduced from the J_{12} values as was reported. Their large J_{12} values suggest that, like the hydroxy compounds reported in this work, they prefer the ee conformation.

The preferred conformation of 1-haloindans can be deduced from data on 1-halo-2-deuterioindans **25** and **26**.[33] Uncorrected coupling constants are, for **25**,



25, X = Br
26, X = Cl

(28) Measurements made on Dreiding models of planar and *ca.* 25° puckered conformations show that the proposed steric interactions are reasonable.

(29) L. P. Kuhn, *J. Amer. Chem. Soc.*, **74**, 2492 (1952).

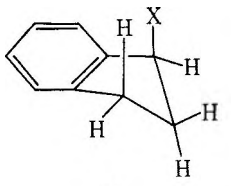
(30) K. Kwestroo, F. A. Meijer, and E. Havinga, *Rec. Trav. Chim. Pays-Bas*, **73**, 717 (1954).

(31) H. H. Baer and B. Achmatowicz, *J. Org. Chem.*, **29**, 3180 (1964).

(32) A. A. Oswald, K. Griesbaum, and W. Naegle, *J. Amer. Chem. Soc.*, **86**, 3791 (1964).

(33) M. J. S. Dewar and R. C. Fahey, *ibid.*, **85**, 2245 (1963).

J_{cis} = 7 Hz and J_{trans} = 2.5 Hz; for **26**, J_{cis} = 6 Hz and J_{trans} = 2.5 Hz.[34] Correction for electronegativity effects gives, for **25**, J^{u}_{cis} = 8 Hz, and J^{u}_{trans} = 3 Hz; for **26**, J^{u}_{cis} = 7 Hz and J^{u}_{trans} = 4 Hz. The small J^{u}_{trans} values indicate a strong preference for the axial conformation (**27**), and the J^{u}_{cis} values suggest a moderate degree of puckering (see Tables III and IV).



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In summary, it has been possible, using data on a related rigid system, to correct vicinal coupling constants in indans for the effects of electronegative substituents. The corrected values can be used as the basis of reasonable conformational proposals which are in accord with what is known about conformations of indans and some related systems. A glance at Tables I and II show that our conformational conclusions could not have been reached without such corrections. While qualitatively these corrections are almost certainly correct, their quantitative aspect must still meet the test of independent data.

Experimental Section

Infrared spectra were recorded using Beckman Model IR-5 and IR-10 instruments, and melting points were determined with a Mel-Temp apparatus (Laboratory Devices, Cambridge, Mass.) and are uncorrected. Preparative vpc was carried out with a Varian-Aerograph A-700 instrument. The Alfred Bernhardt and Schwartzkopf microanalytical laboratories performed the elemental analyses.

Nmr spectra were recorded on Varian Associates A-60 and A-60A instruments using tetramethylsilane as an internal standard. Peak positions were determined on expanded scales by bracketing each group of lines with side bands of the tetramethylsilane signal generated by a Hewlett–Packard 200 CD audio oscillator and calibrated by means of a Hewlett–Packard 5211 B counter. The values used were the average of four determinations, two sweeps in each direction. Spectral parameters were extracted using the LAOCOON II program on a CDC 3600 machine. In appropriate cases several different sets of line assignments were used in part 2 of the program to determine the best set. Coupling constants, except where noted, should be accurate to within ±0.3 Hz; however, chemical shifts were not extrapolated to infinite dilution and should not be regarded as standard values.

Previously Reported 1,2-Disubstituted Indans.—The following compounds are known stereochemistry and were prepared according to descriptions in the reference cited here: **1**,[5] **3**,[35] **4**,[5] **6**,[5] **7**,[5] **8**,[7] **12**,[5] **14**,[36] **15**,[5] **17**,[7] **20**.[37]

***cis*-1,2-Dimethoxyindan (2).**—A solution of diazomethane (*ca.* 88 mmol) in methylene chloride was prepared by the method of Arndt[38] from 13.2 g (150 mmol) of N-nitroso-N-methylurea and was dried over potassium hydroxide pellets for 1.5 hr. This solution was added over the period of 1 hr to a stirring solution of *cis*-1,2-indandiol[5] (3.3 g, 22 mmol) and boron trifluoride ethyl etherate (0.1 ml, 0.7 mmol) in 200 ml of methylene chloride at 0°. After stirring at 0° for 1 more hr, the reaction mixture was washed with water and saturated aqueous sodium bicarbonate and was dried ($MgSO_4$). Evaporation of the solvent under vacuum left a yellow oil. Distillation at 0.01 mm gave fractions [bp 55–59° (0.9 g), 59–60° (1.0 g), and 60–62° (1.1 g)] for a total yield of 80%. Treatment of the middle fraction with Norit in hot acetone, removal of the solvent, and evaporative distillation at 40° (0.01 mm) gave a colorless oil which was analytically pure: ir (neat, cm^{-1}) 1600, 1460 (aromatic C=C), 1125, 1085 (C—O), 750 (*o*-phenylene).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.24; H, 7.98.

***trans*-1,2-Dimethoxyindan (13).**—A dry solution of diazomethane (*ca.* 9.4 mmol) in 200 ml of methylene chloride[38] was added dropwise during 1 hr to a stirring solution of *trans*-1,2-indandiol[5] (0.7 g, 4.7 mmol) and boron trifluoride ethyl etherate (0.3 ml, 1.7 mmol) in 200 ml of dry ethyl acetate held at 5°. After 1 more hour of stirring at 5°, the reaction mixture was washed with saturated aqueous sodium bicarbonate, and was dried ($MgSO_4$). Evaporation of the solvent under vacuum left a yellow oil that was evaporatively distilled at 45° (0.01 mm) to give 0.1 g (9%) of a clear oil. Preparative vpc on a $^3/_8$ in. × 10 ft 25% DC 200 silicone oil on Chromosorb W gave material of analytical purity: ir (CCl_4, cm^{-1}) 1460 (aromatic C=C), 1095 (C—O).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.82; H, 7.92.

***trans*-2-Chloro-1-methoxyindan (18).**—A dry solution of diazomethane (*ca.* 33 mmol) in 100 ml of methylene chloride[38] was added during 0.5 hr to a stirring solution of *trans*-2-chloro-1-indanol[7] (5.0 g, 30 mmol) and boron trifluoride ethyl etherate (1.0 ml, 7 mmol) in 300 ml of dry methylene chloride at 0°. After stirring for 1 more hr at 0°, the reaction mixture was washed with water, saturated aqueous sodium bicarbonate, and again with water, and was dried ($MgSO_4$). Removal of the solvent under vacuum and evaporative distillation at 40° (0.01 mm) gave 1.0 g (18%) of a slightly yellow oil. Treatment with Norit in hot acetone, removal of the solvent, and evaporative distillation at 40° (0.01 mm) gave a clear analytically pure oil: ir (neat, cm^{-1}) 1610, 1480 (aromatic C=C), 1085 (C—O), 740 (*o*-phenylene).

Anal. Calcd for $C_{10}H_{11}OCl$: C, 65.76; H, 6.07; Cl, 19.41. Found: C, 65.65; H, 6.21; Cl, 19.27.

***cis*-1-Acetoxy-2-chloroindan (9).**—Acetyl chloride (3.0 ml, 43 mmol) was added dropwise to a stirring solution of *cis*-2-chloro-1-indanol[7] (1.1 g, 6.6 mmol) in 15 ml of dry pyridine at 0°. The reaction flask was stoppered, and stirring was continued at 0° for 1 hr. The reaction mixture was poured into 100 ml of benzene, and was washed consecutively with water, dilute hydrochloric acid, water, saturated aqueous sodium bicarbonate, and water. Drying ($MgSO_4$) and evaporation of the solvent under vacuum left a red oil. Evaporative distillation at 70° (0.02 mm) gave 0.8 g (85%) of **9** as a light red oil. Treatment with Norit in hot acetone and evaporative distillation gave a colorless analytical sample: ir (neat, cm^{-1}) 1740 (C=O), 1230 (acetate C—O), 1060 (ether C—O), 740 (*o*-phenylene).

Anal. Calcd for $C_{11}H_{11}O_2Cl$: C, 62.71; H, 5.26; Cl, 16.83. Found: C, 62.60; H, 5.72; Cl, 16.73.

***trans*-1-Acetoxy-2-chloroindan (19).**—Acetyl chloride (5.0 ml, 70 mmol) was added dropwise to a stirring solution of *trans*-2-chloro-1-indanol[7] (40 g, 24 mmol) in 30 ml of dry pyridine at 0°. The reaction flask was stoppered, and stirring was continued at 0° for 1 hr. The reaction mixture was taken up in 250 ml of benzene, and the benzene solution was washed consecutively with water, dilute hydrochloric acid, water, saturated aqueous sodium bicarbonate, and water. Drying ($MgSO_4$) and removal of benzene under vacuum gave a red oil that afforded 1.6 g (35%) of **19** as a yellow oil on evaporative distillation at 83° (0.02 mm). Treatment with Norit in hot acetone followed by evaporative distillation at 50° (0.01 mm) afforded an analytically pure colorless oil: ir (neat, cm^{-1}) 1740 (C=O), 1225 (acetate C—O), 1040 (ether C—O), 745 (*o*-phenylene).

Anal. Calcd for $C_{11}H_{11}O_2Cl$: C, 62.71; H, 5.26; Cl, 16.83. Found: C, 62.30; H, 5.48; Cl, 16.68.

***trans*-1-Acetoxy-2-formyloxyindan (16).**—Acetyl chloride (1.5 ml, 20 mmol) was added slowly to a stirring solution of *trans*-2-formyloxy-1-indanol[5] in 15 ml of dry pyridine at 0°, and stirring was continued for 1 hr at room temperature. A solution of the reaction mixture in 75 ml of benzene was washed consecutively with dilute hydrochloric acid, saturated aqueous sodium bicarbonate, and water. Drying ($MgSO_4$) and removal of the

(34) Values from measurements on spectra in ref 33.

(35) P. W. Verkade, J. Coops, A. Verkade-Sandbergen, and C. J. Mann, *Ann. Chem.*, **477**, 280 (1930).

(36) W. F. Whitmore and A. I. Gebhart, *J. Amer. Chem. Soc.*, **64**, 912 (1942).

(37) C. M. Suter and H. B. Milne, *ibid.*, **62**, 3473 (1940).

(38) F. Arndt, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 165.

solvent under vacuum gave a yellow oil that was treated with Norit in hot acetone to give 16 as a clear oil, 0.22 g (50%). Preparative vpc on a 3/8 in. × 10 ft 25% DC 200 silicone oil on chromosorb W column gave material of analytical purity: ir (neat, cm^{-1}) 1745–1735 broad (C=O), 1230 (acetate C—O), 1160 (formate C—O), 740 (*o*-phenylene).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.59; H, 5.38.

***cis*-1,2-Indandiol Carbonate (5).**—A flask containing *cis*-1,2-indandiol[5] (1.6 g, 10.6 mmol) and 10 ml of pyridine in 250 ml of ether was placed in an efficient fume hood and cooled in an ice bath. Phosgene was bubbled slowly into the solution for 1 hr, and the reaction mixture was stirred for an additional 12 hr. Excess phosgene and *ca.* two-thirds of the ether were removed under reduced pressure in the fume hood. The resulting slurry was washed with saturated aqueous sodium bicarbonate, 3 *N* hydrochloric acid, and again with the bicarbonate solution. A white solid formed upon removal of the solvent. Recrystallization from ether gave 0.26 g (14%) of **5** as a white solid: mp 74–75°; ir (Nujol, cm^{-1}) 1790 (C=O), 1060 and 1170 (C—O), 750 (*o*-phenylene).

Anal. Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 67.92; H, 4.67.

Preparation and Dipole Moments and *cis*- (10) and *trans*-1,2-Dichloroindan (21).—A solution of indene[39] (1.0 g, 8.6 mmol) in 25 ml of carbon tetrachloride was cooled in an ice bath and stirred as chlorine was added through a glass frit until its yellow color persisted. Excess chlorine was destroyed by washing the reaction mixture with several portions of saturated aqueous sodium thiosulfate. The solution was dried ($MgSO_4$), and the solvent was evaporated under vacuum to give a mixture of *cis*- and *trans*-1,2-dichloroindans. In benzene solution the H_1 nmr doublets of these isomers were well resolved, and careful integration of the nmr signals showed that the composition of this crude sample was 30% *cis* (J_{12} = 5.1 Hz) and 70% *trans* (J_{12} = 3.3 Hz). Temperatures necessary for vacuum distillation and vpc work caused loss of hydrogen chloride from and decomposition of the crude dichlorides. Column chromatography on Florisil with petroleum ether (bp 50–60°) as eluent gave initial fractions that contained only the *trans* isomer, $n^{25}D$ 1.5675. Though it was impossible to obtain pure *cis* isomer by this method, later fractions were enriched in this isomer and were suitable for subsequent work.

Dipole moments were determined in benzene by the method described by Shoemaker and Garland[40] using a Sargent oscillometer, Model V. Pure *trans* was used but the *cis* sample was 66 mol % *cis* and 34 mol % *trans*. Dipole moments were calculated as *trans* 2.3 ± 0.2 D and "*cis*" 2.7 ± 0.2 D. Use of the equation $\mu^2 = N_1\mu_1^2 + N_2\mu_2^2$ gave a value of 2.9 ± 0.2 D for pure *cis* isomer.

***cis*- and *trans*-1,2-Dibromoindans 11 and 22.**—Bromine was added dropwise to a stirring solution of indene[39] (5.0 g) in 25 ml of dry ethyl ether at 0–5° until a red color persisted. The reaction mixture was washed with saturated aqueous sodium thiosulfate and was dried ($MgSO_4$). Evaporation of the solvent under vacuum left a crude oil which was determined to be 80–90% *trans* isomer by integration of the H_1 nmr signals of a neat sample. The value of J_{12} = 5.0 Hz for the *cis* isomer was obtained by measuring the separation of the H_1 doublet in these spectra. Low-temperature crystallization from petroleum ether as described by Winstein and Roberts[41] afforded pure *trans*-1,2-dibromoindan (22).

***trans*-1-Chloro-2-iodoindan (23).**—Iodine chloride was added slowly to a solution of indene[39] (5.0 g, 43 mmol) in 25 ml of carbon tetrachloride cooled in an ice–salt bath. Addition was regulated to keep the temperature of the reaction mixture below 0° and was discontinued when further addition caused no rise in temperature. The reaction mixture was washed with aqueous sodium thiosulfate and was dried ($MgSO_4$). Evaporation of the solvent under vacuum left a pink oil that rapidly became dark and could not be stored without decomposition even under refrigeration: ir (neat, cm^{-1}) 1610 and 1475 (aromatic C=C), 800–700 (C–Cl and *o*-phenylene). Nmr spectroscopy shows that the product is contaminated by *ca.* 10% *cis*-1,2-dichloroindan.

Registry No.—**1**, 4647-42-1; **2**, 19597-95-6; **3**, 19597-96-7; **4**, 19597-97-8; **5**, 19597-98-9; **6**, 19597-99-0; **7**, 19598-00-6; **8**, 19598-01-7; **9**, 19598-02-8; **10**, 19598-03-9; **11**, 19598-04-0; **12**, 4647-43-2; **13**, 19598-06-2; **14**, 19598-07-3; **15**, 19598-08-4; **16**, 19598-09-5; **17**, 19598-10-8; **18**, 19598-11-9; **19**, 19598-12-0; **20**, 10368-44-2; **21**, 19598-14-2; **22**, 19598-15-3; **23**, 19598-16-4.

Acknowledgment.—We wish to acknowledge grants from the University of Massachusetts Research Council and Research Computing Center in support of this work.

(39) 97.5% stabilized with 90 ppm of *p*-toluhydroquinone, Neville Chemical Co., Neville Island, Pa.

(40) D. P. Shoemaker and C. W. Garland, "Experiments in Physical Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 275.

(41) S. Winstein and R. M. Roberts, *J. Amer. Chem. Soc.*, **75**, 2297 (1953). dibromoindan (22).

Mechanism of the Oxidation Reaction with Nickel Peroxide

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Some aspects of mechanisms of the oxidation reactions using nickel peroxide which is a useful oxidant prepared from nickel sulfate with sodium hypochlorite were examined. The radical species were observed by esr in some oxidation reactions with nickel peroxide. From stoichiometric study using benzhydrol and diphenylacetonitrile, it can be concluded that one equivalent atom of available oxygen in nickel peroxide corresponds to two radical species. Using hexaphenylethane as a reactant the presence of the source of OH radical in nickel peroxide was confirmed. Accordingly, the nature of nickel peroxide can be expressed stoichiometrically by the scheme $2OH\cdot \rightarrow H_2O + O$. The oxidation reaction mechanism of benzhydrol was studied in detail in views of isotope effect and the reactions using ^{18}O-labeled compounds to support the mechanism (eq 5).

Since Nakagawa, Konaka, and Nakata[1] previously found that nickel peroxide was a useful oxidizing agent on the oxidation of alcohols, a lot of the reactions using nickel peroxide have been reported. That is, on the oxidation of amines,[2] phenols,[3] hydrazones,[4] sulfur compounds,[5] nitriles,[6] and phenothiazines,[7] on the oxidative cleavage of α-glycols[8] and *o*-phenylenediamines,[9] on the telomerization,[10] on the polymerization,[11] and on the others,[12] nickel peroxide showed the extremely attractive reactivities.

All above reactions may possibly be explained in terms of the radical reaction mechanisms. However, though the telomerization and the polymerization with nickel peroxide demonstrate the typical radical reaction the evidence of radical character in the oxidation reaction is ambiguous. Nickel peroxide obtained from nickel sulfate with sodium hypochlorite in an alkaline solution is amorphous black powder, insoluble in organic solvents and water other than acidic solvents, and is similar to manganese dioxide in its appearance and some chemical properties. Nickel peroxide has 0.30–0.35 $\times 10^{-2}$ g-atom of available oxygen per gram determined by iodometry, and generally is used in a little excess of stoichiometric amount in most oxidation reactions, but the source of available oxygen is still indistinct. In the present paper, it is clarified that the oxidation reaction with nickel peroxide proceeds through the radical reaction path by esr studies and by product studies on the reaction with a stable radical. Besides, from the stoichiometrical study the source of available oxygen can be expressed in the simple scheme. Furthermore, the mechanism of the oxidation of alcohol is discussed in detail by means of isotope methods.

Electron Spin Resonance Studies.—Esr studies on the oxidation of 2,6-di-*t*-butyl-4-methylphenol (**1**) in benzene showed the presence of 2,6-di-*t*-butyl-4-methylphenoxy radical (**2**),[13] $a^H_p = 11.15$ *G* and $a^H_m = 1.69$ *G*, whose decay in the flow system followed in the first order. In the case of 2,6-di-*t*-butylphenol (**4**) the spectrum of 2,6-di-*t*-butylphenoxy radical (**5**),[14] $a^H_p = 9.58$ *G* and $a^H_m = 1.93$ *G*, was detected only in the flow system. The esr spectrum of 10-phenothiazinyl radical (**8**) was observed upon the oxidation of phenothiazine (**7**) with nickel peroxide in benzene in the static system. Its hyperfine splitting constants, $a^N = 7.04$ *G*, $a^H_{3,7} = 3.67$ *G*, $a^H_{1,9} = 2.85$ *G*, and $a^H_{2,8} = a^H_{4,6} = 0.95$ *G*, were identical with those in the reference.[15] On the esr measurement, at 2.4 min after mixing of **7** and nickel peroxide, 72.2% radical was observed and the concentration of the radical was decayed in the second order ($k = 1.2 \times 10^{-2}$ l./mol sec). On the oxidation of benzophenone oxime with nickel peroxide in benzene, esr spectrum showed the corresponding iminoxy radical,[16] $a^N = 31.55$ *G* and $a^H = 1.41$ *G* (2 H).

Aurich and Baer[17] observed the esr spectra of acyl phenyl nitroxides on the oxidation of N-acyl-N-phenylhydroxylamines with nickel peroxide[18] in benzene. This suggests the oxidation with nickel peroxide may proceed *via* the radical course. On the oxidations of **1** and **4** with nickel peroxide, 3,3′,5,5′-tetra-*t*-butylstylbene-4,4′-quinone (**3**)[3e] and 3,3′,5,5′-tetra-*t*-butyl-4,4′-diphenoquinone (**6**)[3c] are produced in 30% yield and quantitatively, respectively. While in these reactions, the observation of corresponding phenoxy radicals by esr spectroscopy may imply that these reactions proceed in the following schemes, in which eq 1 is the same mechanism as that of Bennet.[19] Since the oxidation products of phenothiazine (**7**) with

(1) K. Nakagawa, R. Konaka, and T. Nakata, *J. Org. Chem.*, **27**, 1597 (1962).

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(3) (a) K. Nakagawa, H. Onoue, and J. Sugita, *Chem. Pharm. Bull. Jap.*, **12**, 1135 (1964); (b) J. Sugita, *Nippon Kagaku Zasshi*, **87**, 603 (1966); (c) J. Sugita, *ibid.*, **87**, 607 (1966); (d) J. Sugita, *ibid.*, **87**, 741 (1966); (e) J. Sugita, *ibid.*, **87**, 1082 (1966); (f) H.-D. Becker, *J. Org. Chem.*, **32**, 2115 (1967); (g) M. F. Ansell and A. F. Gosden, *Chem. Commun.*, 520 (1965).

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(12) (a) K. Nakagawa, H. Onoue, and K. Minami, *Chem. Commun.*, 17 (1966); (b) C. D. Campbell and C. W. Rees, *Proc. Chem. Soc.*, 296 (1964); (c) A. Ujhidy, B. Babos, L. Markó, and A. Müller, *Ber.*, **98**, 2197 (1965).

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(16) (a) J. R. Thomas, *J. Amer. Chem. Soc.*, **86**, 1446 (1964); (b) B. C. Gilbert and R. O. C. Norman, *J. Chem. Soc., B*, 86 (1966).

(17) H. G. Aurich and F. Baer, *Tetrahedron Lett.*, 3879 (1965).

(18) Nickel peroxide used here may have been prepared by the method of Nakagawa, *et al.*,[1] though there is no description in the reference.

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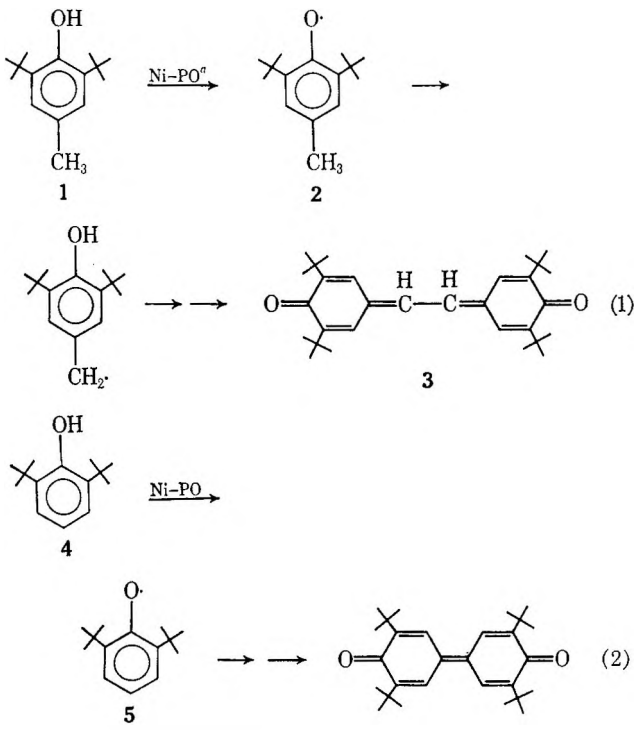
TABLE I
OXIDATION OF BENZHYDROL AND DIPHENYLACETONITRILE WITH NICKEL PEROXIDE[a]

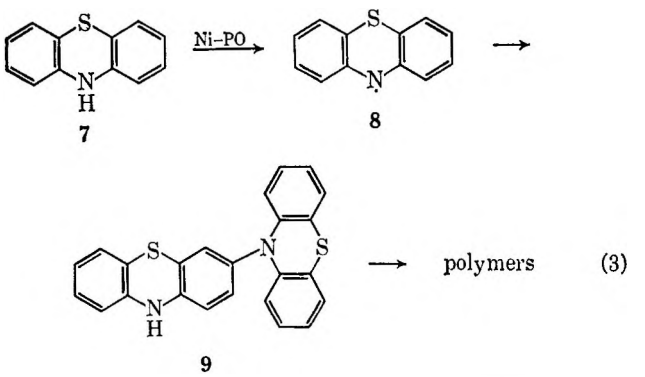
Substrate	Amt, mmol	Ni-PO mg-O*[b]	Reaction time, hr	Product	Yield, %
Benzhydrol	3	3.6	4	Benzophenone	94.5
	3	1.5	8		46.5
Diphenylacetonitrile	39	40	1	*syn*-Dicyanotetraphenylethane	98.8[c]
	20	10	1		96.9

[a] Solvent, benzene; temp, 25°. [b] Means milligram atomic equivalent of available oxygen. [c] Unpublished work by Dr. Sugita.



[a] Ni-PO nickel peroxide

nickel peroxide are 3,10′-biphenothiazinyl (**9**) and polymers,[7] the reaction course may be considered as in reaction 3. Benzophenone is obtained by the oxidation



of benzophenone oxime with nickel peroxide.[20] Presumably, observed iminoxy radical might relate to the formation of benzophenone. As mentioned above, observed radicals by esr spectroscopy can be considered as reaction intermediates in respective oxidation reactions, and it is confirmed that nickel peroxide is capable of abstracting hydrogens of some substrates.

Stoichiometry on the Oxidation with Nickel Peroxide. —In practice, an amount of nickel peroxide needed on the oxidation is determined based on an amount of the available oxygen. For example, an amount of nickel peroxide corresponding to one atomic equivalent of available oxygen converts 1 mol of alcohol into a carbonyl compound. The results indicated in Table I clarify the stoichiometry on the oxidation with nickel peroxide. It is reasonable to explain that the formation of *syn*-dicyanotetraphenylethane is attributed to the dimerization of cyanodiphenylmethyl radical produced by hydrogen abstraction from diphenylacetonitrile with nickel peroxide. The data conclude that one atomic equivalent of available oxygen of nickel peroxide corresponds to two radical species.

Oxidation of Active Methylene and Methine Groups. —On the oxidation of toluene derivatives and diphenylmethane with nickel peroxide, benzoic acid derivatives and benzophenone were produced respectively.[21] In addition, 9,10-dihydroanthracene was oxidized for 3 hr in benzene at room temperature to give anthracene as a major product and anthraquinone as a minor one. Furthermore, on the oxidation of triphenylmethane with nickel peroxide in benzene at 55°, after 10 hr triphenylcarbinol was afforded in 2% yield and the residue was the unchanged starting material. Triphenylmethane seems to be oxidized slowly owing to steric effect.

On the other hand, the composition of nickel peroxide prepared from nickel sulfate was determined as $NiO_{2.77}H_{2.85}$ by means of elementary analysis, chelate titration, and gas chromatography. Consequently, introduction of oxygen atom into the products described above may intimate the participation of a species like OH radical in nickel peroxide.[22] It cannot be inferred, however, whether this species is contained in nickel peroxide originally,[23] or produced by the hydrogen abstraction from the substrate with active oxygen atom in nickel peroxide.[24,25]

(20) Unpublished work by Dr. K. Nakagawa.

(21) Unpublished work by Dr. Sugita.

(22) The molecular formula of nickel peroxide may be written as $Ni_x(OH)_yO_z \cdot nH_2O$ formally.

(23) In this case the following reaction sequence may be written.

$$\geqslant CH + Ni_x(OH)_yO_z \cdot nH_2O \longrightarrow \geqslant C\cdot + Ni(OH)_{y-1}O_z \cdot (n+1)H_2O$$

$$\geqslant C\cdot + Ni_x(OH)_yO_z \cdot nH_2O \longrightarrow \geqslant COH + Ni(OH)_{y-1}O_z \cdot nH_2O$$

(24) In this case the following reaction sequence may be similarly written.

$$\geqslant CH + Ni_x(OH)_yO_z \cdot nH_2O \longrightarrow \geqslant C\cdot + Ni(OH)_{y+1}O_{z-1} \cdot nH_2O$$

$$\geqslant C\cdot + Ni_x(OH)_{y+1}O_{z-1} \cdot nH_2O \longrightarrow \geqslant COH + Ni(OH)_yO_{z-1} \cdot nH_2O$$

(25) Another path might be explained as the following chain mechanism.

$$\geqslant CH + Ni_x(OH)_yO_z \cdot nH_2O \longrightarrow \geqslant C\cdot + Ni_x(OH)_{y-1}O_z \cdot (n+1)H_2O$$

$$\geqslant C\cdot + Ni_x(OH)_yO_z \cdot nH_2O \longrightarrow \geqslant CO\cdot + Ni_x(OH)_yO_{z-1} \cdot nH_2O$$

$$\geqslant CO\cdot + \geqslant CH \longrightarrow \geqslant COH + \geqslant C\cdot$$

Reaction of Nickel Peroxide with Free Radicals.—Phenylazotriphenylmethane was decomposed in benzene at 65° in the presence of 1.1 equivalent amounts of nickel peroxide to yield triphenylcarbinol (56.3%), triphenylmethane (47.7%), and biphenyl (79.2%).[26,27] On the decomposition of phenylazotriphenylmethane itself in benzene, triphenylcarbinol was not produced. Since it is well known that triphenylmethyl radical is produced on the decomposition of phenylazotriphenylmethane, these facts may imply that the formation of triphenylcarbinol may be attributed to the reaction of triphenylmethyl radical with nickel peroxide though the source of OH group is uncertain.

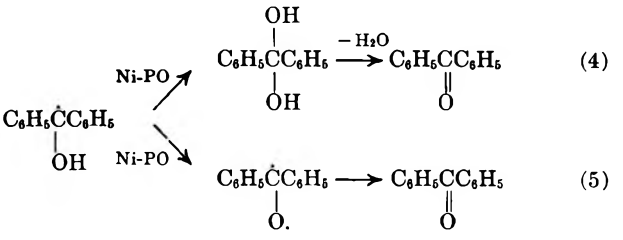
A mixture of hexaphenylethane[28] and 0.6 equivalent amount of nickel peroxide for triphenylmethyl radical dissociated from hexaphenylethane was stirred in benzene for 2 hr at room temperature to give triphenylcarbinol in 90% yield. In benzene-d_6 solution, triphenylcarbinol which did not show the absorption of OD in the ir spectrum was afforded quantitatively by using 1.2 equivalent amounts of nickel peroxide. In both cases, no biphenyl was produced. These results indicate that the source of OH group is in nickel peroxide itself, not produced by the hydrogen abstraction from a reaction system. Furthermore, since 1 mol of triphenylcarbinol was produced from 1 mol of triphenylmethyl radical and about one-half equivalent amount of nickel peroxide, it is reasonable to conclude that one atomic equivalent of available oxygen determined by iodometry in nickel peroxide corresponds to two OH radical species. Consequently, the nature of nickel peroxide may be explained schematically as

$$\text{nickel peroxide} \longrightarrow 2\text{OH}\cdot \longrightarrow \text{O}^* + \text{H}_2\text{O}$$

and in terms of having two characteristic abilities of hydrogen abstraction and OH radical donation. Thus the production of triphenylcarbinol from triphenylmethane or phenylazotriphenylmethane and the formation of other oxygen containing compounds from hydrocarbons can be elucidated by the above characters.

The Oxidation Mechanism of Alcohols with Nickel Peroxide.—The isotope effect for the oxidation of $(C_6H_5)_2CDOH$ was examined to verify the first step of the oxidation of alcohols with nickel peroxide. The reaction rates of the oxidation of $(C_6H_5)_2CHOH$ and $(C_6H_5)_2CDOH$ with excess nickel peroxide at 1° were followed by glpc to give $k_H = 1.693 \times 10^{-4}$ sec^{-1} and $k_D = 2.287 \times 10^{-5}$ sec^{-1}; accordingly $k_H/k_D = 7.4$. This fact shows that the oxidation of benzhydrol with nickel peroxide begins from the hydrogen abstraction on α position of the alcohol. The alternative explanation, the hydrogen abstraction from OH bond, was eliminated.[29,30]

Two mechanisms, eq 4 and 5,[31,32] for the formation of benzophenone after the hydrogen abstraction from the α position appear reasonable. The distinction of the two paths was accomplished by means of benzhydrol labeled with oxygen-18.



(4)

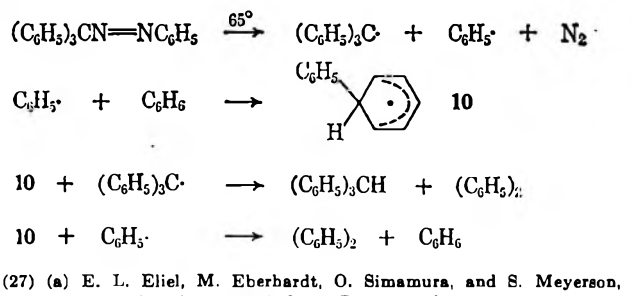
(5)

First in order to check the exchange reaction of oxygen between the product and nickel peroxide, benzophenone-^{18}O and nickel peroxide (1.2 equivalent amounts) were mixed under stirring in benzene at room temperature and the ^{18}O content of isolated benzophenone was analyzed. It was somewhat surprising to find that the considerable fast exchange reaction occurred and the rate of decrease was about 5.7% of excess ^{18}O per hour. Furthermore, the deactivated nickel peroxide and alumina for column chromatography also exchanged oxygen of benzophenone but it was observed that the procedures of glpc of benzophenone and benzhydrol and of mixing of benzophenone and benzhydrol in benzene without nickel peroxide did not cause the exchange reaction. Hence, the oxidation of benzhydrol-^{18}O with nickel peroxide (0.5 equivalent amount) was carried out in a short reaction time (1 hr) at room temperature and the reaction products were separated by means of the preparative glpc and the ^{18}O content was analyzed. According to the above procedure benzophenone of ^{18}O 1.137% content and benzhydrol of ^{18}O 1.204% content were afforded in 22.8 and 77.2% yield, respectively, from benzhydrol of ^{18}O 1.297% content. Subsequently, the oxidation reaction mechanism of benzhydrol with nickel peroxide may be elucidated by the reaction path (5) on the surface of nickel peroxide.

Experimental Section

Materials.—Nickel peroxide was prepared by the method of Nakagawa, *et al.*,[1] and its available oxygen content was 0.318×10^{-2} g-atom per gram. 2,6-Di-*t*-butyl-4-methylphenol and 2,6-di-*t*-butylphenol were Tokyo Kasei E.P. grade and were used without further purification. Phenothiazine, benzhydrol, diphenylacetonitrile, and triphenylmethane were purified by recrystallization from commercial reagents. Benzophenone oxime was prepared from hydroxylamine hydrochloride and benzophenone by the ordinary method. Phenylazotriphenylmethane was prepared by the oxidation of N-phenyl-N-tritylhydrazine prepared from trityl chloride and phenylhydrazine

(26) Triphenylmethane and biphenyl were possibly produced by the following reactions.[27]



(27) (a) E. L. Eliel, M. Eberhardt, O. Simamura, and S. Meyerson, *Tetrahedron Lett.*, 749 (1962); (b) G. A. Russell and R. F. Bridger, *ibid.*, 737 (1963).

(28) M. Gomberg and C. S. Schoeple, *J. Amer. Chem. Soc.*, **39**, 1658 (1924).

(29) Generally, the free-radical reaction mechanism of the oxidation of alcohols is explicable in terms of hydrogen abstraction from α position of alcohols;[30] in the case of the oxidation with nickel peroxide, however, it is probable that the OH group is attacked owing to the decrease of the bond dissociation energy of the O–H bond caused by the adsorption of alcohols on the surface of nickel peroxide.

(30) R. S. Davidson, *Quart. Rev.* (London), **14**, 249 (1967).

(31) Pryor[33] calculated the dissociation energy of $C_6H_5C(OH)C_6H_5 \rightarrow C_6H_5C(O)C_6H_5 + H\cdot$ to be 102 kcal/mol.

(32) W. A. Pryor, "Free Radicals," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, p 75.

according to the method of Cohen, *et al.*[33] All above compounds have the correct melting points.

Electron Spin Resonance Technique.—The esr spectra were recorded with a Varian V-4502 spectrometer having a 12-in. magnet with 100-kHz field modulation. Cells similar to the type proposed by Russell, *et al.*,[34] were used for the static method and esr spectra were measured immediately after mixing the solutions of a substrate and nickel peroxide degassed by introducing prepurified nitrogen. The flow method was carried out according to the method of Huysmans, *et al.*[14] Determinations of the radical concentrations were made compared with a standard solution of diphenylpicrylhydrazyl by using a Varian V-4532 dual-sample cavity.

General Oxidation Procedure.—A mixture of a substrate and a calculated amount of nickel peroxide required stoichiometrically based on the available oxygen was stirred in benzene or ether vigorously by means of a magnetic stirrer at a proper constant temperature. The reaction mixture was filtered to remove the solid of nickel compound. The filtrate was treated in the usual methods of recrystallization, column chromatography, and/or glpc to determine the structures of products and yields.

Composition of Nickel Peroxide.—The composition of nickel peroxide prepared by Nakagawa's method was determined as follows: Ni, chelate titration using EDTA and Cu-PAN indicator,[35] 52.31%; Na, magnesium–uranyl–acetate method,[36] 0.75%; Cl, volumetry using $AgNO_3$, 0.16%; H_2O, gravimetry on decomposition at 900°, 23.01%; O_2, glpc on decomposition at 900°, 5.35%; ash, residue on decomposition at 900°, 67.45%. Assuming that the deficient amount to 100% was volatile impurities, calculating from above data, the molecular formula was $NiO_{2.77}H_{2.85}$.

Reaction of Hexaphenylethane with Nickel Peroxide.—Hexaphenylethane was prepared from triphenylmethyl chloride, mercury, and lead powder in benzene under vacuum at room temperature for 68 hr according to Gomberg's method,[28] and recrystallized from acetone under vacuum, mp 140–145° (lit.[28] mp 145–147°).

A mixture of 162 mg of hexaphenylethane, 251 mg of nickel peroxide (1.2 equivalent amounts), and 5 ml of benzene-d_6 was stirred at room temperature under argon atmosphere. After 2 hr, the nickel compound was filtered off and the filtrate was evaporated. On recrystallization of the residue from *n*-hexane, 169 mg (98%) of pure triphenylcarbinol was obtained. In view of infrared spectrum of this compound, the presence of D was not recognized. Using 0.6 equivalent amount of nickel peroxide in benzene under the condition, 90% yield of triphenylcarbinol was obtained. In both cases, no triphenylmethyl peroxide was observed. While hexaphenylethane did not change in the absence of oxygen in a benzene–water mixture, on exposure to air of this mixture, a 94% yield of triphenylmethyl peroxide was obtained.

Isotope Effect of Oxidation of Benzhydrol with Nickel Peroxide.—In a mixture of 0.5 mmol of benzhydrol and 5 equivalent amount of nickel peroxide 17 ml of ether was added at 1° under vigorous stirring; after the appropriate time the mixture was quenched by 15% HCl aqueous solution, extracted with ether, and dried over calcium chloride, and an amount of benzhydrol was determined by glpc (column, diethylene glycol succinate polyester, 5%, 2.25 m; column temperature, 200°; internal standard, azobenzene). α-Deuteriobenzhydrol prepared by reduction of benzophenone with lithium aluminum deuteride was treated with the same procedure. The reaction rates of both oxidations are shown in Table II. Both reaction rates were expressed by the first-order reaction rate equation and the rate constants were $k_H = 1.693 \times 10^{-4}$ sec^{-1} and $k_D = 2.287 \times 10^{-5}$ sec^{-1}.

(33) S. G. Cohen and C. H. Wang, *J. Amer. Chem. Soc.*, **75**, 5504 (1953).
(34) G. A. Russell, E. G. Janzen, and E. T. Strom, *ibid.*, **86**, 1807 (1964).
(35) H. Flaschka and H. Abdine, *Chem.-Analyst*, **45**, 58 (1956).
(36) E. R. Caley, *J. Amer. Chem. Soc.*, **51**, 1965 (1929).

TABLE II
THE OXIDATION REACTION RATES OF BENZHYDROL AND α-DEUTERIOBENZHYDROL AT 1°

	Reaction time, min				
	10	20	40	60	80
$(C_6H_5)_2CHOH$ (%)	82.3	75.6	60.7	54.8	
$(C_6H_5)_2CDOH$ (%)	92.2	92.0	87.7	86.1	86.8

Preparation of Benzhydrol-^{18}O and Benzophenone-^{18}O.—Benzhydryl bromide (8.1 g) was dissolved in 100 ml of a mixture of water-free THF and $H_2{}^{18}O$ (YEDA Research and Development Co., Ltd., ^{18}O 1.71%), and allowed to stand overnight at room temperature. The reaction mixture was evaporated under vacuum to remove THF and extracted with water-free benzene. After evaporation of benzene and twice recrystallization from *n*-hexane 4 g of benzhydrol was obtained, mp 66°. Tlc showed one spot, and the infrared spectrum showed the same as that of authentic benzhydrol. *Anal.* Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57; O, 8.68. Found: C, 84.92; H, 6.63; O, 8.69. Analysis of ^{18}O content was accomplished by the method of Denney, *et al.*,[37] applying Schütze–Unterzaucher's method.[38] The isotope ratio was determined by Hitachi RMU-6E mass spectrometer with Faraday cup collector. The content of ^{18}O of benzhydrol prepared above was 1.297%. Benzophenone-^{18}O was prepared according to Doering, *et al.*,[39] as follows. A mixture of 10 g of commercial dichlorodiphenylmethane and 5 g of $H_2{}^{18}O$ (^{18}O content 1.71%) was stirred at 90° for 6 hr. The resulting product was evaporated and recrystallized twice from *n*-hexane, giving benzophenone-^{18}O containing 1.49% ^{18}O.

Oxidation of Benzhydrol-^{18}O with Nickel Peroxide.—In order to check the exchange reaction of benzophenone-^{18}O produced during the oxidation of benzhydrol-^{18}O, 100 mg of benzophenone-^{18}O (^{18}O content, 1.49%) was treated with 210 mg of nickel peroxide under the reaction condition to show the decrease of the ^{18}O content as follows: 0 hr, 100%; 0.5 hr, 97.5%; 1 hr, 95.7%; 2 hr, 81.9%; 3 hr, 83.9%; 5 hr, 72.2%; 29 hr, 21.2%. Furthermore, to examine the oxygen exchange reaction of benzophenone-^{18}O in column chromatography for the separation procedure of the reaction mixture, benzophenone-^{18}O was mixed with alumina to result the rapid decrease of the ^{18}O content. However, on mixing benzophenone-^{18}O with benzhydrol in benzene without nickel peroxide and on separation of benzhydrol-^{18}O and benzophenone-^{18}O by glpc (5% diethylene glycol succinate polyester column) oxygen exchange reactions of benzophenone-^{18}O and benzhydrol-^{18}O did not occur within experimental error.

A mixture of 200 mg of benzhydrol-^{18}O (^{18}O content, 1.297%), 200 mg of nickel peroxide (0.5 equivalent amount), and 5 ml of benzene was stirred at room temperature for 1 hr. The reaction mixture was filtered off to remove the nickel compound and evaporated. The yield of benzophenone was 22.8% by glpc analysis and 29.6 mg of benzophenone and 68.34 mg of benzhydrol were obtained by means of preparative glpc. The contents of ^{18}O in the resulting benzophenone and benzhydrol were 1.137 and 1.204%, respectively.

Registry No.—Benzhydrol-^{18}O, 19639-48-6; benzhydrol, 91-01-0; diphenylacetonitrile, 86-29-3; hexaphenylethane, 17854-07-8.

(37) D. B. Denney and M. A. Greenbaum, *ibid.*, **79**, 979 (1957).
(38) This method was checked by the direct measurement based on a parent peak in mass spectrometry and the oxidation method using $HgCl_2$ [D. Rittenberg and L. Ponticorvo, *Int. J. Appl. Radiat. Isotopes*, **1**, 208 (1956); S. Oae, T. Kitao, and Y. Kitaoka, *Ann. Rept. Radiat. Center Osaka Pref.*, **1**, 31 (1961)] to give the same result.
(39) W. von E. Doering and E. Dorfman, *J. Amer. Chem. Soc.*, **75**, 5595 (1953).

Tetrafluorohydrazine Reactions with Unsaturated Nitrogen Compounds[1a]

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Addition reactions of tetrafluorohydrazine with a number of types of unsaturated nitrogen compounds have been demonstrated to occur in the expected manner. Unsaturated amides, carbamates, isocyanates, nitriles, and nitro compounds were investigated. Diallylic-substituted nitrogen compounds formed cyclic bis(difluoramines) as well as the tetrakis(difluoramines). Only the nitro compounds failed to react.

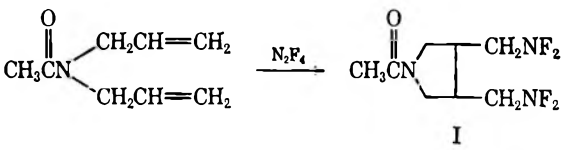
During the past few years, several reports[2,3] have appeared in the literature describing the addition of tetrafluorohydrazine (N_2F_4) to olefins, including a rather comprehensive study by Petry and Freeman.[2] Since only limited studies have been reported on the N_2F_4 addition to olefinic nitrogen-containing compounds,[4] we have extended this reaction to include unsaturated amides, carbamates, isocyanates, nitriles, and nitro compounds. The present work describes the addition reactions and characterization of products.

Although several experimental techniques are suitable for conducting the N_2F_4–olefin reactions, the preparative work was conveniently carried out under pressure in inert solvents such as carbon tetrachloride, chlorobenzene, and Freon 113. Fischer–Porter aerosol pressure tubes were used as reaction apparatus in a remote-controlled environment. Reaction temperatures ranged from 30 to 110° depending upon the reactivity of the olefinic substrate. In many instances, products were isolated by distillation or preparative gas chromatography; however, a number of products were judged to be nonvolatile or too explosive in character for distillation and were analyzed as a crude product or purified by column chromatography over silica gel. Characterization and identification of the products (Table I) were based on infrared and ^{19}F nmr spectral data and elemental analysis. The ^{19}F absorption of the difluoramino groups occurred at relatively low fields (ϕ −25 to −50).[5] Groups attached to primary carbon appeared near ϕ −50 while groups attached to secondary carbon appeared near ϕ −35. Coupling (J_{HF}) of fluorines on nitrogen with α-hydrogen atoms ranged between 27 and 30 cps. Infrared absorption for the difluoramino group was observed in the 800–1000-cm^{-1} region for all adducts. The common functional groups displayed absorption at characteristic frequencies.

Amides.—Several unsaturated amides, when treated with N_2F_4 in inert solvents, gave the expected addition compounds in moderate yields. They were usually obtained as viscous oils which were not amendable to distillation. In these cases, the products were purified by chromatography over silica gel using carbon tetrachloride or benzene as the eluting solvent. These products displayed characteristic infrared spectra and gave reasonably consistent elemental analysis.

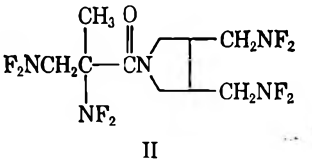
Some difficulty was experienced when N_2F_4 was allowed to react with acrylamide and its N-alkyl or dialkyl derivatives due to polymerization of the substrates at reaction temperatures. The only success realized was with N,N-diethylacrylamide which gave a 56% yield of the addition compound along with polymeric materials. Even this yield could not be duplicated consistently. Similar difficulties had previously been observed when acrylic anhydride or acryloyl chloride was treated with N_2F_4, although N_2F_4 is considered to be a very effective radical trap.[2]

Both N,N-diallylacetamide and N,N-diallylmethacrylamide failed to yield the corresponding tetrakis- or hexakis(difluoramino) derivatives when treated with excess N_2F_4, as would be expected by direct addition of N_2F_4 to all sites of unsaturation. N,N-diallylacetamide gave a bis(difluoramine) of structure I arising through a concomitant addition and cyclization reaction. This structure was assigned on the basis of the elemental analysis and ^{19}F and ^1H nmr spectra. The ^{19}F nmr spectrum displayed only overlapping triplets centered at ϕ −56.7 ($-CH_2NF_2$) for the *cis* and *trans* isomers. No absorption due to olefinic protons was observed in the ^1H nmr spectrum.



I

Similarly, N,N-diallymethacrylamide gave a tetrakis(difluoramino) derivative (II), arising *via* the addition–cyclization reaction. Identification was based on both elemental analysis and ^{19}F and ^1H nmr spectral data as described in the above case. The ^{19}F resonance absorptions were noted at ϕ −54.3 (triplet $-CH_2NF_2$) and at −27.5 (singlet $C-NF_2$) whereas the $-CH_2NF_2$ group attached to the ring showed two overlapping triplets centered at ϕ −56.5 and −56.8. No vinyl protons were present by ^1H nmr spectral analysis. Compounds containing the 1,6-heptadienyl-type system are known[6] to undergo cyclization when treated with N_2F_4 or other radical reagents. A small quantity of a second product, apparently the normal tetrakis(difluoramine), was obtained but could not be freed of the cyclic addition compound for adequate analysis.



II

(1) (a) This work was carried out under the sponsorship of the U. S. Army Missile Command, Redstone Arsenal, Ala., under Contract DA-01-021 ORD-5135. (b) Chemistry Department, Memphis State University, Memphis, Tenn. 38111.

(2) R. C. Petry and J. P. Freeman, *J. Org. Chem.*, **32**, 4034 (1967).

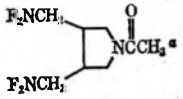
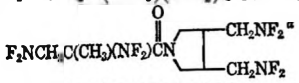
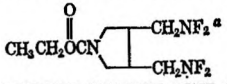
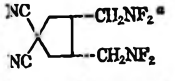
(3) A. J. Dijkstra, J. A. Kerr, and A. F. Trotman-Dickenson, *J. Chem. Soc., A*, 105 (1967).

(4) G. N. Sausen, *J. Org. Chem.*, **33**, 2336 (1968).

(5) F. A. Johnson, C. Haney, and T. E. Stevens, *ibid.*, **32**, 466 (1967).

(6) S. F. Reed, Jr., *ibid.*, **32**, 3675 (1967), and references cited therein.

TABLE I
CHARACTERIZATION DATA ON N_2F_4–OLEFIN ADDITION COMPOUNDS

Olefin	Registry no.	N_2F_4 adduct	Mp or bp (mm), °C	n_D	Calcd, % C	Calcd, % H	Calcd, % F	Calcd, % N	Found, % C	Found, % H	Found, % F	Found, % N
Amides												
N-Allylacetamide		$F_2NCH_2CH(NF_2)CH_2NHCOCH_3$			29.45	4.43	37.43	20.69	29.68	4.70	31.22	20.45
N,N-Diallylacetamide					39.51	5.35	31.27	17.28	39.19	5.52	31.63	18.05
Methacrylamide	19639-82-8	$F_2NCH_2C(CH_3)(NF_2)CONH_2$	70–71		25.39	3.69	40.21	22.22	25.26	3.49	40.44	22.69
N-Phenylmethacrylamide		$F_2NCH_2C(CH_3)(NF_2)CONHC_6H_5$			45.30	4.16	28.65	15.84	45.47	4.21	28.95	15.55
N-Methylolmethacrylamide		$F_2NCH_2C(CH_3)(NF_2)CONHCH_2OH$			27.40	4.12	34.68	19.18	28.37	4.46	34.60	19.27
N-Allylmethacrylamide		$F_2NCH_2C(CH_3)(NF_2)CONHCH_2CH(NF_2)CH_2NF_2$			25.20	3.31	45.65	21.02	25.50	3.44	45.41	21.40
N,N-Diallylmethacrylamide					32.15	4.04	40.72	18.76	32.30	4.17	41.09	19.03
N,N-Diethylacrylamide		$F_2NCH_2CH(NF_2)CON(CH_2CH_3)_2$			36.35	5.62	32.87	18.27	36.53	5.76	32.60	18.09
Allyltrifluoroacetamide		$CF_3CONHCH_2CH(NF_2)CH_2NF_2$			23.34	2.33			23.63	2.32		
Carbamates												
Ethyl N-allylcarbamate	19639-83-9	$CH_3CH_2OCONHCH_2CH(NF_2)CH_2NF_2$	95 (1)	1.4119	30.90	4.76	32.50	18.02	30.52	4.65	32.60	17.97
Ethyl N,N-diallylcarbamate				1.4414	39.56	5.49	26.37	15.38	39.00	5.57	27.10	15.72
Allyl carbamate	19639-84-0	$F_2NCH_2CH(NF_2)CH_2OCONH_2$	55–60		23.41	3.41	37.07	20.49	23.19	3.52	36.94	20.72
Isocyanates												
Vinyl isocyanate	15811-73-1	$F_2NCH_2CH(NF_2)NCO$	49 (52)	1.4169	20.81	1.73	43.93	24.27	20.70	1.89	43.66	24.47
Allyl isocyanate	19639-86-2	$F_2NCH_2CH(NF_2)CH_2NCO$	36–38 (13)	1.4140	25.65	2.67	40.60	22.45	25.51	2.79	40.35	22.69
Allyl isothiocyanate	19639-87-3	$F_2NCH_2CH(NF_2)CH_2NCS$	53–54 (0.75)	1.4752	23.65	2.43	37.46	20.67	23.81	2.48	37.28	20.84
Nitriles												
Methacrylonitrile	19639-88-4	$F_2NCH_2C(CH_3)(NF_2)CN$	44–45 (11)	1.3700	28.07	2.92	44.44	24.55	27.90	2.80	44.29	24.68
3-Butenenitrile	19639-89-5	$F_2NCH_2CH(NF_2)CH_2CN$	56–58 (1)	1.3915	28.04	2.92	44.41	24.55	28.31	2.76	44.53	24.43
1,4-Dicyano-2-butene	19639-49-7	$NCCH_2CH(NF_2)CH(NF_2)CH_2CN$			34.28	2.86	36.18	21.65	34.49	2.69	36.27	21.43
5-Cyano-1,3-pentadiene	19639-50-0	$F_2NCH_2CH(NF_2)CH{=}CHCH_2CN$[b] or $F_2NCH_2CH{=}CHCH(NF_2)CH_2CN$	88 (1)		36.55	3.56	38.54	21.33	36.61	3.38	38.77	21.61
1-Cyano-2,5-hexadiene		$F_2NCH_2CH(NF_2)CH_2CH(NF_2)CH(NF_2)CH_2CN$			26.67	2.88	48.22	22.22	26.85	2.91	47.99	22.62
4,4-Dicyano-1,6-heptadiene					43.31	4.38	30.26	22.30	43.09	4.35	30.49	22.56

[a] Major product from the reactions. [b] Isolated as a mixture.

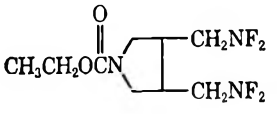
TABLE II

EXPERIMENTAL DATA FOR N_2F_4–OLEFIN REACTIONS

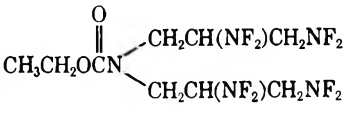
Olefin type	Olefin (mmol)	Solvent (ml)	Temp, °C	Time, hr	Yield, %
Amides	N-Allylacetamide (25)	C_6H_5Cl (50)	90	4.5	75
	N,N-Diallylacetamide (14)	CCl_4 (50)	30	15.0	91[a]
			100	4.0	
	Methacrylamide (100)	Tetrachloroethene (50)	75	5.2	83
	N-Phenylmethacrylamide (43)	C_6H_5Cl (50)	78	3.5	91
	N-Methylolmethacrylamide (55)	CCl_4 (50)	70	4.5	80
	N-Allylmethacrylamide (20)	CCl_4 (50)	80	21.0	82[b]
	N,N-Diallylmethacrylamide (10)	CCl_4 (50)	80	20.0	80[b]
	N,N-Diethylacrylamide (50)	C_6H_5Cl (25)	80	2.5	56
	Allyltrifluoroacetamide (59)	Freon 113	60	6.0	65
Carbamates	Ethyl N-allylcarbamate (52)	Freon 113	40–100	6.0	81.5
	Ethyl N,N-diallylcarbamate (59)	Freon 113	60	6.0	
	Allyl carbamate (50)	C_6H_5Cl (25)	100	24.0	93
Isocyanates	Vinyl isocyanate (100)	CCl_4 (50)	70	4.0	68
	Allyl isocyanate (50)	C_6H_5Cl (50)	100	5.4	81
	Allyl isothiocyanate (50)	CCl_4 (50)	80	6.0	84
Nitriles	Methacrylonitrile (50)	CCl_4 (50)	80	5.0	83
	3-Butenenitrile (100)	CCl_4 (50)	90	12.0	81
	1,4-Dicyano-2-butene (42)	CCl_4 (50)	92	2.0	21
	5-Cyano-1,3-pentadiene (25)	CCl_4 (25)	30	0.5	93[a]
			60	0.5	
			90	1.0	
	1-Cyano-2,5-hexadiene (30)	CCl_4 (25)	92	23.5	76[b]
	4,4-Dicyano-1,6-heptadiene (25)	CCl_4 (25)	90	6.0	97[a]
Nitro compounds	Nitroethylene (25)	CCl_4 (25)	70	2.0	No reaction
	2,3-Dinitro-2-butene (25)	CCl_4 (25)	70–90	2.0	No reaction

[a] Bis(difluoramine). [b] Tetrakis(difluoramine).

Carbamates.—The simple olefinic carbamates reacted normally with N_2F_4 to give the expected bis(difluoramino) derivatives. Addition–cyclization was again observed when ethyl diallylcarbamate reacted with N_2F_4. The cyclic product (III) represented approx-



III



IV

imately 90% of the mixture with the remaining 10% being the tetrakis(difluoramine) (IV) arising through straight addition of N_2F_4 to the sites of unsaturation. The cyclic product (*cis–trans* isomers) (III) was isolated pure by elution chromatography over silica gel. The ^{19}F nmr spectrum of III showed triplets centered at ϕ −56.1 and −56.2 ($-CH_2NF_2$), whereas the simple adduct IV showed a triplet centered at ϕ −56.8 (CH_2NF_2) and a multiplet centered at ϕ −38.8 ($CHNF_2$). Both infrared and ^1H nmr spectra were consistent with the assigned structures.

Isocyanates.—Tetrafluorohydrazine reacted with the olefinic isocyanates to give the bis(difluoramines) in good yield. These products were readily distillable to clear liquids. Allyl isocyanate reacted slowly at lower temperatures. Yields of 7, 25, and 81% were obtained from reactions conducted at 80, 90, and 100° over a 5-hr period. The isocyanate and isothiocyanate addition products reacted normally with alcohols yielding carbamates and underwent hydrolysis readily to give the substituted ureas.

Nitriles.—Tetrafluorohydrazine reacted with the simple unsaturated nitriles to give the bis(difluoramines) in high yields except for 1,4-dicyano-2-butene which reacted slowly to give a 21% yield of the adduct. Acrylonitrile gave a product prone to decompose on standing and it was found difficult to obtain acceptable analysis of this material. A mixture of bis(difluoramine) was obtained from 5-cyano-1,3-pentadiene which represented the 1,2- and 1,4-addition products (V and VI) due to 1,2 or 1,4 addition across the conju-

$$CH_2{=}CHCH{=}CHCH_2CN \xrightarrow{N_2F_4} F_2NCH_2CH(NF_2)CH{=}CHCH_2CN + F_2NCH_2CH{=}CHCH(NF_2)CH_2CN$$

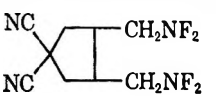
V VI

gated double-bond system. This mixture was resistent to further reaction under our conditions.[2] In contrast 1-cyano-2,5-hexadiene gave the expected tetrakis(difluoramine) (VII) and illustrates the greater ease of

$F_2NCH_2CH(NF_2)CH_2CH(NF_2)CH(NF_2)CH_2CN$

VII

N_2F_4 addition to a nonconjugated diene over addition to a conjugated diene. Cyclization was observed when N_2F_4 was treated with 4,4-dicyano-1,6-heptadiene. The major product VIII (*cis–trans* isomers) was char-



VIII

acterized by its ^{19}F nmr spectrum and elemental analysis. Triplets centered at ϕ −56.8 and −56.2 were observed in the spectrum. No evidence of olefinic protons was observed in the ^1H nmr spectrum.

Nitro Compounds.—The two nitro compounds, nitroethylene and 2,3-dinitro-2-butene, did not react with N_2F_4 or were extremely sluggish. Only nitroethylene absorbed N_2F_4; however, the reaction was limited and after 2 hr a pressure increase was noted followed by termination of the reaction. The product

mixture containing NF_2 compounds continued to decompose on standing at room temperature which precluded any attempts toward isolation. Weakly nucleophilic olefins have previously been shown to resist the N_2F_4 addition reaction.[2]

This study has shown that olefinic nitrogen compounds undergo the addition of N_2F_4 in the expected manner. It has been further demonstrated that compounds containing the 1,6-heptadienyl structure are prone to undergo an addition–cyclization reaction with the ultimate formation of bis(difluoramino) derivatives. It is important to stress the explosive character of these reaction mixtures and products. Mixtures of organic materials and N_2F_4 are potentially explosive and the products are impact-sensitive materials; hence, the experimental work should be performed with requisite precautions.

Experimental Section

Most olefins were purchased from commercial sources and used as received. The tetrafluorohydrazine employed was of 95–99% purity containing CF compounds as impurities. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrophotometer using a sodium chloride prism while nmr spectra were obtained with a Varian Associates Model V-4310 high-resolution spectrometer using a 40-Mc probe (^{19}F). An Aerograph Instrument, Model A-100-C, with a dinonyl phthalate on Chromosorb column was used for all gas chromatography work. The general experimental technique used in all reactions is described for the reaction of tetrafluorohydrazine with N,N-dimethylmethacrylamide. Experimental data for the other reactions are presented in Table II.

Tetrafluorohydrazine-N,N-Dimethylmethacrylamide.—As a typical preparative example, a thick-walled glass Aerosol tube with high-pressure fittings containing 25 ml of carbon tetrachloride and 25 mmol of N,N-dimethylmethacrylamide was attached to a high-pressure stainless steel manifold and the system deaerated by alternately evacuating to low pressure and flushing with nitrogen. The system was then charged with N_2F_4 to 65 psi, placed in an oil bath at 85°, and heated for 6 hr. The pressure was maintained between 30 and 65 psi by frequently recharging the system as necessary. On cooling the excess N_2F_4 was vented, the tube was flushed thoroughly with nitrogen, and the contents were transferred to a round-bottomed flask. On evaporation of the solvent, a dark liquid residue remained which was distilled at reduced pressure on an 18-in. Holtzman column to give 4.9 g (90%), bp 53° (0.6 mm), $n^{20}D$ 1.4262, of N,N-dimethyl-2-methyl-2,3-bis(difluoramino)propionamide. Its infrared spectrum showed absorption at 1665 (-C=O-) and 800–1000 cm^{-1} (NF_2). The ^{19}F nmr spectrum showed signals as a triplet centered at ϕ 54.3 (CH_2NF_2) and a singlet at 26.7 (CNF_2).

Anal. Calcd for $C_6H_{11}F_4N_3O$: C, 33.12; H, 5.07; F, 35.00; N, 19.35. Found: C, 33.61; H, 5.03; F, 34.77; N, 19.66.

Registry No.—Tetrafluorohydrazone, 10036-47-2; N,N-dimethyl-2-methyl-2,3-bis(difluoramino)propionamide, 19639-91-9.

Acknowledgment.—The technical assistance of Mr. F. Hooper and Mr. J. O. Woods is greatly appreciated.

The Mechanism of Alcoholysis of Carboxylic Acid Halides in the Presence of Triethylamine

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The alcoholysis of carboxylic acid halides in the presence of triethylamine and a hydrocarbon solvent proceeds by two competing pathways, an elimination–addition process involving a ketene intermediate and a substitution process involving an acyl quaternary ammonium intermediate. Evidence for the ketene intermediate was obtained by performing the reaction in the presence of methanol-*d* and measuring the proportion of monodeuterated ester (in the absence of polydeuterated ester). The products obtained from the isomeric butenoyl chlorides provide further evidence for the competitive processes and suggest the interconversion of the two intermediates. The effects of the leaving group and of the structure of the acyl halide are also presented.

The reaction of acyl chlorides, possessing α hydrogens, with tertiary amines is an old and commonly used method for the synthesis of ketenes,[1] and is often used for *in situ* generation as in cycloadditions[2] and other reactions typical of ketenes. Having demonstrated the role of sulfene intermediates in the triethylamine-induced alcoholysis of sulfonyl chlorides,[3] the mechanism of alcoholysis of acid chlorides in the presence of triethylamine was investigated by like methods and is reported herein. To determine the relative participation of ketene intermediates, the alcoholysis was carried out using methanol-*d* (MeOD). The ester arising from the reaction of ketene with methanol-*d* would be monodeuterated. The absence of dideuterated ester would preclude deuterium incorporation by simple exchange.

Results

A number of carboxylic acid halides and acetic anhydride were treated with ordinary methanol and methanol-*d* in the presence of triethylamine. The procedure involved adding a solution of the acid halide to a stirred solution of methanol and triethylamine in an inert solvent (pentane, hexane, or octane) at 0°. The identity of the esters was verified by comparison of physical properties with literature values and by nmr[4] analysis. Nmr analysis was also used to show that deuterium incorporation occurred on the carbon α to the carbonyl carbon. The esters were subjected to low voltage mass spectral analysis[5] (used to eliminate the P − 1 peak) to determine the amount of deuterium incorporation[6] and

(1) W. E. Hanford and J. C. Sauer, *Org. Reactions*, **3**, 124 (1947).

(2) G. Opitz and M. Kleeman, *Ann. Chem.*, **665**, 114 (1963).

(3) W. E. Truce and R. W. Campbell, *J. Amer. Chem. Soc.*, **88**, 3599 (1966).

(4) The nmr spectra were obtained using a Varian A-60 or A-60A spectrometer at a sweep width of 500 cps with tetramethylsilane (TMS) as internal standard.

(5) Mass spectra were run at the Purdue Mass Spectral Center on a Hitachi RMU-6a instrument.

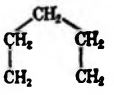
(6) K. Biemann, "Mass Spectrometry," McGraw Hill Book Co., Inc., New York, N. Y., 1962, pp 212–228.

TABLE I

MASS SPECTRAL DATA AND PER CENT MONODEUTERATION FOR ESTERS

$R_1R_2CHCOX \longrightarrow R_1R_2CHCO_2CH_3$

D

R_1[a]	R_2	X	P − 1[b]	P + 1	P + 2	% mono deuteration[c]
H	H	F	0	3.8		0
H	H	Cl	0	67.5	3.6	39
H	H	Br	0	45.2	3.5	29
H	H	I	0	23.4	3.3	16
H	H	CH_3CO_2	0	8.4		5
CH_3	H	Cl	9.9	52.3	4.5	33
CH_3	H	Br	8.7	45	2.9	29
CH_3CH_2	H	Cl	44.5	41.9	5.8	30
CH_3	CH_3	Cl	20.3	6.1		0
CH_3	CH_3	Br	4.7	6.2		0
CH_3CH_2	CH_3CH_2	Cl	0[d]	8.7		0
		Cl	0	9.4		0
Cl	H	Cl	0	51	40	32
Cl	Cl	Cl	3[e]	72	67	41
C_6H_5O	H	Cl	0	39.2	4.1	22
C_6H_5	H	Cl	0	74	8.8	39
C_6H_5[f]	H	Cl	0	72	8.5	38
C_6H_5	H	Cl	0	344	35.1	77[g]
C_6H_5	C_6H_5	Cl	0	30	3.9	12

[a] Solvents: When $R_1 = R_2 = H$, octane was used as solvent. When $R_1 = C_6H_5O$ and $R_2 = H$ and when $R_1 = R_2 = C_6H_5$, hexane was used as solvent. In all other cases (except footnote *f*), pentane was used as solvent. [b] P, parent peak (molecular ion) in mass spectra. P = 100 in all cases except as noted. [c] All values were reproducible within ±1%. [d] *m/e* 99 used as P. [e] *m/e* 83 used as P. [f] Benzene used as solvent. [g] Eight equivalents of CH_3OD were used in the reaction.

TABLE II

ALCOHOLYSIS OF BUTENOYL CHLORIDES

Acid chloride	Alcohol	% CH_2=$CHCH_2CO_2R$	% CH_3CH=$CHCO_2R$
CH_2=$CHCH_2COCl$	CH_3OD	100 (40% deuterated)[a]	0
CH_3CH=$CHCOCl$	CH_3OD	60 (67% deuterated)[a]	40
CH_3CH=$CHCOCl$	CH_3CH_2OH	92	8

[a] Nmr shows that deuterium incorporation occurs α to the carbonyl carbon.

to establish that monodeuteration occurred exclusively. Mass spectral data and per cent monodeuteration for the following reaction are summarized in Table I.

$$R_1R_2CHCOX + Et_3N + MeOD \longrightarrow R_1R_2CH(D)CO_2Me + Et_3NH(D)Cl$$

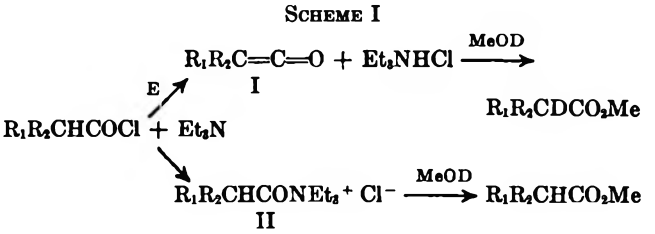
That deuterium incorporation occurs only from the addition of methanol-*d* to the ketenes and not by any simple exchange mechanisms is supported by the following experimental observations. (1) Only monodeuteration occurs. Any exchange process should give significant polydeuteration. (2) When methyl phenylacetate or methyl dichloroacetate, methanol-*d*, triethylamine, and triethylamine deuteriochloride (100% deuterated by nmr) are stirred in hexane for 4 hr at 0°, no deuterium incorporation occurs.[7] (3) When phenylacetyl chloride, triethylamine, and methanol are allowed to react in the presence of triethylamine deuteriochloride (insoluble in medium), again no deuterium incorporation is detected.

2-Butenoyl chloride and 3-butenoyl chloride were subjected to reactions with methanol and methanol-*d* in the presence of triethylamine. 3-Butenoyl chloride yielded only methyl 3-butenoate which was 40% monodeuterated, whereas 2-butenoyl chloride yielded a mixture of the isomeric esters.[8] The isomer distribution and per cent deuterium incorporation are given in Table II and nmr data is presented in Table III.

Discussion

The formation of both monodeuterated and undeuterated esters under the reaction conditions suggests a competition between two reaction pathways, the most likely being competing substitution and elimination processes involving the acyl halide and triethylamine (Scheme I). A ketene (I) would arise from an elimina-

SCHEME I



(7) When methyl phenylacetate was stirred *8 days* at room temperature with the same materials 9% monodeuteration was measured.

(8) The product ratios were determined by nmr. The deuterium incorporation was measured by mass spectral analysis on the product from 3-butenoyl chloride and was determined by nmr on the products from 2-butenoyl chloride. The isomer distributions were determined on crude material prior to distillation.

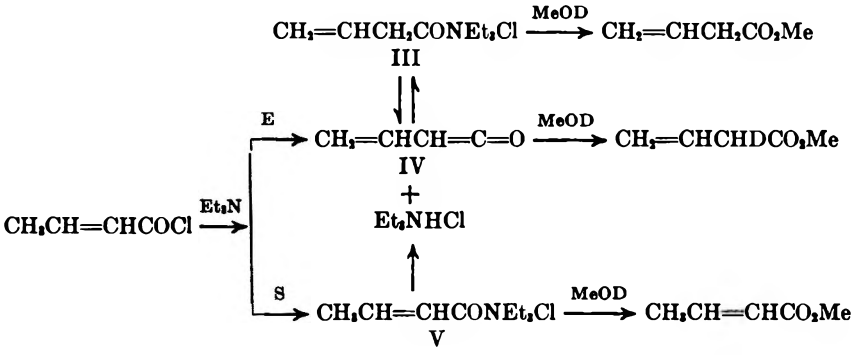
TABLE III

NMR DATA FOR BUTENOATE ESTERS

a b c g
CH_2=CH—$CH_2CO_2CH_3$ d e f g
CH_3CH=$CHCO_2CH_3$

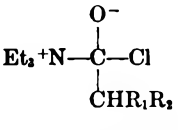
Ester	1.9	3.2	3.8	5.2	6.0	7.1	Relative area
CH_2=$CHCH_2CO_2CH_3$		c (two triplets)	g (singlet)	a (two multiplets)	b (multiplet)		2:3:2:1
CH_3CH=$CHCO_2CH_3$	d (two doublets)		g (singlet)		f (two quartets)	e (sextet)	3:3:1:1
Products from 2-butenoyl chloride + methanol	d (two doublets)	c (two triplets)	g (doublet)	a (two multiplets)	b, f (multiplet)	e (sextet)	1.4:1.1:3 1:1:0.4

SCHEME II



tion reaction and would yield a monodeuterated ester upon reaction with methanol-*d*. However, the intermediate of the substitution reaction, possibly the acyl quaternary ammonium salt (II), would undergo displacement by methanol-*d* to yield an undeuterated ester.

The formation of monodeuterated ester is ample evidence for the ketene intermediate. There is also strong precedent for the acyl quaternary ammonium salt. It is well known that tertiary amines catalyze the acylation of amines, alcohols, and phenols by acid chlorides and anhydrides.[9] Even the hydrolysis of some acid derivatives such as acetyl phosphate[10] and acetic anhydride[11] is strongly catalyzed by even small amounts of pyridine. In most of these reactions an acyl quaternary ammonium salt intermediate has been proposed and in some instances these salts have been prepared and shown to be intermediates. Adkins and Thompson[12] have prepared, isolated, and analyzed several acyl quaternary ammonium chlorides from acid chlorides and triethylamine or pyridine. These salts have also been prepared from α,β-unsaturated acid chlorides and tertiary amines.[13,14] There is evidence that a tetrahedral adduct may precede formation of the salt.[11,15,16]



When phenylacetyl chloride reacts in the presence of excess methanol-*d*, the amount of monodeuteration almost doubles (39 to 77%). This indicates that a considerable amount of the initially formed ketene (I) collapses with triethylamine hydrochloride yielding the quaternary ammonium intermediate (II), which then reacts with methanol-*d* producing undeuterated ester. In the presence of excess methanol-*d* the ketene is trapped more efficiently, thus accounting for the tremendous increase in deuterium incorporation.

Further evidence for the competing elimination and substitution pathways and the proposed interconversion of I and II is provided using the isomeric butenoyl chlorides (Table II and Scheme II). The following experimental observations should be considered.

(1) When 3-butenoyl chloride is treated with methanol-*d* under the reaction conditions only methyl 3-butenoate (40% monodeuterated) is formed. This indicates that only 1,2 addition of methanol-*d* to the ketene (CH_2=CHCH=C=O) is possible since 1,4 addition would result in the conjugated isomer.

(2) When 2-butenoyl chloride is treated with methanol-*d* and triethylamine, 60% methyl 3-butenoate (67% deuterated[17]) and 40% methyl 2-butenoate (undeuterated) are formed. Methyl 2-butenoate can arise only from the substitution pathway since the intermediate ketene (IV) produced by elimination can only yield methyl 3-butenoate by 1,2 addition. Therefore in this system, the elimination is favored 3:2. Further, since the final product of the elimination route, methyl 3-butenoate, is not completely deuterated (67%), it is probable that some of ketene IV is collapsing to the triethylammonium complex (III) which gives undeuterated ester.

(3) When 2-butenoyl chloride is treated with *ethanol*, 92% ethyl 3-butenoate and 8% ethyl 2-butenoate are formed in contrast to 60 and 40% for the corresponding methyl esters. Since the formation of intermediates from the acyl chloride and triethylamine is the same in both cases, it is probable that the reaction of ethanol with the quaternary ammonium derivative (V) is slower than methanol, thus giving V a greater opportunity to

(9) M. L. Bender, *Chem. Rev.*, **60**, 77 (1960).
(10) D. E. Koshland, Jr., *J. Amer. Chem. Soc.*, **74**, 2286 (1952).
(11) V. Gold and E. G. Jefferson, *J. Chem. Soc.*, 1406 (1953).
(12) H. Adkins and Q. E. Thompson, *J. Amer. Chem. Soc.*, **71**, 2242 (1949).
(13) H. E. Baumgarten, *ibid.*, **75**, 1239 (1953).
(14) P. W. Hickmott, *J. Chem. Soc.*, 883 (1964).
(15) C. A. Bunton and T. A. Lewis, *Chem. Ind.* (London), 180 (1956).
(16) R. F. Hudson, *Chimia* (Aarau), **15**, 394 (1961).

(17) The methyl 3-butenoate is more highly deuterated than that formed from 3-butenoyl chloride since in its formation it must proceed through a ketene intermediate, whereas that produced from 3-butenoyl chloride can result from either the elimination or substitution mechanism.

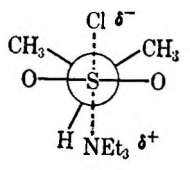
convert into ketene IV. Payne[18] has shown that the acyl quaternary ammonium chloride formed from 3-methylcrotonyl chloride and trimethylamine is convertible into the following corresponding ketene which was trapped by 1,2 cycloaddition to ethyl vinyl ether.

$$CH_2{=}\overset{CH_3}{\overset{|}{C}}CH{=}C{=}O$$

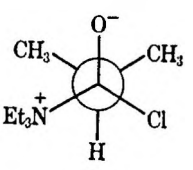
Thus the experiments with the isomeric butenoyl chlorides are consistent with the existence of competing elimination–addition and substitution mechanisms and indicate that the respective intermediates are interconvertible.

As the effectiveness of the leaving group is increased in these systems, the amount of monodeuteration shows a steady decrease [CH_3COX (X = Cl, 39%; X = Br, 29%; X = I, 16%; X = OAc, 5%)]. A very small but opposite effect was observed in the methanesulfonyl system [CH_3SO_2X (X = Cl, 47.7%; X = Br, 48.3%; X = CH_3SO_3, 53%)].[3] Although the rate of both the substitution and elimination should be increased by increasing the effectiveness of the leaving group, in the carboxylic acid halide system it appears that the substitution mechanism is enhanced more than the competing elimination.

All experiments with dialkylacetyl chlorides resulted in no deuterium incorporation. This is in direct contrast to the sulfonyl chlorides[3] in which an increase in monodeuteration is observed (propanesulfonyl chloride, 47.5%; isopropanesulfonyl chloride, 57%). With the sulfonyl chlorides it was suggested that the substitution mechanism was less favored owing to steric interactions between the pentavalent sulfonyl intermediate (VI) and the two α-methyl groups thus making the elimination (sulfene) route in which steric effects are decreased[19] more attractive. However, with the acyl chloride the intermediate (VII) would be tetra-



VI



VII

valent and inhibition to the substitution mechanism would not be so important. Ugi and Beck[20] have shown that α,α-alkyl disubstitution has little effect on the rate of hydrolysis of acid chlorides in aqueous acetone [$k \times 10^4$/sec; $CH_3CH_2CH_2COCl$, 5.85; $(CH_3)_2CHCOCl$, 4.41]. However, it is known[21] that alkyl substitution can greatly affect the rate of ionization of acidic hydrogens (k_1; $CH_3COCH_2COCH_3$, 1.0; $CH_3COCHCH_3COCH_3$, 5×10^{-3}). Thus with alkyl disubstituted acid chlorides the elimination sequence is less favorable owing to decreased acidity of α hydrogens. However, if the acidity of the α hydrogens is increased sufficiently, even disubstituted acetyl chlorides will undergo elimination and incorporate deuterium (See dichloro- and diphenylacetyl chloride in Table I).

(18) G. B. Payne, *J. Org. Chem.*, **31**, 718 (1966).
(19) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1962, p 488.
(20) I. Ugi and F. Beck, *Chem. Ber.*, **94**, 1839 (1961).
(21) R. G. Pearson and R. L. Dillon, *J. Amer. Chem. Soc.*, **75**, 2439 (1953).

It should be realized that, since the intermediates of the two pathways are interconvertible, no strict rules can be laid down to explain each case. For example, the fact that propionyl chloride, chloroacetyl chloride and phenylacetyl chloride give similar results is rather distressing. However, it is reasonable that the chlorine and phenyl group are able to stabilize the ketene by π overlap, making it less reactive with the alcohol and thus giving it a greater opportunity to recombine with the triethylamine hydrochloride to give the intermediate of the substitution pathway.

In summary the preceeding work has shown that the alcoholysis of acyl halides possessing α hydrogens proceeds by competing elimination–addition and substitution mechanisms, the intermediates of which are interconvertible.

Experimental Section

Materials.—Triethylamine (Matheson Coleman and Bell reagent), methanol-*d* (Volk, 100% O-D; Merck Sharp and Dohme, 99% O-D), methanol (Baker Analyzed Reagent), *n*-pentane (Phillips 66, 99% pure), hexane (Baker Analyzed Reagent), *n*-octane (Matheson Coleman and Bell), benzene (Baker Analyzed Reagent), acetyl chloride (Mallinckrodt), acetyl bromide (Eastman), acetyl iodide (Columbia), acetyl fluoride (Hynes, Columbia) phenylacetyl chloride (Eastman, Matheson Coleman and Bell), propionyl chloride (Eastman), propionyl bromide (Eastman), isobutyryl chloride (Eastman), isobutyryl bromide (Eastman), 2-ethylbutyryl chloride (Eastman), cyclohexane carbonyl chloride (Eastman), phenoxyacetyl chloride (Eastman), diphenylacetyl chloride (Columbia), chloroacetyl chloride (Eastman), dichloroacetyl chloride (Eastman), crotonyl chloride (Eastman), butyryl chloride (Eastman), and 3-butenoic acid (Columbia) were used. 3-Butenoyl chloride was prepared from 3-butenoic acid and thionyl chloride.

General Procedure for the Reaction of Acyl Halides with Alcohol and Triethylamine.—The following procedure was used for all acyl halides except the acetyl halides. The acyl halide (0.10 mol) dissolved in pentane (50 ml) or hexane (50 ml) was added dropwise to a stirred solution of triethylamine (0.10 mol) and alcohol (0.10 mol) in pentane (60 ml) or hexane (60 ml) at 0–5° in a 200-ml three-neck round-bottom flask equipped with an addition funnel, mechanical stirrer, and reflux condensor. The system was flame dried prior to use and the reactions were run under nitrogen. After stirring for a total of 4 hr at 0° the triethylamine hydrohalide (almost quantitative yield) was removed by filtration. The solvent was then removed on a Rinco rotary evaporater and the ester was purified by distillation.[22]

General Procedure for the Reaction of Acetyl Halides and Acetic Anhydride with Alcohol and Triethylamine.—The acetyl halide (0.10 mol) dissolved in octane (25 ml) was added dropwise to a stirred solution of triethylamine (0.10 mol) and alcohol (0.10 mol) in octane (25 ml) at 0–5° in a 100-ml three-neck flask equipped with an addition funnel, mechanical stirrer, and reflux condensor. The mixture was allowed to stir a total of 4 hr. Any solid ammonium salt was removed by filtration,[23] and the methyl acetate was then distilled directly from the reaction solution.

Check on Hydrogen–Deuterium Exchange between Methyl Phenylacetate and Methanol-*d* in the Presence of Triethylamine and Triethylamine Deuteriochloride under the Reaction Conditions.—Methyl phenylacetate (0.05 mol), triethylamine (0.05 mol), methanol-*d* (0.055 mol), and triethylamine deuteriochloride[24] (0.05 mol) were stirred in pentane (60 ml) at 0° for 4 hr. The pentane, methanol-*d*, and triethylamine were removed on a rotary evaporater and the remaining methyl phenylacetate was

(22) Methyl diphenylacetate was sublimed [45° (1 mm), mp 60–61°]. The product ratio of methyl butenoates was determined by nmr after evaporation of pentane but prior to distillation.
(23) No ammonium salt was isolated from acetyl fluoride or acetic anhydride.
(24) The triethylamine deuteriochloride was isolated from the reaction of isobutyryl chloride with methanol-*d* and triethylamine and was shown to be 100% deuterated by nmr.

purified by distillation. Low voltage mass spectral analysis showed the ester to be completely undeuterated.

A similar check on hydrogen–deuterium exchange between methyl dichloroacetate and methanol-*d* was made. Before work-up the reaction mixture was treated with acetyl chloride. The triethylamine hydrochloride was filtered, and the pentane and methyl acetate were removed on a rotary evaporater, leaving the methyl dichloroacetate which was shown to be undeuterated by nmr analysis.

Reaction of Phenylacetyl Chloride with Methanol in the Presence of Triethylamine and Triethylamine Deuteriochloride.—Phenylacetyl chloride (0.10 mol) dissolved in pentane (50 ml) was added dropwise to a stirred mixture of methanol (0.10 mol), triethylamine (0.10 mol), and triethylamine deuteriochloride (0.10 mol) in pentane (60 ml) at 0°. The reaction was worked up according to the general procedure yielding methyl phenylacetate which was shown to be completely undeuterated by mass spectral analysis.

Registry No.—Triethylamine, 121-44-8; methyl 3-butenoate, 3724-55-8; methyl 2-butenoate, 18707-60-3.

Acknowledgment.—The authors wish to express their appreciation for financial support of this work by Public Health Service Research Grant No. CA 04536-10 from the National Cancer Institute and by National Science Foundation Grant No. GP 05175.

Photochemical Oxidations. II. Rate and Product Formation Studies on the Photochemical Oxidation of Ethers

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The rates of oxygen uptake during the photochemical oxidation of ethers have been determined. The rates correlate with the orders of basicity of acyclic and cyclic ethers to substantiate further the earlier postulated role of charge-transfer complexes in the photochemical oxidation of ethers. The products of the ether oxidations were determined for an acyclic ether, diethyl ether, and for a cyclic ether, tetrahydrofuran. Mechanisms are postulated for the products formed which involve hydroperoxide intermediates.

Work done by Chien has shown that the excitation of charge-transfer complexes is partially responsible for the photooxidation of hydrocarbons.[2] Also, in a previous publication we have presented evidence that the initial step in the photooxidation of diethyl ether is the absorption of light by a charge-transfer complex of molecular oxygen with ether.[3] In this paper we shall discuss additional studies on this reaction in which a series of ethers, both cyclic and acyclic, were used. The discussion will center on the mechanistic implications of the results of an analysis of the products formed and the relative rates of reaction as indicated by both the rates of oxygen uptake and product formation during irradiation.

All of the ethers studied (Table I) reacted when they were saturated with oxygen and irradiated. The ethers had been previously subjected to a rigorous purification to eliminate the possibility of impurities participating in the reactions. On being irradiated for several hours, each of the ethers gave a mixture of products, but a major product was always the ester or lactone. In addition, each irradiated reaction mixture contained peroxides. Since it has been previously shown that trimethylene oxide[4] and propylene oxide[5] may undergo photochemical decomposition, these compounds were first irradiated under a nitrogen atmosphere to see if they would decompose under the conditions used in these experiments. The results indicate that they do not decompose, and therefore we can be sure that the reaction observed with oxygen is not due to photodecomposition of ethers.

TABLE I

O_2 UPTAKE AFTER 1 HR AND pK_a VALUES FOR ETHERS

	O_2 uptake, mol	pK_a
Diethyl ether	2.0×10^{-3}	−3.59
Di-*n*-propyl ether	1.3×10^{-3}	−4.40
Diisopropyl ether	1.1×10^{-3}	−4.30
Di-*n*-butyl ether	0.9×10^{-3}	−5.40
Propylene oxide	0.1×10^{-3}	
Trimethylene oxide	2.7×10^{-3}	
Tetrahydrofuran	2.2×10^{-3}	−2.08
Tetrahydropyran	1.2×10^{-3}	−2.79

Diethyl ether and tetrahydrofuran, as representative cyclic and acyclic compounds, were chosen for a more detailed examination. As the irradiation time was decreased to a few minutes, it was found that tetrahydrofuran gave three products, butyrolactone, α-hydroxytetrahydrofuran, and water (see Figure 1). Thus the other unidentified compounds found for the longer irradiation times are formed as the result of secondary reactions. It is likely that some of these are the products of the photodecomposition of butyrolactone.[6] On the other hand, the products found when diethyl ether is irradiated, *i.e.*, ethyl acetate, ethyl formate, ethyl alcohol, and acetaldehyde,[7] appear even when the reaction is run for a very short time (Figure 2). Thus, it would seem that the cyclic and acyclic ethers may have slightly different reaction mechanisms.

That the mechanism involves the excitation of charge-transfer complexes for both cyclic and acyclic ethers with the difference in the reaction path for the two series occurring after this step can be inferred also from an examination of the relative rates of oxygen

(1) Taken in part from Ph.D. thesis, C. T. Wang, University of North Dakota, 1969.

(2) J. C. W. Chien, *J. Phys. Chem.*, **69**, 4317 (1965).

(3) V. I. Stenberg, R. D. Olson, C. T. Wang, and N. Kulevsky, *J. Org. Chem.*, **32**, 3227 (1967).

(4) J. D. Margerum, J. N. Pitts, Jr., J. G. Rutgers, and S. Searles, *J. Amer. Chem., Soc.*, **81**, 1549 (1959).

(5) R. Gomer and W. A. Noyes, Jr., *ibid.*, **72**, 101 (1950).

(6) R. Simonaites and J. N. Pitts, Jr., *ibid.*, **90**, 1389 (1968).

(7) The presence of acetaldehyde was verified by vpc. It could not be trapped owing to its low concentration. Its well-known photodecomposition most probably is the cause of its low concentration.

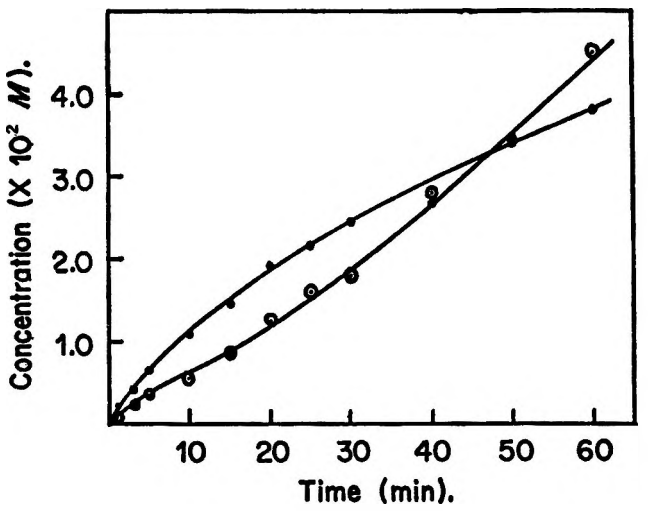


Figure 1.—Rates of product formation during the photooxidation of tetrahydrofuran. The products are butyrolactone, ⊙, and peroxide •. These data were obtained using a flame ionization detector which is insensitive to water.

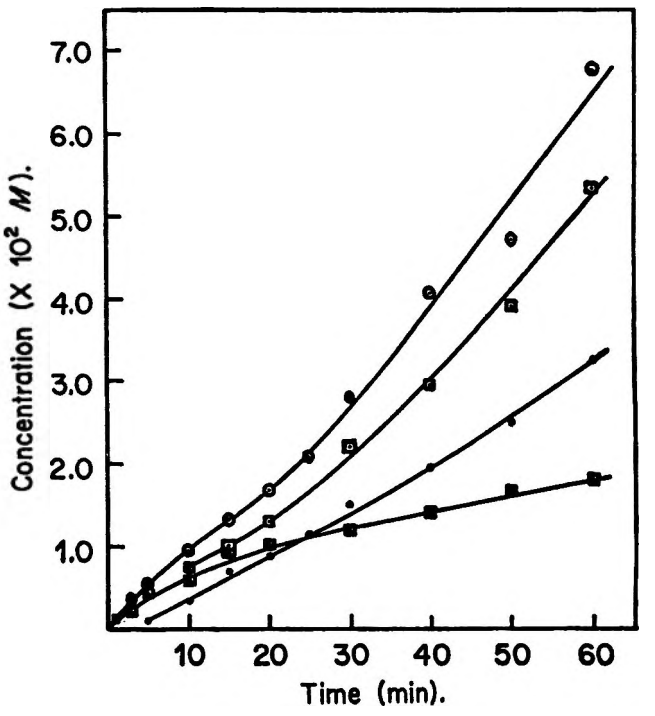


Figure 2.—Rates of product formation during the photooxidation of diethyl ether. The rates illustrated are for ethyl acetate, ⊙, ethyl alcohol, ⊡, ethyl formate •, and peroxide, ◪.

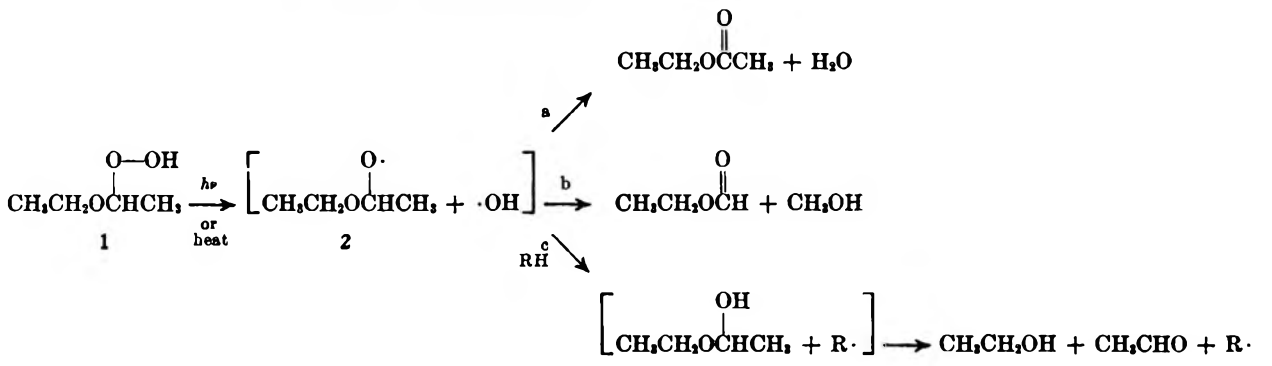
uptake during irradiation. The results of these experiments are shown in Table I, where the amount of oxygen uptake after 1 hr for the several ethers is presented. During this time, only *ca.* 2% of the reaction has taken place and thus the effects of the secondary reactions mentioned above are minimal. Each of the values given have been corrected for the relative solubility of oxygen in the different ethers, using diethyl ether as the standard. Since the formation of the complex is the initial step in the reaction, it might be expected that there would be a correlation between ability to form a complex and the rate of reaction. As a measure of the complexing ability we have chosen the pK_a values of the ethers (Table I).[8] If all of the compounds are examined, there is a poor correlation. However, if the cyclic and acyclic ethers are grouped separately, it can be seen that, in each group, there is a correlation in which the rate of reaction decreases with decreasing basicity. Although the results show an inversion in the order of *n*-propyl and isopropyl ethers, both the differences in basicity and oxygen uptake are small. If these differences are meaningful, the inversion can be attributed to steric factors. The O_2 molecule is larger than the hydrogen ion, and thus its ability to interact with isopropyl ether is less than that of the hydrogen ion.

For propylene oxide and trimethylene oxide, there are no values of pK_a reported; however, the basicity of these compounds toward $CHCl_3$[9] and I_2[10] indicate that the basic order is four- > five- > six- > three-membered cyclic ethers. Propylene oxide, the weakest base is also the least reactive of the ethers studied here. The weak basicity of propylene oxide is also indicated by the ultraviolet (uv) spectra of oxygen-saturated solutions. All of the ethers except propylene oxide, when saturated with oxygen, show a very great enhancement of absorption in the 280- to 210-mμ region, which is attributed to the charge-transfer complex. The propylene oxide–oxygen solution has only a very small absorption peak in this region even though oxygen is more soluble in propylene oxide than in several of the other ethers, thus indicating its very weak basicity. This order of basicity of propylene oxide also correlates well with the spectroscopic work of Fleming, *et. al.*[11] The fact that there is a correlation of rate with basicity within each series indicates that a major feature of the reaction is the formation of the charge-transfer complex. Since the two series cannot be correlated with each other, we can again assume that there is a difference in the mechanism of the reaction as it involves cyclic and acyclic compounds.

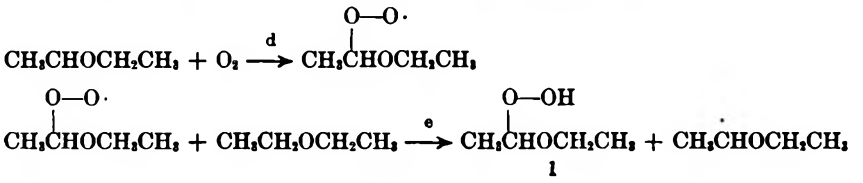
To further explain the differences observed between cyclic and acyclic compounds, the detailed mechanism of the reaction must be examined. The initial step as postulated before[2] must be the excitation of the charge-transfer complex to form the intermediate peroxide. Three modes of decomposition of the peroxide (Scheme I) are suggested to explain the products found. Reaction pathways a and c have been proposed earlier[12] to explain the products derived from the ozonation of ethers, where a similar intermediate, the radical 2, has also been proposed. Reaction b is both new and unexpected; however, considering the bond energies involved when a C–C bond is broken and a C–O bond along with a π-C–O bond is formed, it is quite reasonable. It is noteworthy that the ozonation of diethyl ether also gives ethyl formate.[13] On the basis of statistical considerations, RH in reaction c would be another molecule of ether. It is likely that the well-known nonphotochemical reactions d and e (Scheme II) assume importance once the peroxide concentration has reached a respectable level by means of the excitation of the complex. The reactions d and e are chain-

(8) (a) E. M. Arnett and C. Y. Wu, *J. Amer. Chem. Soc.*, **84**, 1680 (1962); (b) *ibid.*, **84**, 1684 (1962).
(9) S. Searles and M. Tamres, *ibid.*, **73**, 3704 (1951).
(10) M. Brandon, M. Tamres, and S. Searles, Jr., *ibid.*, **82**, 2129 (1960).
(11) G. Fleming, M. M. Anderson, A. J. Harrison, and L. W. Pickett, *J. Chem. Phys.*, **30**, 351 (1959).
(12) For a review, see P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).
(13) (a) F. G. Fisher, *Ann.*, **476**, 233 (1929); (b) *ibid.*, **486**, 83 (1931).

SCHEME I
THE THREE MODES OF DECOMPOSITION OF THE PEROXIDE OF DIETHYL ETHER



SCHEME II
CHAIN PROPAGATION REACTIONS FOR THE GENERATION OF PEROXIDE



propagation reactions which continually add to the concentration of 1 in the reaction mixture.

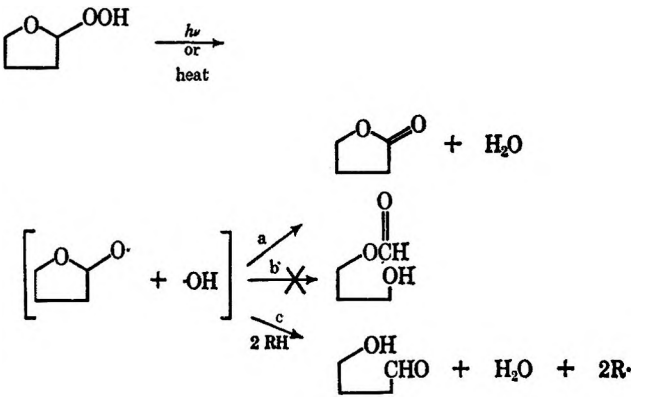
The lack of induction periods in the reactions of ethers is especially interesting, when compared with the induction periods observed during the photochemical oxidation of hydrocarbons.[2] There are two sources of the peroxide intermediates in the ether reaction solutions. The first is directly from the charge-transfer complex and the second is from the chain processes of reactions d and e. That no induction period is observed can be attributed to the rate of reaction of the charge-transfer complex exceeding the rate of formation of peroxide from reactions d and e, both initially and after the steady-state concentration of the peroxide has been obtained. In the case of hydrocarbons the analogous reaction rates might not be in the same ratio because the concentration of the complexes in the hydrocarbon solution is much lower owing to a lesser basicity than ethers; thus, an induction period is observed in these reactions.

Also noteworthy in the reaction of diethyl ether with oxygen is that after a period of time the rate decreases with time rather than increases. The uv absorption of ethyl acetate, one of the principal products, is such [λ_{max} 204 mμ (ϵ 60)] that it acts as an internal filter for the absorption of the charge-transfer complex of ether and oxygen. Hence, after *ca.* 3% ethyl acetate has been formed in the reaction mixture, the oxygen uptake is greatly retarded.

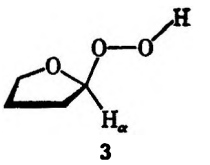
In direct contrast to the diethyl ether reaction is the tetrahydrofuran–oxygen reaction in which the principal isolable products are water, α-hydroxytetrahydrofuran, and butyrolactone. The water is formed much more rapidly in this reaction solution than for the reaction of diethyl ether. This clearly illustrates that, for tetrahydrofuran, paths analogous to reactions a and c for diethyl ether are the predominant reactions (Scheme III). However, it appears that path b is not operative for tetrahydrofuran.

Stereochemical effects must cause the nearly rigid ring system of the tetrahydrofuran to change the

SCHEME III
THE PHOTOOXIDATION OF TETRAHYDROFURAN



pattern of formation of products. The principal conformation of the hydroperoxide of tetrahydrofuran is shown in structure **3**. This conformation minimizes the spacial interaction of the hydrogens and oxygen of the ring with the peroxide group. In this conformation the OH of the peroxide is *cis* in its orientation to the H_α. When the O–O bond is broken, the hydroxy radical is in the vicinity of H_α and removes it in preference to reacting with the carbon chain (path b).[14]



3

These radicals also abstract a hydrogen atom from solvent (path c). Thus, paths a and c are the predominant paths for the cyclic ether, whereas paths a, b, and c are all allowed in a freely rotating ether such as diethyl

(14) NOTE ADDED IN PROOF.—In more current work, there is evidence that butyrolactone is also formed directly from the excitation of tetrahydrofuran and oxygen.

ether. This concept of *cis* elimination in a free-radical reaction is a good illustration of stereochemical requirements for radical reactions.

Experimental Section

Reagents.—Diethyl ether and tetrahydrofuran (Fisher reagent grade), di-*n*-propyl ether and tetrahydropyran (from Matheson Coleman and Bell), diisopropyl ether (from Eastman Organic Chemicals), and di-*n*-butyl ether (spectroquality reagent, from Matheson Coleman and Bell) were purified as described previously[3] except, instead of lithium aluminum hydride, sodium borohydride was used in the purification of tetrahydropyran. Purified diisopropyl ether and tetrahydropyran were further fractionally distilled in a Wheeler GE-125-2H "All Glass" fractionating column to remove traces of benzene. Trimethylene oxide (from Aldrich Chemical) and propylene oxide (from Eastman Organic Chemicals) were fractionally distilled over dry KOH, using the Wheeler column and the center cut of the distillations were collected. The purity of the ethers was checked by uv spectra and no detectable amount of impurities were shown. The ethers were then stored under nitrogen prior to use. The oxygen used in this work was brought from the Linde Co. and was specified as 99.69% pure.

Apparatus.—The photooxidations of ethers in the liquid phase were carried out in a cylindrical quartz reaction cell 30 cm long and 2.5-cm outside diameter. The top of the cell was connected, by means of a graded seal, to a three-way Teflon stopcock. The upper part of the cell was blanked out by aluminum paint so that the light irradiated only the liquid phase of the sample. The cell was then connected by glass tubing, with Tygon joints for flexibility, to a gas reservoir. The latter consisted of a mercury manometer and a Teflon stopcock for the admission of oxygen and for connection to the grease-free vacuum pumpout system. A 550-W Hanovia high pressure mercury arc lamp, mounted in a water-cooled immersion well, was used as a source of uv radiation. The reaction cell and the immersion well were immersed in a water bath through which distilled water, monitored for uv transparency, was circulated at 15 ± 0.25° from a constant-temperature bath. The arc was 3.0 cm from the front of the reaction cell. The reaction cell was very carefully cleaned before each run with ethanolic potassium hydroxide. It was then rinsed well with distilled water and dried under vacuum.

The operation of the complete apparatus, when making an oxygen uptake determination, is described as follows. The reaction cell was connected to the gas reservoir and the whole system was evacuated and then filled with 1 atm of oxygen. From the stopcock on the top of the cell 5 ml of ether was introduced into the reaction cell by means of a syringe with a long needle. The cell was then quickly closed, and the whole system was again filled with oxygen up to 1.5 atm. The ether was vigorously stirred by means of a small glass-covered magnetic stirring bar, and sufficient time was allowed for thermal equilibrium. Practically, there was no oxygen uptake before irradiation. After irradiation, subsequent manometric readings were made at 1-hr intervals and were computed as number of moles of oxygen uptake. The irradiations of the different ethers were taken in random fashion to avoid systematic error. Each ether was irradiated several times and the values reported in Table I are averages.

Solubility of Oxygen in Ethers.—The solubilities were determined by making use of the Van Slyke–Neill manometric apparatus which is based upon the principle of extracting the gas from the solvent and measuring the pressure of the liberated gas.[15] Solubilities of oxygen in eight different ethers at 15.0°, under oxygen pressures of 1 atm and 1.5 atm, were determined. The vapor pressure of ether needed for calculation of solubility was determined by the conventional isoteniscope method.

Product Determination.—The irradiation products of diethyl ether and tetrahydrofuran were preliminarily analyzed by preparative gas chromatography using an Aerograph Autoprop A-700 equipped with a Carbowax column (10 ft × $^3/_8$ in.). The identification of the products was accomplished by the usual instrumental methods, *i.e.*, comparing their ir (using Beckman IR-12) and nmr (using Varian A-60) spectra with those of the authentic samples. The product yield as a function of irradiation time was determined by injecting each freshly irradiated sample into a Varian Aerograph 1200 gas chromatograph equipped with a flame ionization detector and a Carbowax column (10 ft × $^1/_4$ in.). Quantitative measurements were made by comparing the irradiated samples with that of standard solutions. The analytical procedure used for all hydroperoxide estimations was the method described by Wagner, *et al.*[16] This iodometric determination was made immediately after each irradiation and was reproducible. α-Hydroxytetrahydrofuran was quantitatively determined by ir spectroscopy and identified as the 2,4-dinitrophenylhydrazone.

Registry No.—Diethyl ether, 60-29-7; di-*n*-propyl ether, 111-43-3; diisopropyl ether, 108-20-3; di-*n*-butyl ether, 142-96-1; propylene oxide, 75-56-9; trimethylene oxide, 503-30-0; tetrahydrofuran, 109-99-9; tetrahydropyran, 142-68-7.

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(15) F. S. Orcutt and M. H. Seevers, *J. Biol. Chem.*, **117**, 501 (1936).
(16) C. D. Wagner, R. H. Smith, and E. D. Peters, *Anal. Chem.*, **19**, 976 (1947).

Synthesis of 11-Hydroxy-2,3,9,10-tetramethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine. A Contribution to the Structure of Stepharotine[1]

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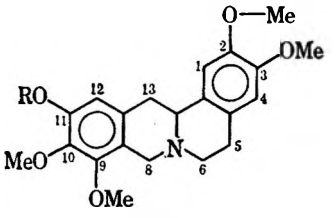
(±)-11-Hydroxy-2,3,9,10-tetramethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine (1) has been prepared by reduction of 11-hydroxy-2,3,9,10-tetramethoxybenzo[a]acridizinium bromide (13), afforded by hydrobromic acid catalyzed cyclization of quaternary salt 12 formed when 2,3-dimethoxy-4-hydroxybenzyl bromide (11) reacts with 6,7-dimethoxyisoquinoline-1-carboxaldoxime. Benzyl bromide 11 was prepared in four steps from the known 2,3-dimethoxy-4-hydroxybenzoic acid 7. The infrared spectrum of the title compound differs significantly from that of the alkaloid stepharotine.

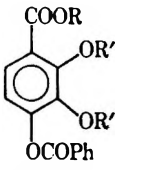
Tomita, Kozuka, and Uyeo[2] have isolated from the root of the *Stephania rotunda Loureiro* a new levorotatory phenolic base to which they have given the name stepharotine. Since stepharotine on methylation with diazomethane gave a product spectroscopically identical with synthetic 2,3,9,10,11-pentamethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine (2) prepared by a modification of the method of Späth and Meinard,[3]



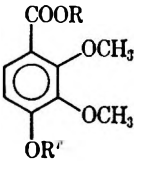
1, R = H
2, R = Me
3, R = Ph

and since phenyl ether 3 on reduction with metallic sodium in liquid ammonia gave a product identified as tetrahydropalmatine, the alkaloid was assigned the structure 11-hydroxy-2,3,9,10-tetramethoxy-5,6,13,-13a-tetrahydro-8H-dibenzo[a,g]quinolizine (1). The present communication describes the first synthesis of 1.

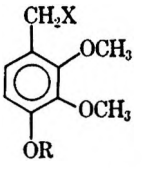
In order to apply the general method developed earlier[4,5] for the synthesis of tetrahydroberberine derivatives, it was necessary to have available the unknown 2,3-dimethoxy-4-hydroxybenzyl bromide (11). The most promising starting material appeared to be the 2,3-dimethoxy-4-hydroxybenzoic acid (7) of Pascu.[6] Unfortunately, the structure assigned by Pascu to this important compound had been placed in serious doubt by the subsequent work of Critchlow, Haworth, and Pauson,[7] who reported that, like 3,5-diacetoxy-4-benzoxybenzoic acid,[8] Pascu's intermediate, 2,3-diacetoxy-4-benzoyloxybenzoic acid (4), when heated with hydrochloric acid underwent not only the expected hydrolysis of the acetoxy groups, but also *ortho* migration of the benzoyl group. This claim was backed by the observation that reacetylation of the hydrolysis product did not lead back to the starting material 4, and that an elaborate transformation of the hydrolysis product afforded a substituted phthalic acid of a structure explicable only on the basis of rearrangement. These earlier observations, coupled with our own, that the melting point of the dihydroxybenzoxybenzoic acid obtained by hydrolysis of 2,3-diacetoxy-4-benzoyloxybenzoic acid (4) was 250–252° instead of 211° as reported by Pascu,[6] or 227° as reported by the British authors,[7] led us to examine as carefully as possible all lines of evidence bearing on the structure of our products.



4, R = H; R' = Ac
5, R = H; R' = H
6, R = Me; R' = Me



7, R = R' = H
8, R = Me; R' = H
9, R = Me; R' = $PhCH_2$



10, X = OH; R = $PhCH_2$
11, X = Br; R = H (not isolated)

Like Pascu we found that our dihydroxybenzoyloxybenzoic acid (5) on reacetylation gave back the original diacetoxy compound (4). Under no hydrolysis conditions, including those recommended by Critchlow, *et al.*,[7] were we able to obtain a product in which the benzoyl group had migrated. An attempt to decarboxylate our sample of 2,3-dihydroxy-4-benzoyloxybenzoic acid resulted in the evolution of carbon dioxide at 255° and the crude, easily oxidized decarboxylation product was methylated with an excess of diazomethane and subjected to vapor phase chromatography. On a column which could separate authentic samples of 1,2-dimethoxy-3-benzoyloxybenzene and 1,3-dimethoxy-2-benzoyloxybenzene the methylated decarboxylation product of 5 gave evidence (peak matching) of being largely the 1,2-dimethoxy-3-benzoyloxybenzene with no trace of the isomer.

(1) This research was supported by Public Health Service Research Grant No. H-2170 of the National Heart Institute.

(2) M. Tomita, M. Kozuka, and S. Uyeo, *Yakugaku Zasshi*, **86**, 460 (1966); *Chem. Abstr.*, **65**, 10633 (1966).

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(5) C. K. Bradsher and N. L. Dutta, *J. Org. Chem.*, **26**, 2231 (1961).

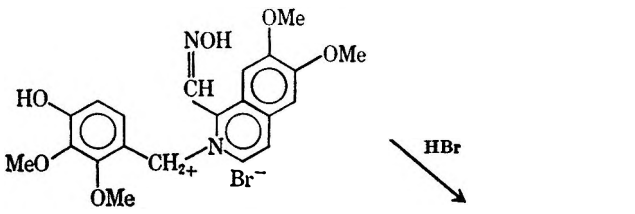
(6) E. Pascu, *Ber.*, **56**, 407 (1923).

(7) A. Critchlow, R. D. Haworth, and P. L. Pauson, *J. Chem. Soc.*, 1318 (1951).

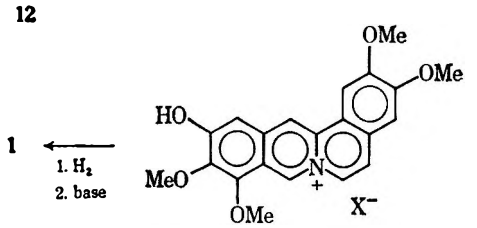
(8) E. Fischer, M. Bermann, and W. Lipschitz, *Ber.*, **51**, 45, 71 (1918).

It seems probable that the significant difference in the melting point of 2,3-dihydroxy-4-benzoyloxybenzoic acid (**5**) observed by us and that reported by Pascu may be a typographical error since good correspondence was found in the physical constants of the dimethyl ether–methyl ester (**6**) and its alkaline hydrolysis product (**7**). The nmr spectrum of hydroxy ester **8** in dimethyl sulfoxide solution was compared with that of its anion according to the directions of Highet and Highet.[9] The base-induced upfield shift of the signals due to the aromatic protons (0.73 and 0.30 ppm) corresponds well with the values reported[9] for one aromatic hydrogen *meta* and one *ortho* to the hydroxyl group, where there is a carbonyl group in the *para* position.

The hydroxy ester was converted in excellent yield into its benzyl ether (**9**) for the lithium aluminum hydride reduction. The reduction product (**10**) was a liquid which could not be distilled, but was obtained analytically pure by chromatography. No method was found for the conversion of the 4-benzyloxy-2,3-dimethoxybenzyl alcohol (**10**) into the corresponding benzyl bromide without simultaneous cleavage of the benzyl ether linkage to afford 2,3-dimethoxy-4-hydroxybenzyl bromide (**11**). Bromide **11** was very unstable and best results were obtained when it was prepared quickly at low temperature by the reaction of hydrogen bromide on alcohol **10**. The crude bromide was allowed to react in anhydrous dimethylformamide with an excess of 6,7-dimethoxyisoquinoline-1-carboxaldoxime[6] affording an over-all yield (from **10**) of the expected quaternary salt **12** of 25%. Cyclization of salt **12** in hydrobromic acid afforded an 84% yield of 11-hydroxy-2,3,9,10-tetramethoxybenzo[*a*]acridizinium bromide (**13**).



12



13, X = Br
14, X = ClO_4
15, X = picrate

Catalytic reduction of **13** over Adams catalyst followed by addition of sodium carbonate afforded 11-hydroxy-2,3,9,10-tetramethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[*a*,*g*]quinolizine (**1**). Methylation of base **1** with diazomethane afforded pentamethoxy derivative **2** identical with an authentic sample prepared by a modification of the directions of Späth and Meinard.[3] Comparison, under the same conditions, of the infrared spectrum of our hydroxy base (**1**) in carbon tetrachloride solution with that of an authentic sample of stepharotine revealed that the two samples are not spectroscopically identical. It is not remarkable that our racemic product **1**, mp 190–192°, should be higher melting than the optically active stepharotine, but it does appear significant that the supposedly pure stepharotine base should be so low melting that it has never been obtained in a crystalline form. An impurity in natural stepharotine might be responsible for the observed differences in ir spectra or the natural product may have a structure other than **1**.

While the structure of our hydroxy base (**1**) could be regarded as demonstrated by the synthetic method used, additional support is afforded by physical evidence. Our hydroxy base (**1**), when heated in dimethyl sulfoxide containing deuterium chloride in deuterium oxide, undergoes exchange of one aromatic hydrogen which must therefore be either *ortho* or *para* to the hydroxyl group.[10] Since the upfield shift (0.22 ppm) observed when hydroxy base **1** was converted into the anion[9] is so small, the possibility that there is an aromatic proton *para* to the hydroxyl group could be eliminated.

Experimental Section[11]

2,3-Dihydroxy-4-benzoyloxybenzoic acid (**5**) was made by hydrolysis of 2,3-acetoxy-4-benzoyloxybenzoic acid[6] as described by Pascu.[6] Since the melting point observed, 250–252°, was significantly higher than previously reported (lit.[6] mp 210–211°) the product was submitted for elemental analysis.

Anal. Calcd for $C_{14}H_{10}O_6$: C, 61.31; H, 3.67. Found: C, 61.31; H, 3.64.

Even when the specific directions of Critchlow, Haworth, and Pauson[7] were followed, only the product reported above was obtained and no isomeric acid, mp 227°, was found. Also in contrast to the report of the British authors[7] we found that reacetylation of the product, as reported by Pascu,[6] leads back to 2,3-diacetoxy-4-benzoyloxybenzoic acid, mp 162–164°, identified by infrared spectra and mixture melting point.

Decarboxylation of 2,3-Dihydroxy-4-benzoyloxybenzoic Acid (**5**).—**5** was decarboxylated when heated at 255° for 5 min. The crude product was dissolved in methanol and an excess of an ether solution of diazomethane added. After 2 days the solvents were removed under reduced pressure and the residual oil, which could not be crystallized, was subjected to vapor phase chromatography on an F & M Model 402 apparatus using a 1.2-m 4% SE-30 on an Aeropack-30 column at 160° which had previously been demonstrated to be capable of separating authentic samples of 1-benzoxy-2,6-dimethoxybenzene[12] and 1-benzoxy-2,3-dimethoxybenzene.[12] The oil was shown (peak-matching technique) to be free of 1-benzoxy-2,6-dimethoxybenzene and to contain a considerable quantity of 1-benzoxy-2,3-dimethoxybenzene.

2,3-Dimethoxy-4-hydroxybenzoic Acid (**7**).—4-Benzoyloxymethyl ester **6**, mp 79–81° (lit.[6] mp 79–80°), and hydroxy acid **7**, mp 154–156° (lit.[6] 154–155°), were prepared essentially as described by Pascu.[6] We have confirmed Pascu's observations concerning the elemental analysis for both benzoate and hydroxy acid and the failure of the hydroxy acid to give a color with ferric chloride solution. Hydroxy acid **7** is not easily decarboxylated and on heating either sublimes or undergoes deep-seated decomposition.

An authentic sample of 3,4-dimethoxy-2-hydroxybenzoic acid, mp 170–172°, prepared[13] for comparison, gave a strong

(9) R. J. Highet and P. F. Highet, *J. Org. Chem.*, **30**, 902 (1965).

(10) G. W. Kirby and L. Ogunkoya, *J. Chem. Soc.*, 6914 (1965).

(11) Analyses were by Janssen Pharmaceutica Research Laboratories, Beerse, Belgium, or by Galbraith Laboratories, Knoxville, Tenn. The ultraviolet absorption spectra were measured in 95% ethanol using 1-cm quartz cells in a Cary Model 14 spectrometer. All nmr measurements are in reference to tetramethylsilane as an internal standard and unless otherwise indicated were made with a Varian A-60 spectrometer.

(12) J. Hertzig and J. Pollak, *Monatsh.*, **25**, 519 (1904).

(13) F. Mauthner, *J. Prakt. Chem.*, [2] **89**, 304 (1914); *cf.*, E. Späth and F. Boschau, *Monatsh.*, **63**, 141 (1933).

purple color with ferric chloride and was shown by mmp 133–138° and infrared spectrum to be different from 7.[14]

Methyl 2,3-Dimethoxy-4-hydroxybenzoate (8).—A slow stream of hydrogen chloride was passed through a solution of 9.9 g of hydroxy acid 7 in 30 ml of methanol for about 1 hr. The solution was allowed to stand overnight at room temperature and concentrated under vacuum. The residual colorless oil solidified on standing at room temperature. The ester was recrystallized from chloroform–petroleum ether (bp 60–90°) as colorless aggregates: mp 86–88°; yield 10 g (95%).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.75; H, 5.57.

The nuclear magnetic resonance spectrum of **8** in dimethyl sulfoxide was compared with that of the sodium salt in the same solvent following the directions of Highet and Highet.[9] The two aromatic protons (AB quartet) in basic solution showed an upfield shift of 0.73 and 0.30 ppm. From the data obtained by Highet and Highet for simple *p*-carbonyl phenols these observations appear to correspond well with one *ortho* (lit.[9] 0.60–0.84 ppm) and one *meta* proton (lit.[10] 0.22–0.47 ppm).

Methyl 2,3-Dimethyl-4-benzyloxybenzoate (9).—A mixture of 10.6 g of hydroxy ester **8**, 8.55 g of benzyl bromide, 0.5 g of potassium iodide, and 5 g of anhydrous potassium carbonate in 250 ml of dry acetone was stirred and refluxed for 12 hr. The solids were removed by filtration and washed with acetone. The combined filtrates were concentrated under vacuum and benzene was added to the residual oil to precipitate dissolved salts. Removal of the remaining salts by filtration, followed by concentration of the filtrate and distillation of the residue, afforded 13.8 g (92%) of pale yellow oil, bp 175–180° (0.3 mm).

Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.53; H, 6.00. Found: C, 67.07; H, 6.00.

2,3-Dimethoxy-4-benzyloxybenzyl Alcohol (10).—A solution of 12.01 g of ester **9** in 50 ml of anhydrous ether was added dropwise to a stirred suspension containing 3.04 g (excess) of lithium aluminum hydride in 80 ml of dry ether. The mixture was refluxed for 8 hr, then decomposed with ethyl acetate and worked up in the usual way. The resulting orange oil was dissolved in 20 ml of carbon tetrachloride and passed through a neutral alumina column (10 × 3 cm) followed by elution with 150 ml of carbon tetrachloride. Evaporation of the solvent, finally at 100° under reduced pressure, yielded 10.4 g (95%) of a pale yellow viscous oil of analytical purity. Attempts to distil the oil at 0.3 mm resulted in extensive decomposition.

Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61. Found: C, 69.99; H, 6.46.

N-(2′,3′-Dimethoxy-4′-hydroxybenzyl)-6,7-dimethoxy-1-carboxaldoximinoisoquinolinium Bromide (12).—A solution of 2.74 g of benzyl alcohol **10** in 20 ml of methylene chloride was maintained at 0° protected from moisture and mechanically stirred while a slow stream of hydrogen bromide (dried by passage through concentrated sulfuric acid at 0°) was passed through for 10 min. After an additional 15 min most of the excess hydrogen bromide was entrained by passing dry nitrogen through the solution. Anhydrous magnesium sulfate (5 g) was added and the mixture stirred an additional 30 min under a nitrogen atmosphere. The magnesium sulfate was removed by filtration and washed with methylene chloride as rapidly as possible to avoid contact with the moisture of the air. The combined filtrates were evaporated *in vacuo* in a rotary evaporator at 20–25° and the resulting light brown viscous oil was maintained at 0° for 1 hr at 0.1-mm pressure and finally dry nitrogen was passed through until the oily product reached constant weight (3.4–3.8 g). The crude bromide obtained in this way is unstable and decomposes on standing for a few hours at room temperature. It appears to be destroyed if the temperature reaches as high as 35–40° during the evaporation procedure or if the reaction with hydrogen bromide is allowed to continue too long.

Nmr observations on the crude oil showed it to have undergone cleavage of the benzyloxy group affording an impure sample of 2,3-dimethoxy-4-hydroxybenzyl bromide (**11**). Attempts to prepare a bromide by the use of phosphorus tribromide instead of hydrogen bromide failed.

(14) It was felt important to make this distinction between 3,4-dimethoxy-2-hydroxybenzoic acid and 2,3-dimethoxy-4-hydroxybenzoic acid (**7**) since the experiment involving the decarboxylation of the intermediate 2,3-dihydroxy-4-benzoyloxybenzoic acid (**5**) did not eliminate the possibility that the correct structure of the intermediate was 3,4-dihydroxy-2-benzoxybenzoic acid.

The crude bromide described above was dissolved with shaking in a warm solution of 2.82 g (excess) of 6,7-dimethoxyisoquinoline-1-carboxaldoxime[5] in 29 ml of pure anhydrous dimethylformamide[15] and the mixture allowed to stand for 7 days at room temperature in a well-stoppered flask. If a precipitate formed it was collected and washed with a few drops of dimethylformamide. The crystals were identified as the hydrobromide (mp 190–192°) of 6,7-dimethoxyisoquinoline-1-carboxaldoxime identified by comparison with an authentic sample.

The filtrate was mixed with 200 ml of anhydrous ether and 200 ml of ethyl acetate and allowed to stand for 6 hr at −15°. The solvents were then decanted and the viscous green residue was dissolved in 10 ml of methanol and precipitated by the addition of a mixture containing acetone, ether, and ethyl acetate in a ratio 40:20:10. The crude yellow crystals were recrystallized from methanol affording 1.2–1.3 g (25–27%) of very pale yellow aggregates, mp 209–211°.

Anal. Calcd for $C_{21}H_{23}BrN_2O_6$: C, 52.61; H, 4.83; Br, 16.67; N, 5.84. Found: C, 52.81; H, 4.79; Br, 16.35; N, 5.67.

11-Hydroxy-2,3,9,10-tetramethoxybenzo[*a*]acridizinium Bromide (13).—A solution of 1.19 g of quaternary salt **12** in 8 ml of 48% hydrobromic acid was heated on a steam bath for 30 min. The reaction mixture turned deep orange and yellow crystals usually formed. Methanol (16 ml) was added and the product allowed to crystallize. The product was recrystallized from methanol as orange-yellow needles: mp 246–248° dec; λ_{max} 220 mμ (log ε 4.05), 240 sh (4.12), 244 (4.13), 275 sh (4.12), 305 (4.34), 312 sh (4.33), 337 (4.08), 367 sh (3.71), 415 sh (3.69), 438 (3.78). The crystals turned dark within a few days.

Anal. Calcd for $C_{21}H_{20}BrNO_5 \cdot 1.5\ H_2O$: C, 53.30; H, 4.89; N, 2.96. Found: C, 53.64, 53.67; H, 4.70, 4.54; N, 2.89, 2.96.

The **perchlorate** was obtained as a very insoluble yellow powder which was purified simply by refluxing it in methanol for several minutes: mp 323–324° dec.

Anal. Calcd for $C_{21}H_{20}ClNO_9 \cdot 1H_2O$: C, 52.13; H, 4.58; N, 2.89. Found: C, 52.55; H, 4.31; N, 2.86.

The **picrate** was likewise very insoluble and was purified in the same way affording orange crystals, mp 225–257° dec.

Anal. Calcd for $C_{27}H_{22}N_4O_{12}$: C, 54.54; H, 3.73; N, 9.42. Found: C, 54.55; H, 3.65; N, 9.42.

11-Hydroxy-2,3,9,10-tetramethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[*a*,*g*]quinolizine (1).—A suspension of 500 mg of the benzacridizinium compound (**13**) and 200 mg of platinum oxide catalyst in 150 ml of methanol was hydrogenated at atmospheric pressure and room temperature. After 5 hours, the theoretical quantity of hydrogen had been absorbed and the reaction was stopped. The catalyst was removed by filtration and the solution was evaporated to dryness. The crude hydrogenation product was suspended in 15 ml of water, the mixture was brought to pH 8.0–8.5 by the addition of 2 *N* sodium carbonate solution, and the base was extracted with methylene chloride. The dark red organic solution was treated with Norit, filtered through Supercel, and finally evaporated to dryness. The pale orange crystals were twice recrystallized from methanol affording very pale yellow aggregates: rectangular prisms; mp 192–193° dec; λ_{max} 224 mμ sh (log ε 3.96), 273 sh (3.36), 283 (3.55), 292 sh (3.38); nmr ($CDCl_3$) τ 6.17, 6.14 (each s, 3, CH_3), 6.11 (s, 6, two CH_3), 4.57 (s, 1, OH), 3.53, 3.36, 3.25 (each s, 1, aromatic H).

Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.90; H, 6.78; N, 3.77; OCH_3, 33.42. Found: C, 68.05, 67.67; H, 6.79, 6.82; N, 3.68, 3.60; OCH_3, 33.21, 33.41.

When the nmr of the base **1** was determined in dimethyl sulfoxide-d_6 and compared with the nmr of the sodium salt of the anion,[9] one aromatic proton signal was shifted upfield by only 0.22 ppm while the other two proton signals were relatively unaffected (<0.05 ppm). While this shift is lower than that reported[9] for aromatic hydrogens *ortho* to a hydroxyl group (0.42–0.59) it is not unlikely that the result could be rationalized by a study of models more closely related to **1**.

(15) The dimethylformamide was purified as recommended in Houben-Weyl, "Methoden der organischen Chemie," Vol. I, Part 2, George Thieme, Stuttgart, Germany, 1959, p 831. Probably owing to the great sensitivity of the 2,3-dimethoxy-4-hydroxybenzyl bromide to moisture, no quaternary salt was formed when unpurified commercial dimethylformamide was used, a large part of the 6,7-dimethoxyisoquinoline-1-aldoxime being recovered as the hydrobromide.

When base 1 was dissolved in dimethyl sulfoxide-d_6 and a solution of deuterium chloride in deuterium oxide added, the resulting salt solution displayed signals for the individual aromatic protons at τ 3.28, 3.16, and 2.98. After the mixture had been heated for 24 hr at 100° only the aromatic proton signal at τ 3.28 had disappeared.

The **hydrobromide** crystallized from methanol as colorless needles: mp 258–260° dec; $\lambda_{max}^{95\% EtOH}$ 224 mμ sh (log ε 3.91), 273 sh (3.34), 282 (3.53), 288 sh (3.51), 290 sh (3.42).

Anal. Calcd for $C_{21}H_{28}BrNO_5$: C, 55.78; H, 5.79; N, 3.09; OCH_3, 27.50. Found: C, 55.66; H, 5.80; N, 3.03; OCH_3, 27.41.

Comparison of 11-Hydroxy-2,3,9,10-tetramethoxy-5,6,13,13a-tetrahydro-8H-dibenzo[*a*,*g*]quinolizine (1) with Stepharotine.—About 1 mg of stepharotine hydrobromide was dissolved in water and the base liberated by addition of ammonia solution. The mixture was evaporated to dryness under reduced pressure. The residue was extracted with methylene chloride, filtered, and concentrated under reduced pressure, and the residue taken up in carbon tetrachloride.

The infrared spectrum of the resulting solution was determined using a 2-μl microcell with a Perkin-Elmer Model 21 spectrophotometer. Our hydroxy base (1) measured in the same way showed significant differences, particularly in the 8–11-μ region. Similar differences were reported to us by Dr. Kozuka who kindly compared our hydroxy base (1) with stepharotine, using chloroform as the solvent and making the infrared measurements with a Hitachi instrument.

2,3,9,10,11-Pentamethoxy-5,6,13,13a-tetrahydro-8H-dibenzo-[*a*,*g*]quinolizine (2).—To a solution of 300 mg of hydroxy base 1 in 50 ml of acetone, 1.6 g (excess) of diazomethane in 150 ml of ether was added followed by 20 ml of methanol. After 12 hr at 0° the mixture was allowed to stand 48 hr at room temperature before removal of the solvents and excess diazomethane under reduced pressure. The residue was dissolved in 50 ml of methylene chloride, then chromatographed on neutral alumina (8 × 1 cm column), and eluted with 75 ml of the same solvent. The yellow oil obtained by evaporation was crystallized from methylene chloride–ether affording 200 mg (64%) of almost colorless rectangular needles, mp 138–140° (lit.[3] mp 148–149°). In our hands a sample of the pentamethoxy compound (2) prepared by a method essentially that of Tomita, *et al.*, also melted at 138–140°. Samples of 2 prepared by the methylation of the hydroxy base and by the method of Tomita, *et al.*,[2] were found identical by means of infrared spectra and the mixture melting point: $\lambda_{max}^{75\% EtOH}$ 224 sh (log ε 3.97), 275 sh (3.34), 283 (3.48), 286 sh (3.44), 293 sh (3.30); nmr ($CDCl_3$) τ 6.20, 6.14, 6.10 (each s, 3, CH_3), 6.16 (s, 6, two CH_3), 3.52, 3.39, 3.26 (each s, 1, aromatic H).

Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.47; H, 7.11; N, 3.62.

Registry No.—**1**, 19598-17-5; 1 HBr, 19598-18-6; **2**, 7668-86-2; **5**, 19587-70-3; **8**, 19587-71-4; **9**, 19587-72-5; **10**, 19587-73-6; **12**, 19613-63-9; **13**, 19587-74-7; **14**, 19587-75-8; **15**, 19587-76-9.

Acknowledgment.—The authors wish to acknowledge the gracious cooperation of Drs. M. Tomita and M. Kozuka in providing us with a sample of stepharotine and of the synthetic[2] pentamethoxy compound 2 as well as numerous nmr and infrared spectra. We are also indebted to Mr. Ernest C. Sunas of the Liggett and Myers Research Laboratories for a spectrometric comparison of our hydroxy base with stepharotine and to Dr. Charles G. Moreland of North Carolina State University for some 100-Mc nmr measurements.

The Resolution and Absolute Configuration of the Racemic Isomer of Anaferine

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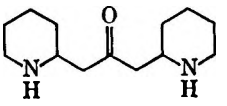
The absolute configuration of the isomers of the alkaloid anaferine, 1,3-bis(2-piperidyl)-2-propanone, was established by ORD analysis of the hydrochloride and the base obtained from the resolved dimandelates and of the isomers of pipecolic acid derived from the hydrochlorides. L-(+)-1,3-bis(2-piperidyl)-2-propanone is (*S*,*S*)-(+)-1,3-bis(2-piperidyl)-2-propanone and D-(−)-1,3-bis(2-piperidyl)-2-propanone is (*R*,*R*)-(−)-1,3-bis-(2-piperidyl)-2-propanone.

Anaferine (1) [1,3-bis(2-piperidyl)-2-propanone] was reported for the first time as a naturally occurring compound by Rother, *et al.*, in 1962.[1] This compound was originally obtained by Anet, *et al.*,[2] in their attempted synthesis of sparteine by condensation of 5-aminopentanal with acetonedicarboxylic acid at pH 11. It has also been synthesized by Schöpf, *et al.*,[3] by condensation of Δ^1-piperideine and acetonedicarboxylic acid at pH 11.5. Later it was prepared in this laboratory[4] in admixture with hygrine, cuscohygrine, anahygrine, and isopelletierine (2) from Δ^1-piperideine, 2-hydroxy-1-methylpyrrolidine, and acetonedicarboxylic acid at pH 12.

Three stereoisomers are possible: (+)-, (−)-, and *meso*-1,3-(2-piperidyl)-2-propanones. Schöpf, *et al.*,[3] separated *meso*- and DL-1,3-bis(2-piperidyl)-2-propanones as the hydrobromides and picrates. Anaferine isolated from *Withania somnifera* corresponds to the *meso* isomer.[5]



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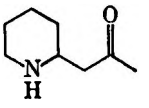

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We have separated *meso*-1,3-bis(2-piperidyl)-2-propanone as the L-(+)- and D-(−)-dimandelate, (+)-1,3-bis(2-piperidyl)-2-propanone as the L-(+)-dimandelate, and (−)-1,3-bis(2-piperidyl)-2-propanone as the D-(−)-dimandelate. Using L-(+)-mandelic acid to resolve the isomeric mixture, *meso*-1,3-bis(2-piperidyl-2-propanone L-(+)-dimandelate and (+)-1,3-bis(2-piperidyl)-2-propanone L-(+)-dimandelate

(1) A. Rother, J. M. Bobbitt, and A. E. Schwarting, *Chem. Ind.* (London), 654 (1962).

(2) E. F. L. J. Anet, G. K. Hughes, and E. Ritchie, *Aust. J. Sci. Res.*, **3A**, 635 (1950).

(3) C. Schöpf, G. Benz, F. Braun, H. Hinkel, and R. Rokohl, *Angew. Chem.*, **65**, 161 (1953).

(4) M. M. El-Olemy, A. E. Schwarting, and W. J. Kelleher, *Lloydia*, **29**, 58 (1966).

(5) A. E. Schwarting, J. M. Bobbitt, A. Rother, C. K. Atal, K. L. Khanna, J. D. Leary, and W. G. Walter, *ibid.*, **26**, 258 (1963).

were obtained sequentially. In the same manner, using D-(−)-mandelic acid, *meso*-1,3-bis(2-piperidyl)-2-propanone D-(−)-dimandelate, and (−)-1,3-bis-(2-piperidyl)-2-propanone D-(−)-dimandelate were obtained. Each of the dimandelate salts was converted into the corresponding dihydrochloride and dipicrate.

(+)-1,3-Bis(2-piperidyl)-2-propanone dihydrochloride yielded L-(−)-pipecolic acid and (−)-1,3-bis(2-piperidyl)-2-propanone dihydrochloride yielded D-(+)-pipecolic acid on chromic acid oxidation. (+)-1,3-Bis(2-piperidyl)-2-propanone thus possesses the L configuration and (−)-1,3-bis (2-piperidyl)-2-propanone the D configuration.

Optical rotatory dispersion curves obtained for (+)- and (−)-1,3-bis(2-piperidyl)-2-propanone dihydrochlorides as well as (+)- and (−)-1,3-bis(2-piperidyl-2-propanone bases, generated from this salt, gave curves (Figure 1) which, when compared with those[6] of (+)- and (−)-isopelletierine sulfates and bases (2), confirm the conclusion that (+)-1,3-bis-(2-piperidyl)-2-propanone possesses the L configuration and (−)-1,3-bis(2-piperidyl)-2-propanone the D configuration.

ORD curves obtained for the pipecolic acid enantiomers obtained from the oxidation of (+)- and (−)-1,3-bis(2-piperidyl)-2-propanone dihydrochlorides corresponded to the curves of reference L-(−)- and D-(+)-pipecolic acids and are similar to those reported by Craig and Roy.[7] These data prove unambiguously that (−)- and (+)-1,3-bis(2-piperidyl)-2-propanones possess the D and L configuration, respectively.

Thus L-(+)-1,3-bis(2-piperidyl)-2-propanone is (*S*,*S*)-(+)-1,3-bis(2-piperidyl)-2-propanone[8] and D-(−)-1,3-bis(2-piperidyl)-2-propanone is (*R*,*R*)-(−)-1,3-bis-(2-piperidyl)-2-propanone.

Experimental Section[9]

Δ^1-Piperideine (≡ α-Tripiperideine) (4).—This compound, prepared according to the procedure of Schöpf, *et. al.*,[10] gave mp 59–60° (lit.[10] mp 61–62°).

Preparation of 1,3-Bis(2-piperidyl)-2-propanone Isomers.—Δ^1-Piperideine (2.28 g) was dissolved in 0.1 *N* sodium hydroxide solution (150 ml). Acetonedicarboxylic acid (2 g) was added and the reaction was conducted as previously described.[4] Analysis by tlc[9] showed the presence of *meso*- and DL-1,3-bis(2-piperidyl)-2-propanone and isopelletierine (2) (R_f 0.68).

The mixture (3 g) was separated by a countercurrent distribution system.[4] The mixture, distributed in the first four tubes, was carried through 95 transfers to provide the anaferine isomers (tubes 65–90) and isopelletierine (tubes 50–64).

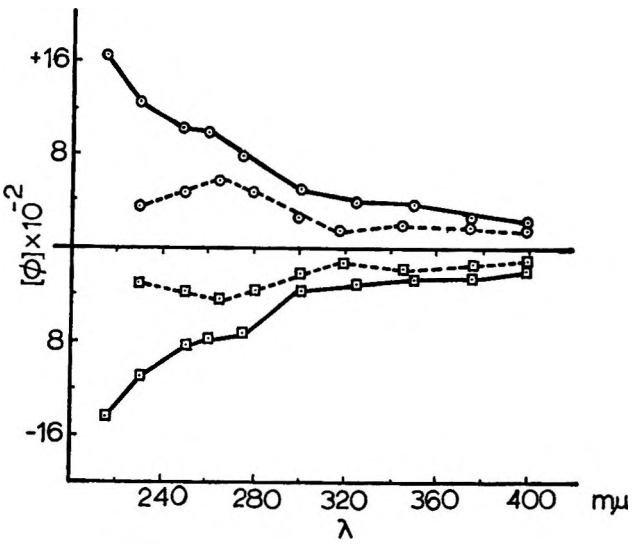

Figure 1.—Optical rotatory dispersion of (+)-1,3-bis(2-piperidyl)-2-propanone dihydrochloride (—⊙—), (+)-1,3-bis(2-piperidyl)-2-propanone (- -⊙- -), (−)-1,3-bis(2-piperidyl)-2-propanone dihydrochloride (—⊡—), and (−)-1,3-bis(2-piperidyl)-2-propanone (- -⊡- -).

The hydrochloride was prepared by dissolving the isomeric mixture in anhydrous ether and anhydrous methanol. Dry hydrogen chloride was passed through the solution and the mixture was refrigerated. The crystals were collected by filtration. Analysis by tlc showed the presence of both *meso*- and DL-1,3-bis(2-piperidyl)-2-propanone.[9]

***meso*-1,3-Bis(2-piperidyl)-2-propanone L-(+)-Dimandelate (5).**—A solution of 1,3-bis(2-piperidyl)-2-propanone hydrochloride (3.11 g) in water was basified with sodium hydroxide solution and extracted with chloroform. After drying with anhydrous sodium sulfate, the chloroformic solution was evaporated to dryness *in vacuo* at 40°. The residue, in 40 ml of ethanol, was mixed with L-(+)-mandelic acid (3.16 g) in 10 ml of ethanol. The solution was brought to boiling and passed through a pad of charcoal in a Büchner funnel, then concentrated to 35 ml, and cooled. The crystals (1.6 g) were collected and washed with ethanol. Recrystallization twice from methanol gave 0.7 g of white needles of **5**, mp 169.7–171°, $[\alpha]^{22}D$ +67.4 ± 2° (c 0.503, water–methanol, 1:1).

Anal. Calcd for $C_{29}H_{40}N_2O_7$: C, 65.89; H, 7.63; N, 5.30. Found: C, 66.01; H, 7.79; N, 5.14.

(+)-1,3-Bis(2-piperidyl)-2-propanone L-(+)-Dimandelate (6).—The original mother liquor of *meso*-1,3-bis(2-piperidyl)-2-propanone L-(+)-dimandelate was evaporated to dryness *in vacuo* at 40°. The residue was dissolved in 4 ml of methanol, 60 ml of acetone was added, and the solution was cooled overnight. The crystals (660 mg), washed with methanol–acetone (1:10), were recrystallized twice from methanol–acetone to give 380 mg of **6**, mp 141–142.5°, $[\alpha]^{22}D$ +96.3 ± 2° (*c* 0.456, water–methanol, 1:1).

Anal. Calcd for $C_{29}H_{40}N_2O_7$: C, 65.89; H, 7.63; N, 5.30. Found:[11] C, 65.98; H, 7.51; N, 5.34.

An additional amount of **6** was obtained by resolving a sample of DL-1,3-bis(2-piperidyl-2-propanone dihydrochloride (0.78 g) with L-(+)-mandelic acid to give 185 mg of the product, mp 141–142.5°, $[\alpha]^{22}D$ +95.5 ± 2° (*c* 0.492, water–methanol, 1:1).

***meso*-1,3-Bis(2-piperidyl-2-propanone D-(−)-Dimandelate (7).**—1,3-Bis(2-piperidyl-2-propanone hydrochloride (2.66 g) was treated as above except for the addition of 2.7 g of D-(−)-mandelic acid. The crystals (1.2 g) were collected and recrystallized twice from methanol to give 400 mg of **7**, mp 169.5–171.5°, $[\alpha]^{22}D$ −66.8 ± 2° (*c* 0.489, water–methanol, 1:1).

(−)-1,3-Bis(2-piperidyl-2-propanone D-(−)-Dimandelate (8).—The original mother liquor from **7** was treated as before to obtain 412 mg of (−)-1,3-bis(2-piperidyl-2-propanone D-(−)-dimandelate which after three recrystallizations from methanol–

(6) H. C. Beyerman, L. Maat, and J. P. Visser, *Rec. Trav. Chim. Pays-Bas*, **86**, 80 (1967).

(7) J. C. Craig and S. K. Roy, *Tetrahedron*, **21**, 391 (1965).

(8) According to the sequence rule developed by Cahn, *et al.* See R. S. Cahn, C. R. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).

(9) Microanalysis was done by Ilse Beetz Mikroanalytisches Laboratorium, 8640 Kronach, West Germany. The countercurrent separation was done using a Craig-Post countercurrent apparatus, Model 2B (number of shakings 20, number of transfers 95, and settling times 5 min). All melting points are corrected and were taken on a Thomas–Hoover capillary melting point apparatus, Arthur H. Thomas Co. Mixture melting points were taken with equal amounts of the two compounds in question. Optical rotations were taken with a Rudolph visual polarimeter, Model 80, O. C. Rudolph & Sons, Inc., using a 0.5-dm tube. ORD data were measured on a Rudolph recording spectropolarimeter, Model 260/658/850/810-609, using a 0.1-dm tube. Thin layer chromatography (tlc) was used routinely in monitoring the reactions and in the separation and resolution of the isomers. The system used was aluminum oxide G with freshly prepared benzene–diethylamine–methanol (99:5:1). The Dragendorff reagent was used to develop the chromatograms. *meso*-1,3-bis(2-piperidyl)-2-propanone gives R_f 0.24 and DL-1,3-bis(2-piperidyl)-2-propanone give 0.36.

(10) C. Schöpf, A. Komzak, F. Braun, and E. Jacobi, *Ann.*, **559**, 1 (1948).

(11) Average of duplicate analyses.

acetone gave 260 mg of **8**, mp 142–143°, $[\alpha]^{22}D$ −96.1 ± 2° (*c* 0.489, water–methanol, 1:1).

An additional amount of **8** was obtained by resolving DL-1,3-bis(2-piperidyl-2-propanone dihydrochloride (0.78 g) using D-(−)-mandelic acid to obtain 188 mg of the product, mp 141–142°, $[\alpha]^{22}D$ −95.7 ± 2° (*c* 0.497, water–methanol, 1:1).

(+)-1,3-Bis(2-piperidyl)-2-propanone Dipicrate (9).—Picric acid (63 mg) was added to a solution of (+)-1,3-bis(2-piperidyl-2-propanone L-(+)-dimandelate (53 mg) in water (2 ml). The mixture was brought to boiling with stirring then cooled for 15 min. The mixture was washed by stirring three times, each with 6 ml of water-saturated ether, removing the ether after each addition. The last traces of ether were removed by a current of air and the mixture was brought to boiling and cooled. The crystals (51 mg) were filtered and washed with ethanol and ether. These were dissolved in 1.1 ml of ethanol and held at 35° (slow evaporation permitted) to obtain 36.5 mg of **9**, mp 128.5–129.5°, $[\alpha]^{22}D$ +12.2 ± 2° (*c* 0.493, methanol–acetone, 1:1).

Anal. Calcd for $C_{25}H_{30}N_8O_{15}\cdot H_2O$: N, 16.00. Found: N, 15.97.

(−)-1,3-Bis(2-piperidyl)-2-propanone Dipicrate (10).—(−)-1,3-Bis(2-piperidyl)-2-propanone D-(−)-dimandelate (53 mg) was treated as above to obtain 54 mg of the product which after two recrystallizations from ethanol gave 25 mg of **10**, mp 128.5–129.5°, $[\alpha]^{22}D$ −11.9 ± 2° (*c* 0.556, methanol–acetone, 1:1), mmp 117–123° with **9**.

Anal. Calcd for $C_{25}H_{30}N_8O_{15}\cdot H_2O$: N, 16.00. Found: N, 16.01.

***meso*-1,3-Bis(2-piperidyl)-2-propanone Dipicrate (11). A.**—*meso*-1,3-Bis(2-piperidyl)-2-propanone L-(+)-dimandelate (53 mg) was treated as above to obtain 64.5 mg of the picrate; this product was recrystallized from ethanol to give 52 mg of **11**, mp 191–192° (lit.[3] mp 195°), $[\alpha]^{22}D$ 0.0° (*c* 0.567, methanol–acetone, 1:1).

B.—*meso*-1,3-Bis(2-piperidyl)-2-propanone D-(−)-dimandelate (53 mg) was treated as above to give, after two recrystallizations from ethanol, 36 mg of **11**, mp 192–193.5° (lit.[3] mp 195°), $[\alpha]^{22}D$ 0.0° (*c* 0.76, methanol–acetone, 1:1), mmp 192–193° (undepressed) with **11** obtained by method A.

DL-1,3-Bis(2-piperidyl)-2-propanone, Dipicrate (12).—A mixture of **9** and **10** (8 mg each) was crystallized from ethanol at 35° to yield 10 mg of **12**, mp 177–179° (lit.[3] mp 179°).

(+)-1,3-Bis(2-piperidyl)-2-propanone Dihydrochloride (13).—A solution of **6** (330 mg) in 4.1 ml of 0.667 *N* hydrochloric acid was extracted four times, each with 15 ml of water-saturated ether, and the aqueous solution was evaporated *in vacuo* over P_2O_5. The residue was dissolved in a minimum volume of methanol, two volumes of acetone were added, and the solution was cooled. The crystals were washed with methanol–acetone (1:2) and recrystallized from methanol–acetone to give 75 mg of **13**, mp 242.5–244°, $[\alpha]^{22}D$ +50.7 ± 2° (*c* 0.736, water–methanol, 1:1).

Anal. Calcd for $C_{13}H_{26}N_2OCl_2$: Cl, 23.905. Found: Cl, 23.68.

(−)-1,3-Bis(2-piperidyl)-2-propanone Dihydrochloride (14).—A solution of **8** (344 mg) in 4.1 ml of 0.667 *N* hydrochloric acid was treated as above (to obtain **13**) to give, after two recrystallizations from methanol–acetone, 73 mg of **14**, mp 242.5–243.5°, $[\alpha]^{22}D$ −49.8 ± 2° (*c* 0.529, water–methanol, 1:1), mmp 240.5–241.5° with **13**.

***meso*-1,3-Bis(2-piperidyl)-2-propanone Dihydrochloride (15).**—A solution of 1.631 g of mixed **5** and **7** in 15 ml of 0.667 *N* hydrochloric acid was treated the same as above (to obtain **13**) to yield, after two recrystallizations from boiling methanol, 585 mg of **15**, mp 224–225.5° (lit. mp 224–225°,[4] 222.5–223.5°[5]).

L-(−)-Pipecolic Acid from (+)-1,3-bis(2-piperidyl)-2-propanone Dihydrochloride.—Chromic acid (238 mg) in water (2 ml) was added to a solution of (+)-1,3-bis(2-piperidyl)-2-propanone dihydrochloride (85 mg) in 50% v/v sulfuric acid solution (8 ml). The mixture was allowed to stand for 30 min, refluxed for 3 hr, and cooled. Sulfur dioxide gas was passed through the solution and excess sulfur dioxide was removed by a current of air. Barium carbonate (30 mg) and saturated solution of barium hydroxide (150 ml) were added. The slightly acidic mixture was neutralized with dilute ammonium hydroxide solution and then filtered. The filtrate was evaporated to dryness and the residue was dissolved in 1.5 ml of methanol. This solution was applied as a streak on a Whatman No. 2 filter paper strip (58 × 25 cm); this was developed with 1-butanol–acetic acid–water (6:1:2). After development to 45 cm, the paper was dried and test strips were sprayed with ninhydrin reagent[12] and developed at 110° for 10 min. The chromatogram was reconstructed and the pipecolic acid area (R_f 0.34) was cut and extracted with ethanol by elution chromatography. The eluate was evaporated to dryness, the residue was dissolved in 0.5 ml of methanol, acetone was added to incipient turbidity (*ca.* 3 ml), and the mixture was cooled. The pipecolic acid obtained (7 mg) was crystallized from methanol–acetone to give 4.5 mg of (−)-pipecolic acid, mp 270–272° dec, $[\alpha]^{23}D$ −26.3 ± 2° (*c* 0.323, water) {lit.[13] mp 268°, $[\alpha]^{24}D$ −26 (*c* 0.43, water)}, mmp 270–272° with reference L-(−)-pipecolic acid (mp 272–274°), mmp 252–257° with reference D-(+)-pipecolic acid (mp 272–274°).

D-(+)-Pipecolic Acid from (−)-1,3-Bis(2-piperidyl)-2-propanone Dihydrochloride.—(−)-1,3-Bis(2-piperidyl)-2-propanone dihydrochloride (76 mg) was oxidized as above. The pipecolic acid isolated (6.5 mg) was crystallized from methanol–acetone to give 4 mg of (+)-pipecolic acid, mp 269–271° dec, $[\alpha]^{23}D$ +25.8 ± 2° (*c* 0.395, water) {lit.[13] mp 268–272°, $[\alpha]^{24}D$ +27° (*c* 0.13, water)}, mmp 269–271° with reference D-(+)-pipecolic acid, mmp 252–257° with reference L-(−)-pipecolic acid.

DL-Pipecolic Acid from *meso*-1,3-Bis(2-piperidyl)-2-propanone Dihydrochloride.—*meso*-1,3-Bis(2-piperidyl)-2-propanone dihydrochloride (104 mg) was oxidized as above and the pipecolic acid isolated (6.5 mg) was recrystallized from methanol–acetone to yield 4.2 mg of DL-pipecolic acid, mp 270–272°, mmp 270–272° with reference DL-pipecolic acid.

ORD Data.—ORD data for the following compounds are listed: (+)-1,3-bis(2-piperidyl)-2-propanone dihydrochloride (*c* 0.205, CH_3OH), $[\phi]^{29}_{400}$ +211°, $[\phi]_{300}$ +478°, $[\phi]_{250}$ +1013°, $[\phi]_{230}$ +1233°, $[\phi]_{215}$ +1630°; (+)-1,3-bis(2-piperidyl)-2-propanone, $[\phi]^{29}_{400}$ +148°, $[\phi]_{345}$ +192°, $[\phi]_{318}$ +138°, $[\phi]_{300}$ +255°, $[\phi]_{280}$ +468°, $[\phi]_{265}$ +569° (broad peak), $[\phi]_{250}$ +468°, $[\phi]_{230}$ +349°; (−)-1,3-bis(2-piperidyl)-2-propanone dihydrochloride (*c* 0.260, CH_3OH), $[\phi]^{29}_{400}$ −196°, $[\phi]_{300}$ −363°, $[\phi]_{250}$ −841,° $[\phi]_{230}$ −1113°, $[\phi]_{215}$ −1457°; (−)-1,3-bis(2-piperidyl)-2-propanone, $[\phi]^{29}_{400}$ −138°, $[\phi]_{345}$ −198°, $[\phi]_{318}$ −129°, $[\phi]_{300}$ −231°, $[\phi]_{280}$ −396°, $[\phi]_{265}$ = −440° (broad trough), $[\phi]_{250}$ −378°, $[\phi]_{230}$ −310°; (−)-pipecolic acid from oxidation of (+)-1,3-bis(2-piperidyl)-2-propanone dihydrochloride (*c* 0.323, H_2O), $[\phi]^{27.6}_{400}$ −40°, $[\phi]_{300}$ −62°, $[\phi]_{270}$ −76°, $[\phi]_{238}$ 0°, $[\phi]_{223}$ +136° (peak), $[\phi]_{215}$ −40°; L-(−)-pipecolic acid (standard) (*c* 0.380, H_2O), $[\phi]^{27.6}_{400}$ −37.4°, $[\phi]_{300}$ −57.7°, $[\phi]_{270}$ −64.5°, $[\phi]_{238}$ 0°, $[\phi]_{223}$ +139.5° (peak), $[\phi]_{215}$ −34°; (+)-pipecolic acid from oxidation of (−)-1,3-bis(2-piperidyl)-2-propanone dihydrochloride (*c* 0.395, H_2O), $[\phi]^{27.6}_{400}$ +32.8°, $[\phi]_{300}$ +66.5°, $[\phi]_{270}$ +75°, $[\phi]_{238}$ 0°, $[\phi]_{223}$ −147° (trough), $[\phi]_{215}$ +13°; D-(+)-pipecolic acid (standard) (*c* 0.419, H_2O), $[\phi]^{27.6}_{400}$ +35.5°, $[\phi]_{300}$ +61.5°, $[\phi]_{270}$ +77°, $[\phi]_{238}$ 0°, $[\phi]_{223}$ −144.5° (trough), $[\phi]_{215}$ +27.7°.

Registry No.—**5**, 19519-46-1; **6**, 19519-47-2; **7**, 19519-48-3; **8**, 19519-49-4; **9**, 19519-50-7; **10**, 19519-51-8; **13**, 19519-52-9; **14**, 19519-54-1; (+)-1,3-bis(2-piperidyl)-2-propanone, 19519-53-0; (−)-1,3-bis(2-piperidyl)-2-propanone, 19519-55-2; L-(−)-pipecolic acid, 3105-95-1; D-(+)-pipecolic acid, 1723-00-8.

Acknowledgment.—Sincere thanks are due Dr. G. Lyle, University of New Hampshire, for her assistance in the ORD measurements.

(12) 0.19% ninhydrin in 1-butanol–10% acetic acid (95:5).

(13) H. C. Beyerman, L. Maat, A. Van Veen, A. Zweistra and W. von Philipsborn, *Rec. Trav. Chim. Pays-Bas*, **84**, 1367 (1965).

Friedelin and Related Compounds. X. Products from Ultraviolet Irradiation of Friedelin

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Ultraviolet irradiation of friedelin (1) in ether solution yields a complex mixture of products from which 5-ethyl-10β-vinyldes-A-friedelane (2) and norfriedelane (4) have been separated and identified. In contrast, irradiation of 1 in reagent grade chloroform solution gives, in high yield, ethyl 3,4-secofriedelan-3-oate (7, R = C_2H_5), characterized by hydrolysis to the corresponding acid (7, R = H) and reduction to the corresponding alcohol (8, R = H).

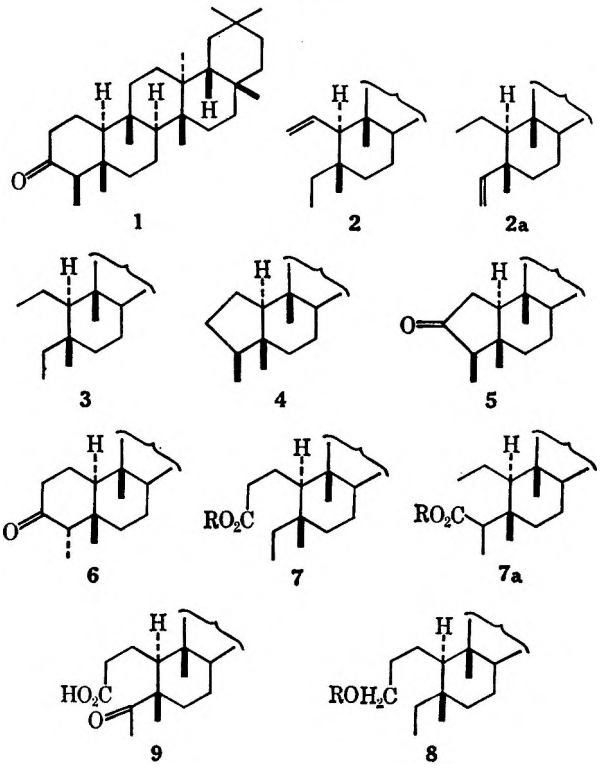
In extension of our studies[1] of general aspects of the chemistry of the pentacyclic triterpene ketone, friedelin (1), a well-known constituent of cork, we have examined the nature of some products obtained by solution ultraviolet (uv) photolysis. Regarded from the viewpoint of irradiation of a naturally occurring cyclohexanone system, friedelin, an α-methylcyclohexanone, affords a structurally interesting variant between the extensively studied steroid 3-ketones (lacking α-alkyl group) and triterpenoid 3-ketones (usually with α,α-dimethyl substitution). The general behavior of the latter types have been well treated in the more comprehensive reviews of nonconjugated cyclic ketone photochemistry.[2-8] Some preliminary work describing the photodecarbonylation of friedelin has been reported[9] and a note which has a bearing on the results reported here has recently appeared.[10]

With regard to the solvents commonly used in the photoirradiation of organic compounds, friedelin is very sparingly soluble in methanol, ethanol, 2-methyl-2-propanol, and acetic acid at room temperature. It is, however, slightly soluble in dioxane (*ca.* 0.6 g/l.) and ether (*ca.* 1 g/l.) and this consideration governed our initial choice of the latter for our study. The progress of the irradiation could be conveniently monitored by thin layer chromatography (tlc) on silica gel G. In this way, four product classes, designated as hydrocarbon, aldehyde, ketone, and hydroxycarbonyl fractions, were readily detected and subsequently separated by column chromatography on alumina.

The hydrocarbon fraction was readily obtained crystalline, but the broad melting point range indicated that it was a mixture. This was fully confirmed by thin layer chromatographic examination, and a partial separation could be effected by the use of silver nitrate impregnated silica gel G and carbon tetrachloride–cyclohexane as the developing medium. In this way, three products of R_f 0.09, 0.42, and 0.66 were obtained. The most strongly absorbed (and minor) product was difficult to crystallize and the nuclear magnetic resonance (nmr) spectrum indicated that it was still a mixture. It was not further examined.

Elemental analysis and the mass spectrum of the product of R_f 0.42 indicated that it was a hydrocarbon, $C_{29}H_{50}$. The presence of a double bond was indicated by a positive tetranitromethane test and the likelihood of its being a vinyl group suggested by strong infrared (ir) bands at 6.11, 9.98, and 10.92 μ. On this evidence, it was considered that the hydrocarbon should have structure 2 or 2a (Chart I). A decision in favor of 2

CHART I



was made on a detailed examination of the nmr spectrum,[11] reproduced and analyzed in Figures 1–3. This hydrocarbon is consequently formulated as 5-ethyl-10β-vinyldesA-friedelane (2). As expected, the double bond was readily reduced on catalytic hydrogenation to yield 5,10β-diethyldesA-friedelane (3), the $C_{29}H_{52}$ empirical formula being confirmed by the mass spectrum.

(1) Part IX: A. S. Samson and R. Stevenson, *J. Chem. Soc., C*, 2342 (1968).

(2) G. Quinkert, *Angew. Chem. Intern. Ed. Engl.*, **4**, 211 (1965).

(3) R. Srinivasan in "Advances in Photochemistry," Vol. 1, W. A. Noyes, Jr., G. S. Hammond, and J. N. Pitts, Jr., Ed., Interscience Publishers, New York, N. Y., 1963, p 83.

(4) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p. 224.

(5) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N. Y., 1966, p 377.

(6) R. O. Kan, "Organic Photochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, p 71.

(7) D. O. Neckers, "Mechanistic Organic Photochemistry," Reinhold Publishing Corp., New York, N. Y., 1967, p 53.

(8) J. N. Pitts, Jr., and J. K. S. Wan in "The Chemistry of the Carbonyl Group," S. Patai, Ed., John Wiley & Sons, London, 1966, p 823.

(9) F. Kohen and R. Stevenson, *Chem. Ind.* (London), 1844 (1966).

(10) T. Tsuyuki, S. Yamada, and T. Takahashi, *Bull. Chem. Soc. Jap.*, **41**, 511 (1968).

(11) We are indebted to Dr. C. F. Hammer, Georgetown University, for a spectrum of this compound, determined on a Varian HA-100 spectrometer.

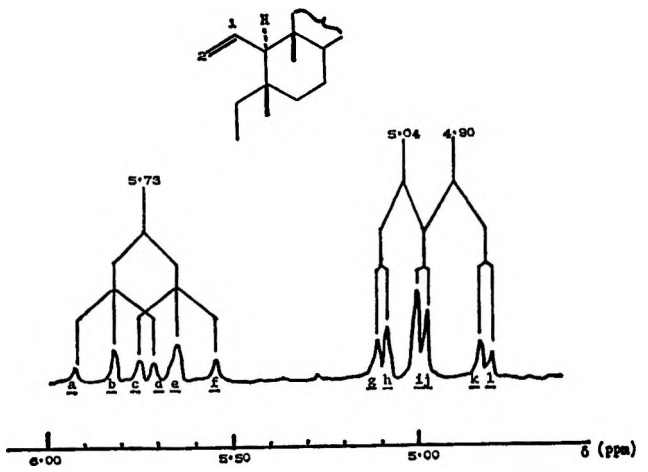


Figure 1.—Nmr spectrum (olefinic region) of hydrocarbon 2, determined using Varian HA-100 spectrometer.

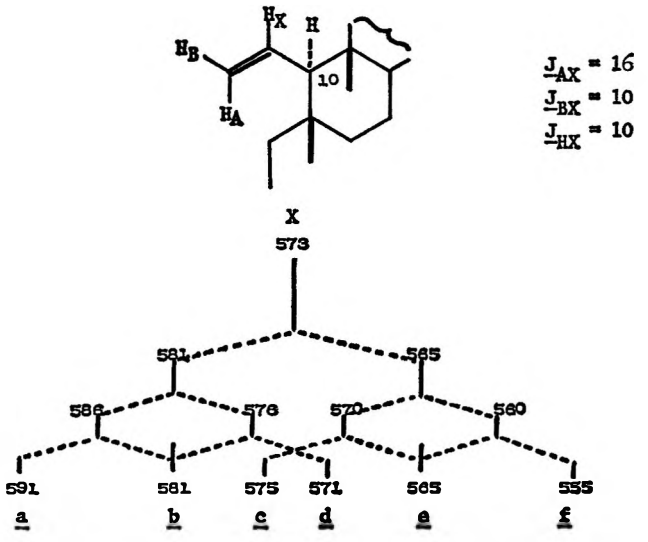


Figure 2.—Pattern ascribed to vinyl proton at C-1 (the X proton).

The remaining hydrocarbon of R_f 0.66, which represented 30–40% of the total hydrocarbon mixture, readily crystallized but melted over a rather wide range and required further chromatographic treatment for purification. The mass spectrum and empirical analysis indicated that it was isomeric with 2, but no unsaturation could be detected from the nmr and ir spectra and it gave a negative tetranitromethane test. It was therefore considered to be pentacyclic and a direct comparison with norfriedelane (4), prepared by Huang-Minlon reduction of norfriedelanone (5), established its identity. This provides an interesting example of a photodecarbonylation of an unstrained saturated cyclic ketone, which although common in the gas phase is considered of more rare occurrence in the condensed phase,[3] unless facilitated by certain structural features, notably homoconjugation or cyclopropylcarbinyl substitution.[12]

The aldehyde fraction was one of the minor products (5–10% yield) and was, from tlc examination, still a mixture of at least two compounds. There appeared to be considerable instability attendant upon isolation and attempted recrystallization, and no reproducible homogeneous product was obtained. The hydroxy-

(12) J. E. Starr and R. H. Eastman, *J. Org. Chem.*, **31**, 1393 (1966).

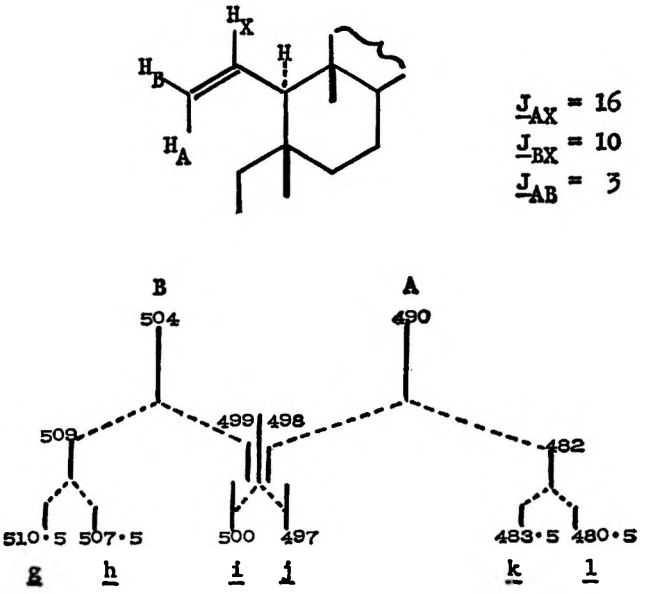


Figure 3.—Pattern ascribed to vinyl protons at C-2 (A, B protons).

carbonyl fraction likewise was a mixture of at least three constituents which we were unable to obtain crystalline.

The ketone fraction could be reproducibly isolated and after crystallization had mp 249–253°. Since, on base treatment, it readily yielded friedelin, mp 263–265°, we considered the likelihood that it had the structure of 4-epifriedelin (6). An attempt to substantiate this by comparing the nmr spectrum in both deuteriochloroform and benzene solution with that of friedelin, a method for determining whether the methyl group of an α-methylcyclohexanone has an equatorial or axial conformation,[13] showed that the "photo ketone" and friedelin were indistinguishable. On passing from $CDCl_3$ to C_6H_6, the signal due to the methyl group at C-4 undergoes a downfield shift ($\Delta\delta$ − 0.08) as expected for friedelin. Similarly, a comparison of the ir and mass spectra and optical rotatory dispersions confirmed the close similarity. In the recent report of the irradiation of friedelin suspended in refluxing ethanol,[10] there was obtained in about 5% yield a ketone, mp 257.5°, which also was epimerized by base to friedelin and accordingly formulated as 6. Although no spectrometric data are therein reported, we have been informed[14] that this product and friedelin are distinct by nmr and ir spectra, but that 6 is converted into 1 on exposure to alumina, *i.e.*, under our conditions of isolation. We conclude that the "photo ketone" which we isolated is predominantly the more stable ketone 1. As expected, the alcohol obtained by lithium aluminum hydride reduction was identified as friedelan-3β-ol.

In contrast to this complex mixture of products obtained by irradiation of friedelin in ether solution, there was readily isolated a homogeneous product in 80% yield when the irradiation was conducted in untreated reagent grade chloroform, in which 1 is much more soluble. This was accompanied only by a small

(13) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 165–170.

(14) Professor T. Takahashi, Department of Chemistry, University of Tokyo, Japan, personal communication, 1968.

hydrocarbon fraction from which norfriedelane (4) was isolated. The principal product showed carbonyl absorption (λ 5.75 μ) in the ir but was unlikely to be a ketone since it failed to yield an oxime; the Beilstein and tetranitromethane tests indicated that it was halogen free and saturated. The parent peak of the mass spectrum (*m/e* 472) indicated an increase in molecular weight over friedelin (426 mass units) corresponding to addition of the elements of ethanol. The presence of an ethyl ester function was suggested by the nmr spectrum from the two proton quartet at δ 4.14 (J = 6 cps) characteristic of the methylene protons of the carbethoxyl group, and this was confirmed by the mass spectrum which gave strong fragment signals appropriate for $(M - C_2H_5)^+$ and $(M - OC_2H_5)^+$. This information established the empirical formula for the irradiation product as $C_{32}H_{56}O_2$ and its nature as a tetracyclic carboxylic acid ethyl ester. The formulation, ethyl 3,4-secofriedelan-3-oate (**7**, R = C_2H_5) and also the less likely alternative (**7a**, R = C_2H_5) satisfied those requirements. The ethyl seco ester (**7**, R = C_2H_5) would be regarded as an unexceptional product of irradiation in *ethanol* solution as a consequence of α cleavage on the side of the more highly substituted carbon atom, followed by an intramolecular disproportionation (by migration of a hydrogen atom from C-2 to C-4) and reaction of the consequent ketene with solvent. The fact that it is produced by irradiation in the normal chloroform of commerce shows that **1** is an extremely efficient scavenger of the ethanol which is present as a preservative.

The ethyl ester structure (**7**, R = C_2H_5) was confirmed by base hydrolysis to yield the corresponding carboxylic acid (**7**, R = H) with correct molecular weight. Reduction of the ethyl ester with lithium aluminum hydride gave the alcohol (**8**, R = H) which was characterized by acetylation to yield 3,4-secofriedelan-3-yl acetate (**8**, R = Ac). The nmr spectra of both alcohol and acetate show that the carbinol protons are adjacent to a carbon atom bearing two hydrogen atoms and consequently excludes the alternative structure (**7a**) of the ethyl ester. The same conclusion has been reached by chemical interconversion[10] involving Huang-Minlon reduction of friedonic acid (**9**) to give **7** (R = H).

Experimental Section

All melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. Specific rotations were determined in chloroform solution. Nmr spectra were determined in $CDCl_3$ solution with tetramethylsilane as internal reference using a Varian A-60 spectrometer, unless otherwise stated. For analytical tlc, silica gel G in 0.25-mm layers was used, and detection was effected by exposure to an iodine atmosphere.

Friedelin (1).—The material used in this work was isolated from cork[15] or cork "smoker wash solids,"[16] as previously described. Crude friedelin, so obtained, had mp 253–257°. Tlc using benzene–chloroform (1:1) indicated an impurity (R_f 0.58), in addition to friedelin (R_f 0.39). A solution of crude friedelin (900 mg) in benzene (15 ml) was chromatographed on alumina (Merck acid, 30 g). Elution with petroleum ether (bp 30–60°, 150 ml) yielded a fraction (152 mg) containing both friedelin and the impurity. Elution with benzene–petroleum ether (1:4) gave pure friedelin as needles (685 mg), R_f 0.39, mp 266–269°. This is the highest melting point yet reported for friedelin. The nmr spectrum (methyl group region) in $CDCl_3$ showed signals at 44 (1), 50 (1/2), 54 (1), 57 (1/2), 58 (1), 61 (2), 64 (1), and 72 (1) cps. The nmr spectrum (methyl group region) in C_6H_6 showed signals at 40 (1), 46 (1), 55 (1/2), 59 (1), 62 (1/2), 64 (1), 65 (1), 66 (1), and 75 (1) cps.

Irradiation of Friedelin in Ether Solution.—A solution of friedelin (250 mg, mp 266–269°) in ether (250 ml) was irradiated in a quartz vessel at room temperature for 1.75 hr using a high pressure quartz mercury vapor lamp (Hanovia, 8A-36). This was repeated twice, and the combined residue [R_f 0.06, 0.13, 0.22, 0.38, 0.58, and 0.88 using benzene–chloroform (1:1)] obtained after solvent removal, was dissolved in petroleum ether–benzene (5 ml) and chromatographed on alumina (Moore, 30 g). Elution with petroleum ether (100 ml) yielded the **hydrocarbon fraction** (200 mg, R_f 0.88). Elution with petroleum ether–benzene (4:1) yielded the **aldehyde fraction** (88 mg). Elution with petroleum ether–benzene (1:1, 375 ml) yielded the **ketone fraction** (332 mg) and with chloroform (250 ml) there was obtained the **hydroxycarbonyl fraction** (240 mg, R_f 0.06, 0.13, 0.22).

Some experiments to determine the variation in product composition with time of irradiation indicated that the hydrocarbon and hydroxycarbonyl fractions increased at the expense of the aldehyde and ketone fractions (Table I).

TABLE I
FRACTIONS ISOLATED FROM FRIEDELIN[a]

	Mg				
	1 hr	1.75 hr	4.5 hr	6 hr	17 hr
Hydrocarbon	19	40	61	80	83
Aldehyde	11	16	24		
Ketone	107	65	48	12	
Hydroxycarbonyl	32	48	52	92	97

[a] 200 mg.

Examination of the Hydrocarbon Fraction.—Crystallization from methylene chloride–methanol gave prisms: mp 155–162°; $[\alpha]_D$ +35° (*c*, 1.7); λ^{KBr} 6.10, 9.92, 10.90 μ. Examination by tlc on silver nitrate impregnated silica gel G, using carbon tetrachloride–cyclohexane as developing solvent and detecting with 2% perchloric acid, indicated three spots of R_f 0.09, 0.42, and 0.66. A separation of this mixture (105 mg) was effected by preparative tlc and the fractions were eluted with petroleum ether.

The product (R_f 0.09, 15 mg) resisted crystallization and the nmr spectrum (unsharp absorption signals in methyl group region) indicated that it was still a mixture.

The product (R_f 0.42, 32 mg) crystallized from methylene chloride–methanol to give **5-ethyl-10β-vinylde-A-friedelane (2)** as small needles: mp 191–192°; $[\alpha]_D$ +36° (*c*, 1.87); λ^{KBr} 6.11, 9.98, 10.92 μ.

Anal. Calcd for $C_{29}H_{50}$: C, 87.36; H, 12.64. Found: C, 87.26; H, 12.48.

It gave a pale yellow color with tetranitromethane in chloroform solution. The nmr spectrum included signals at 43, 48, 52, 54, 59, and 71 cps (methyl groups) and at δ 4.90, a pair of doublets (*trans* "A" proton at C-2, J_{AX} = 16 cps, J_{AB} = 3 cps), at 5.04, a pair of doublets (*cis* "B" proton at C-2, J_{BX} = 10 cps, J_{AB} = 3 cps), and at 5.73, a pair of triplets (octet with two coincident signals, J_{AX} = 16 cps, J_{BX} = 10 cps, $J_{10\alpha-HX}$ = 10 cps). The product (R_f 0.66, 34 mg) crystallized from methylene chloride–methanol as prisms, mp 163–170°, and showed no high intensity uv absorption above 200 mμ. This was dissolved in petroleum ether and chromatographed on neutral alumina (Woelm), eluted with the same solvent, and crystallized from methylene chloride–methanol as prisms (mp 203–205°, 17 mg). This was again chromatographed in the same way and crystallized to give norfriedelane (4) as platelets (8 mg), mp 215–217°, $[\alpha]_D$ +43° (*c*, 1.7) with ir spectrum (KBr) identical with that of a specimen obtained by Huang-Minlon reduction of norfriedelanone (see below).

Anal. Calcd for $C_{29}H_{50}$: C, 87.36; H, 12.64. Found: C, 87.14; H, 12.67.

Examination of the Aldehyde Fraction.—Crystallization of this product from methylene chloride–methanol gave small needles: mp 166–168°; $[\alpha]_D$ +15.5° (*c*, 1.93); λ^{KBr} 3.65, 5.79 μ. It gave no high intensity uv absorption above 200 mμ and a negative tetranitromethane test.

(15) N. L. Drake and R. P. Jacobsen, *J. Amer. Chem. Soc.*, **57**, 1570 (1935).

(16) R. Stevenson, *J. Org. Chem.*, **26**, 2142 (1961).

Anal. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Calcd for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 84.29; H, 12.00.

The nmr spectrum (methyl group region) in $CDCl_3$ showed signals at 48 (1), 53 (1), 57 (1), 59 (2), 62 (1), and 71 (1) cps. There were also signals at δ 2.32, multiplet (two protons adjacent to carbonyl), and at 9.78, triplet (aldehyde proton, J = 2–3 cps).

Tlc examination of this product [benzene–chloroform (1:1)] indicated the presence of two constituents, R_f 0.58 (major) and 0.47 (minor). Recrystallization from acetone gave the aldehyde as small needles with the same mp 166–168°, from which the minor impurity was absent, but with considerable attendant loss.

Examination of the Ketone Fraction.—Crystallization from methylene chloride–methanol gave the "photo ketone" as needles: mp 249–253°; $[\alpha]D$ −15° (c, 1.9); λ^{KBr} 5.82 μ.

Anal. Calcd for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.40; H, 11.68.

The nmr spectrum (methyl group region) in $CDCl_3$ showed signals at 44 (1), 50 (1/2), 53.5 (1), 56 (1/2), 57 (1), 60 (2), 63.5 (1), and 71 (1) cps. The nmr spectrum (methyl group region) in C_6H_6 showed signals at 38 (1), 43.5 (1), 54 (1/2), 58 (1), 60.5 (1/2), 63 (2), 65 (1), and 74 (1) cps.

Examination of Hydroxycarbonyl Fraction.—Tlc inspection indicated that this was a mixture of at least three constituents (R_f 0.06, 0.13, and 0.22): λ^{CHCl_3} 2.90, 5.85 μ. No homogeneous crystalline products could be isolated.

Norfriedelane (4) from Norfriedelanone (5).—A mixture of norfriedelanone[17] (118 mg), hydrazine hydrate (99%, 1.8 ml), and diethylene glycol (13 ml) was heated at 150° for 10 min, potassium hydroxide (1.2 g) was then added, and heating was continued at 150° for 45 min. Solvent was then removed by distillation, until a solution temperature of 210° was attained; the mixture heated for a further 6 hr, cooled, poured into water, and extracted with chloroform. The washed and dried extract was evaporated, and the residue was dissolved in petroleum ether and chromatographed on alumina (Moore). Elution with the same solvent (50 ml) yielded norfriedelane (76 mg), which crystallized from methylene chloride–methanol as platelets: mp 219–221°; $[\alpha]D$ +46° (c, 1.59) (lit.[18] mp 220–221° for norfriedelane prepared by catalytic hydrogenation of norfriedelene).

5,10β-Diethylde-A-friedelane (3).—A solution of 5-ethyl-10β-vinylde-A-friedelane (50 mg) in acetic acid (20 ml) and cyclohexane (20 ml) was stirred under a hydrogen atmosphere at atmospheric pressure and temperature using prereduced platinum oxide (31 mg) as catalyst. When hydrogen uptake had ceased (2 hr), catalyst and solvent were removed, and a solution of the residue in petroleum ether was chromatographed on alumina (Moore). Elution with the same solvent gave **5,10β-diethylde-A-friedelane** (38 mg) which crystallized from methylene chloride–methanol as small needles: mp 208–209°; $[\alpha]D$ +25° (c, 1.4). It gave a negative tetranitromethane test.

Anal. Calcd for $C_{29}H_{52}$: C, 86.92; H, 13.08. Found: C, 87.12; H, 13.11.

Action of Base on the "Photo Ketone."—A solution of the "photo ketone" (mp 243–246°, 36 mg) in ethanolic potassium hydroxide solution (1%, 25 ml) was heated under reflux for 2 hr. On cooling, crystals separated, were collected, and recrystallized from methylene chloride–methanol to give friedelin, mp and mmp 263–265°.

Action of Lithium Aluminum Hydride on the "Photo Ketone."—Lithium aluminum hydride (65 mg) in ether (25 ml) was added to a solution of the "photo ketone" (100 mg) in the same solvent (25 ml); the mixture was heated under reflux for 6 hr, then worked up in the usual way. Crystallization of the product gave friedelan-3β-ol, mp 273–277°, $[\alpha]D$ +19° (c, 1.2), identified by tlc and ir comparison with an authentic specimen (mp 279–281°, $[\alpha]D$ +21°) obtained in a similar manner from friedelin.

Irradiation of Friedelin in Chloroform Solution.—A solution of friedelin (101 mg, mp 253–258°) in chloroform (150 ml, Fisher Certified ACS, containing 0.75% ethyl alcohol as preservative) was irradiated in a Pyrex vessel under a nitrogen atmosphere for 12 hr, after which no starting material remained by tlc analysis. Evaporation of the solvent yielded a residue (127 mg) which was chromatographed on alumina (40 g, Thomas, neutral). Elution with petroleum ether (30 ml) gave a product (6 mg) and with petroleum ether–benzene (1:1, 60 ml) gave a solid (84 mg) which was further purified by preparative tlc (R_f 0.45 with benzene–chloroform (1:1)) and crystallized from methylene chloride–methanol to give **ethyl 3,4-secofriedelan-3-oate** (7, R = C_2H_5) as fine needles (72 mg): mp 110–111°, raised to 114.5–115° on recrystallization; λ^{KBr} 5.75 μ; $[\alpha]D$ −6° (c, 1.0). It gave negative tetranitromethane and Beilstein tests.

Anal. Calcd for $C_{32}H_{56}O_2$: C, 81.29; H, 11.94. Found: C, 81.30; H, 12.01.

The nmr spectrum (methyl group region) showed signals at 48, 53, 57.5, 59.5, 61, 68.5, and 71 cps and also at δ 4.14, quartet (J = 6 cps) (OCH_2CH_3), and 2.42, multiplet (C-2 protons). The mass spectrum had prominent peaks at m/e 472 (M^+), 457 ($M - CH_3$)$^+$, 443 ($M - C_2H_5$)$^+$, and 427 ($M - OC_2H_5$)$^+$.

The petroleum ether eluted product from several experiments were combined (43 mg) and recrystallized from methylene chloride–methanol to give a solid (28 mg) shown by tlc to be a mixture. Purification by preparative tlc on silver nitrate impregnated silica gel G using carbon tetrachloride gave the major constituent (R_f 0.71, 11 mg) which on crystallization from methylene chloride–methanol gave norfriedelane (4), mp 217–219°, with ir spectrum identical with that of authentic specimen.

Performing the same experiment in $CHCl_3$ from which the preservative C_2H_5OH had been removed (either by appropriate treatment with alumina or concentrated sulfuric acid) yielded only a noncrystalline intractable mixture.

3,4-Secofriedelan-3-oic Acid (7, R = H).—Ethyl 3,4-secofriedelan-3-oate (50 mg) was added to 5% ethanolic potassium hydroxide solution (45 ml); the mixture was heated under reflux for 1 hr, then worked up in the usual way. Crystallization from ethyl acetate–methanol, then acetone–methanol, gave **3,4-secofriedelan-3-oic acid** as fine needles: mp 208.5–210°; $[\alpha]D$ −5° (c, 1.2).

Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79. Found: C, 80.70; H, 11.41.

The nmr spectrum (methyl group region) showed signals at 48.5, 53.5, 58, 60, 61, and 71.5 cps. The mass spectrum had prominent peaks at m/e 444 (M^+), 429 ($M - CH_3$)$^+$, and 415 ($M - C_2H_5$)$^+$.

3,4-Secofriedelan-3-ol (8, R = H).—Lithium aluminum hydride (21 mg) was added to a solution of ethyl 3,4-secofriedelan-3-oate (25 mg) in ether (10 ml), the mixture was heated under reflux for 1 hr and worked up in the usual way, and the product was crystallized from chloroform–methanol to give **3,4-secofriedelan-3-ol** as needles: mp 182.5–184°; $[\alpha]D$ −14° (c, 0.4).

Anal. Calcd for $C_{30}H_{54}O$: C, 83.56; H, 12.64. Found: C, 83.90; H, 12.62.

The nmr spectrum (methyl group region) showed signals at 47, 53, 53.5, 59.5, 61, and 71 cps and also at δ 2.23, triplet (C-3 protons). The mass spectrum shows peaks at m/e 430 (M^+), 415 ($M - CH_3$)$^+$, and 401 ($M - C_2H_5$)$^+$.

3,4-Secofriedelan-3-yl Acetate (8, R = Ac).—The alcohol (52 mg) was dissolved in pyridine (2.5 ml) and acetic anhydride (2.5 ml) was added. The mixture was heated at 100° for 1.5 hr and worked up in the usual way and the product was crystallized from chloroform–methanol as fine needles (38 mg): mp 121.5–122.5°; $[\alpha]D$ −8° (c, 0.9).

Anal. Calcd for $C_{32}H_{56}O_2$: C, 81.29; H, 11.94. Found: C, 80.99; H, 11.87.

The nmr spectrum (methyl group region) showed signals at 48, 54, 59, 61, 62, and 72 cps and also at δ 3.98 t (J = 6 cps, C-3 protons) and 1.95 (acetate).

Registry No.—1, 559-74-0; 2, 14356-57-1; 3, 14363-60-1; 4, 7506-14-1; 7 (R = C_2H_5), 19553-16-3; 7 (R = H), 19553-17-4; 8 (R = H), 19553-18-5; 8 (R = Ac), 19553-19-6.

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(17) L. Ruzicka, O. Jeger, and P. Ringnes, *Helv. Chim. Acta*, **27**, 972 (1944).

(18) N. L. Drake and J. K. Wolfe, *J. Amer. Chem. Soc.*, **61**, 3074 (1939).

The Synthesis of Cyclopenin and Isocyclopenin[1]

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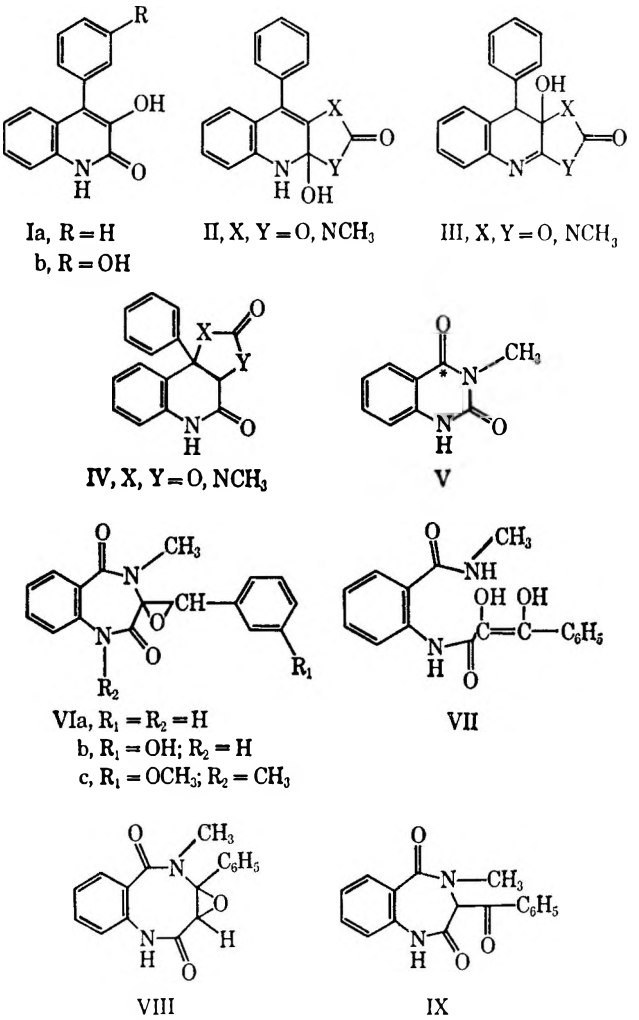
The spiro(styrene oxide-3,4-dihydro-4-methyl-1H-1,4-benzodiazepine-2,5-dione) structure postulated for cyclopenin, a metabolite of *Penicillium cyclopium*, has been confirmed by synthesis. The synthesis proceeded *via* condensation of 3,4-dihydro-4-methyl-1H-1,4-benzodiazepine-2,5-dione with benzaldehyde to give a mixture of the 3-*cis*- and *trans*-benzylidene compounds which were separated by chromatography and stereochemically characterized by nuclear magnetic resonance. Epoxidation of the *trans* isomer with *m*-chloroperbenzoic acid led to *dl*-cyclopenin whereas *dl*-isocyclopenin was obtained by similar epoxidation of the *cis* isomer. Both cyclopenin and isocyclopenin give viridicatin on treatment with hydrochloric acid.

Penicillium cyclopium and related mould species are the source of a number of nitrogeneous metabolites, including cyclopenin, cyclopenol, viridicatin, and viridicatol. The structures of viridicatin and viridicatol have been established as 3-hydroxy-4-phenyl-2-quinolone and 3-hydroxy-4-(3-hydroxyphenyl)-2-quinolone (Ia and Ib), respectively, by degradation and by synthesis.[4-7] Cyclopenin, $C_{17}H_{14}N_2O_3$, first isolated[5] from *P. cyclopium* Westling, was subsequently shown[6] to be accompanied by and separable from a closely related phenolic metabolite, cyclopenol, $C_{17}H_{14}N_2O_4$.

Cyclopenin and cyclopenol are optically active and in dilute acid or alkali their optical activity is lost with concomitant appearance in high yield of viridicatin (Ia)[5] and viridicatol (Ib),[6] respectively, and methylamine and carbon dioxide. To accommodate these observations, a quinolinooxazolidinone structure (II or III) was assigned[5] to cyclopenin, and it was subsequently pointed out[8] that fusion at the 3,4 position (IV) was also permissible.

An extensive reinvestigation[7] of the metabolites of *P. cyclopium* and *P. viridicatum* disclosed a number of features incompatible with the quinolinooxazolidinone structures. Cyclopenin-^{14}C, prepared by *in vivo* incorporation of anthranilic acid-^{14}COOH, was degraded with loss of carbon dioxide-^{14}C to radioinactive viridicatin by dilute acid. An enzyme preparation from the mycelium of *P. viridicatum* also converted cyclopenin into viridicatin with carbon dioxide evolution.[7] Biosynthetic studies further indicated that the intact carbon skeleton of phenylalanine serves as precursor for viridicatin and viridicatol[9,10a] and for cyclopenin and cyclopenol.[10b] Incorporation of anthranilic acid and phenylalanine into cyclopenin accounted for all of the carbons except the N-methyl carbon, which presumably was derived from methionine.[7]



More cogent evidence for dismissing structures II, III, and IV was the observation that oxidation of cyclopenin with hydrogen peroxide in acetic acid yielded 3-methyl-2,4-quinazolinedione (V),[7] benzoic acid, benzaldehyde, carbon dioxide, and anthranilic acid, radioactive quinazoline V being obtained from radioactive cyclopenin. On the basis of these data Luckner and Mohammed[7] proposed that cyclopenin (VIa) and cyclopenol (VIb) are seven-membered cyclic dipeptides formed from anthranilic acid and phenylalanine with an N-methyl group supplied by methionine. The epoxide moiety of VIa was suggested as more consistent with the ir absorption than hydroxyl or ketone groups. Further chemical and spectroscopic support cited[4] for the proposed structure of cyclopenin were (a) infrared (ir) absorptions at 3900 (NH), 1700, 1630 (CON), 990, and 885 cm^{-1}; (b) nuclear magnetic resonance (nmr) singlet at δ 4.04 (benzylic epoxide proton); and (c) reaction with diazomethane in which cyclopenin and

(1) (a) Supported in part by the U. S. Army Research Office, Durham, N. C. (b) Part of these results have been reported in a preliminary communication [H. Smith, P. Wegfahrt, and H. Rapoport, *J. Amer. Chem. Soc.*, **90**, 1668 (1968)].

(2) U. S. Public Health Service Postdoctoral Fellow.

(3) National Institutes of Health Predoctoral Fellow.

(4) K. G. Cunningham and G. G. Freeman, *Biochem. J.*, **53**, 328 (1953).

(5) A. Bracken, A. Pocker, and H. Raistrick, *ibid.*, **57**, 587 (1954).

(6) J. H. Birkinshaw, M. Luckner, Y. S. Mohammed, K. Mothes, and C. E. Stickings, *ibid.*, **89**, 196 (1963).

(7) M. Luckner and Y. S. Mohammed, *Tetrahedron Lett.*, 1987 (1964).

(8) J. T. Edwards, *Ann. Rept. Prog. Chem.* (Chem. Soc., London), **51**, 247 (1954).

(9) M. Luckner and K. Mothes, *Tetrahedron Lett.*, 1035 (1962); *Arch. Pharm.*, **296**, 18 (1963).

(10) (a) Y. S. Mohammed and M. Luckner, *Tetrahedron Lett.*, 1953 (1963); (b) M. Luckner, *European J. Biochem.*, **2**, 74 (1967).

cyclopenol form mono- and dimethyl derivatives, respectively.

The above spectroscopic, chemical, and biosynthetic data, while providing strong support, do not unambiguously delineate the structure of cyclopenin. First, the facile acid or alkaline decarboxylation and rearrangement of cyclopenin to viridicatin is not consistent with known decarboxylation rates of anthranilic acid and its derivatives.[11] Opening of the epoxide to yield the suggested[7] intermediate VII followed by quantitative liberation of methylamine and carbon dioxide from the acylaminobenzamide derivative with ring closure to viridicatin seems unlikely under the mild conditions employed.

Second, O-methyl analysis of methylcyclopenin and dimethylcyclopenol indicated none in the former and one O-methyl group in the latter, requiring that the other methyl be located on nitrogen or carbon. The ir assignments[10] of the 1680- and 1655-cm^{-1} bands to the CONH group in methylcyclopenin and the 1690- and 1645-cm^{-1} bands to the CONH group in dimethylcyclopenol imply that the other methyl group is on carbon, a conclusion in conflict with structure VI.

Third, the reported spectroscopic properties of cyclopenin are inadequate to differentiate VIa from related structures, *e.g.*, VIII and IX, which could accommodate the ir and nmr data. Therefore, our first objective was to prepare model compounds for spectral correlation with cyclopenin and this was closely followed by efforts to synthesize the postulated structure VIa.

Results and Discussion

Cyclopenin and cyclopenol were obtained[12] from the culture filtrate of *P. cyclopium* Westling by a modification of the described procedure.[5] Since the styrene oxide portion should have little effect on the characteristic ultraviolet (uv) absorption of cyclopenin [λ_{max} 211 nm (ϵ 37,200), 290 (2060)], a reasonable model would be 3,4-dihydro-1H-1,4-benzodiazepine-2,5-dione (Xa).[13] The similarity of the spectra of Xa [λ_{max} 215 nm (ϵ 41,200), 272 (12,500), 293 (3500)] and cyclopenin prompted synthesis of 3,4-dihydro-4-methyl-1H-1,4-benzodiazepine-2,5-dione (Xb)[14] which was accomplished *via* ethyl *o*-nitrobenzoylsarcosinate without isolation of the intermediate amine. The uv absorption of Xb [λ_{max} 215 nm (ϵ 32,100), 291 (2180)] is in full correspondence with that of cyclopenin.

To help to settle the question of the diazomethane reaction with cyclopenin and cyclopenol, 3,4-dihydro-1,4-dimethyl-1H-1,4-benzodiazepine-2,5-dione (Xc) was prepared by methylation of Xb with diazomethane or by the procedure of Lee.[15] The spectrum of Xc [λ_{max} 288 nm (ϵ 1970)] is quite similar to that of methylcyclopenin and dimethylcyclopenol. This indicates that diazomethane reaction has indeed led to N methylation and this was confirmed by repeating the methylation of cyclopenol with diazomethane. Dimethylcyclopenol has three-proton singlets at δ 3.69, 3.43, and 3.72. Since it has been established that dimethylcyclopenol contains one O-methyl group, the other new methyl group must be N-methyl in accordance with its chemical shift, and the original ir assignments[10] are incorrect. Thus cyclopenin and cyclopenol contain an acidic NH group, as does the model benzodiazepine Xb.

Although no analogy could be found for the extremely facile loss of carbon dioxide from cyclopenin upon treatment with acid (*e.g.*, the benzodiazepines X lost less than 10 mol % carbon dioxide upon boiling in 2 *N* hydrochloric acid for 3 hr), the chemical and spectroscopic evidence now seemed sufficiently persuasive to accept structure VIa as an objective for synthesis. However, before undertaking its synthesis, degradation of cyclopenin to a simpler compound containing some of its unique features was undertaken.

The route chosen was to deepoxidize cyclopenin and then to synthesize the corresponding olefin. For example, ethyl phenylglycidate has been converted into ethyl cinnamate on treatment with thiourea[16] or tributylphosphorus.[17] Also, chalcone oxide[18] with chromous chloride in acetic acid was rapidly deepoxidized. Cyclopenin was unchanged on treatment with chromous chloride. Although cyclopenin reacted slowly with tributylphosphorus at 85° during 48 hr, most was recovered; phenylglycidanilide afforded cinnamanilide under these conditions. Phenylglycidanilide also yielded cinnamanilide in excellent yield after 4-hr reaction with thiourea. Under similar conditions with thiourea cyclopenin was partially converted after 7 days reaction into a product, tentatively assigned structure XIa or XIb.[19] Attempts to convert this thiourea derivative into deoxycyclopenin were not successful. The sluggish reactions with thiourea and thiosulfate,[20] respectively, indicate then the epoxide group of cyclopenin is in an unusual and unreactive environment. Failure in these degradations attempts turned our efforts directly to synthesis.

The synthesis of the isomeric *dl*-cyclopenins of structures XIIa and XIIb required a 3-substituted benzodiazepine-2,5-dione, and, among the numerous 1,4-benzodiazepine and 1,4-benzodiazepinedione derivatives,[21,22] few with 3 substituents have been described.[13,23] Our approach was to synthesize first the benzylidene compounds XIc and XId *via* Xb in analogy to similar condensation of amides, hydantoin, diketopiperazine, and creatine with benzaldehyde.[24-26] Condensation of Xb with benzaldehyde using Perkin reaction conditions[27] gave the isomeric 3-benzylidene-4-methyl-1H-1,4-benzodiazepine-2,5-diones (XIc and XId) and the N-acetyl derivative XIe. An alternative

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(12) The crude isolate was obtained by H. R. while a guest in the laboratory of Dr. H. Raistrick during March 1956.

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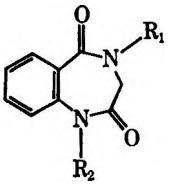
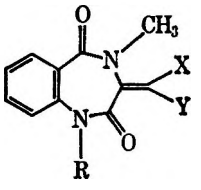
synthesis of XIc and XId *via* *o*-nitrobenzoylsarcosine and condensation with benzaldehyde to XIVa followed by reduction and ring closure gave an inferior yield. Also, Xc was unreactive under conditions which gave the monomethylbenzylidine derivative XIc.

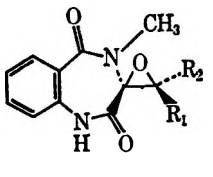
That XIc and XId have the stereochemistry shown is evident from examination of their respective nmr spectra. The major product, mp 207–208°, assigned structure XIc, showed N-methyl and vinyl hydrogen resonances as singlets at δ 3.20 and 6.95, respectively. The minor isomeric product, mp 185°, exhibited N-methyl resonance at δ 3.50 and vinyl hydrogen resonance at 6.72. The upfield shift (18 Hz) observed for the N-methyl resonance of the major isomer (XIc), with respect to that of the minor isomer (XId), is consonant[28] with its interaction with the π electrons of the proximate benzene ring. This interaction requires a *cis* stereochemistry for the two groups. The expected[25,28] downfield shift (13.8 Hz) of the vinylic hydrogen of XIc relative to XId caused by interaction with the 2-carbonyl was also observed.



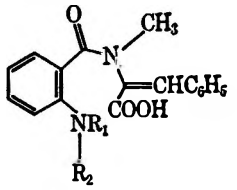
Xa, $R_1 = R_2 = H$
b, $R_1 = CH_3$; $R_2 = CH_3$
c, $R_1 = R_2 = CH_3$



XIa, R = H; X = C_6H_5; Y = SC(=NH)NH_2
b, R = H; X = SC(=NH)NH_2; Y = C_6H_5
c, R = H; X = C_6H_5; Y = H
d, R = H; X = H; Y = C_6H_5
e, R = $COCH_3$; X = C_6H_5; Y = H
f, R = Cl; X = C_6H_5; Y = H



XIIa, $R_1 = H$; $R_2 = C_6H_5$
b, $R_1 = C_6H_5$; $R_2 = H$



XIIIa, $R_1, R_2 = O_2$
b, $R_1 = H$; $R_2 = COCH_3$

Alkaline hydrolysis of the N-acetyl compound XIe resulted in preferential cleavage of the benzodiazepine ring to yield XIIIb. However, in view of the ketonic character of imides, sodium hypochlorite was next tried and the N-acetyl group was successfully removed, yielding the N-chloro derivative XIf. This was readily decomposed in ethanol or with potassium iodide and thiosulfate to give XIc.

Epoxidation of XIc was complicated by adverse steric and electronic features, and no precedent exists for epoxidation of a double bond so substituted. Numerous attempts were made, without success, to epoxidize XIc with alkaline oxidizing agents[29] and trifluoroperacetic acid;[30] all gave complex mixtures of products. Prolonged reaction of XIc with *m*-chloroperbenzoic acid gave a product in 37% yield, $C_{17}H_{14}N_2O_3$, mp 194–195°, which was readily hydrolyzed to viridicatin (I) in 2 *N* hydrochloric acid solution. The ir and uv spectra (Table I) of the product are identical with those of *l*-cyclopenin; the nmr spectrum of the epoxide shows the same aromatic hydrogens multiplet at δ 6.6–7.8 as cyclopenin, and the N-methyl and benzylic hydrogens have the same chemical shift (δ 3.20 and 3.94, respectively) and the same ratio (3:1) as those observed for natural cyclopenin. Further, the anomalous nmr singlets of cyclopenin at δ 4.51 and 2.55 were observed in the synthetic product.[31] Finally, the mass spectra of *dl*-cyclopenin and *l*-cyclopenin were superimposable. Cyclopenin is therefore assigned structure XIIa as required from the *cis* relationship of the N-methyl and phenyl groups of the immediate precursor XIc.

The product obtained by oxidation of XId, $C_{17}H_{14}N_2O_3$, was easily converted into viridicatin; its uv spectrum exhibited maxima at 290 and 211 nm; and its ir spectrum exhibited carbonyl absorptions at 5.85, 6.05 and 7.2 μ. The nmr spectrum (Table I) showed proton resonances at δ 6.4–7.8, 3.82, and 3.11, in a ratio of 9:1:3 and were assigned to aromatic, benzylic, and N-methyl hydrogens, respectively; this product therefore is isocyclopenin (XIIb).

Experimental Section[32]

Cyclopenin (VIa) and Cyclopenol (VIb).—Cultures of *P. cyclopium* LSHTM strain no. 72 were harvested after 15 days. The culture was filtered, the mycelium was pressed, the combined filtrates were adjusted to pH 2 with concentrated hydrochloric acid, and the solution was treated with 120 g of charcoal. The mixture was stirred for 2 hr and filtered and the charcoal was washed with five 500-ml volumes of water. Chloride ion was not detected after the third wash. The charcoal was dried *in vacuo*, slurried with 1 l. of methanol, and packed into a column, eluting with four 2-l. portions of methanol. Evaporation of the first two portions and crystallization of the residue from methanol gave 3.5 g as a mixture of cyclopenin and cyclopenol. Fractional crystallization of the mixture from ethyl acetate–benzene (1:3 v/v) afforded impure cyclopenol. Cyclopenin was obtained from the mother liquors by (a) paper chromatography,[6] (b) silica gel chromatography (elution with 3:1 methylene chloride–benzene), or (c) alumina chromatography (elution with 3:1 benzene–ethyl acetate); the last procedure gave a poor recovery of cyclopenol.

Recrystallization of chromatographed cyclopenin from ether–methylene chloride solution gave pure cyclopenin (VIa): mp 179–180°; $[\alpha]^{23}_{5461}$ −301° (*c* 1.0, methanol) [lit.[6] mp 183–184°; $[\alpha]^{20}_{5461}$ −291° (*c* 1.0, methanol)].

(28) K. Brocklehurst, H. S. Price, and K. Williams, *Chem. Commun.*, 884 (1968).

(29) (a) W. C. Anthony, *J. Org. Chem.*, **31**, 77 (1966); (b) G. B. Payne, *ibid.*, **23**, 2048 (1958); (c) E. C. Kornfeld, E. J. Kornfeld, G. B. Kline, M. J. Mann, and D. E. Morrison, *J. Amer. Chem. Soc.*, **78**, 3087 (1958); (d) N. C. Yang and F. A. Finnegan, *ibid.*, **80**, 5848 (1958).

(30) W. D. Emmons and A. S. Pagano, *ibid.*, **77**, 89 (1955).

(31) These anomalous minor peaks are tentatively suggested to result from conformational equilibria and will be considered in detail in a future paper.

(32) Nmr spectra were determined with Varian A-60 and HA-100 instruments, using tetramethylsilane as internal reference (δ 0). Melting points, uncorrected, were determined on a Mel-Temp melting point apparatus. Ir spectra were determined for Nujol suspensions with Perkin-Elmer Model 127 and Model 137 instruments unless otherwise noted. Uv spectra were obtained with a Cary Model 14 spectrophotometer. Mass spectra were obtained with a Varian M-66 spectrometer; microanalyses were performed by the Micro Analytical Laboratories, University of California at Berkeley, Berkeley, Calif.

TABLE I

SPECTROPHOTOMETRIC PROPERTIES OF CYCLOPENIN AND SOME RELATED COMPOUNDS

Compound	Mp, °C	Uv, nm (ε)[a]	Nmr, δ[b]	Ir, μ[c]
Xa	327–327.5	293 (3,500) 272 (12,500) 215 (41,250)		3.07 (NH), 5.85, 5.93 (CONH)
Xb	241–242	291 (2,180) 215 (32,140)	7–7.9 (m, 4, ArH), 3.38 (s, 2, CH_2), 3.11 (s, 3, NCH_3) (in d_6-DMSO)	5.89 (CONH), 6.10 ($CONCH_3$)
Xc	142–143	288 (1,970)	7.2–8.2 (m, 4, ArH), 4.05 (q, 2, CH_2), 3.4 (s, 3, NCH_3), 3.4 (s, 3, NCH_3), 3.52 (s, 3, NCH_3)	5.97, 6.09 ($CONCH_3$)
XIc	207–208	286 (12,400) 255 (14,200) 239 (15,800) 213 (37,400)	7.38 (m, 9, ArH), 6.95 (s, 1, = CH), 3.20 (s, 3, NCH_3)	3.05 (NH), 5.90, 6.10 (CON), 6.20
XId	185	276 (15,600) 245 (18,300) 215 (43,700)	7.27 (m, 9, ArH), 6.72 (s, 1, =CH), 3.50 (s, 3, NCH_3)	5.93, 6.15 (CON)
l XIIa	179–180	290 (2,060) 211 (37,200)	7.30, 7.10, 6.56 (m, 9, ArH), 3.95 (s, 1, CHAr), 3.20 (s, 3, NCH_3) [4.51 (s, 0.08, CHAr), 2.56 (s, 0.24, NCH_3)]	2.97, 3.11 (NH), 5.85 (CONH), 6.0 ($CONCH_3$), 7.22, 9.12
dl XIIa	193–195	290 (2,100) 211 (37,900)	7.30, 7.10, 6.56 (m, 9, ArH), 3.94 (s, 1, CHAr), 3.20 (s, 3, NCH_3) [4.51 (s, 0.08, CHAr), 2.56 (s, 0.24, NCH_3)]	2.97, 3.11 (NH), 5.84 (CONH), 6.05 ($CONCH_3$), 7.22, 9.12[d]
XIIb	210–213	290 (2,200) 212 (34,200)	7.85, 7.12, 6.46 (m, 9, ArH), 7.12, 6.46 (m, 9, ArH), 3.82 (s, 1, CHAr), 3.14 (s, 3, NCH_3)	2.95 (NH), 5.85 (CONH), 6.05 ($CONCH_3$), 7.20
VIc	168–168.5	284 (3,340)	6.8–7.7, 6.12 (m, 8, ArH), 3.85 (s, 1, CH), 3.69 (s, NCH_3), 3.43 (s, 3, NCH_3), 3.72 (s, 3, OCH_3)	

[a] In ethanol. [b] In $CDCl_3$ with internal tetramethylsilane (TMS) unless otherwise stated: s, singlet; m, multiplet; q, quartet. [c] In Nujol except where indicated. [d] In chloroform.

Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 69.4; H, 4.8; N, 9.5; mol wt, 294. Found: C, 69.2; H, 4.9; N, 9.3; mol wt, 294 (mass spectroscopy).

Cyclopenol (VIb) was recrystallized from ethyl acetate–benzene: mp 210–211°; $[\alpha]_{5462}^{20}$ −310° (c 1.0, methanol) [lit.[6] mp 215°; $[\alpha]_{5461}^{20}$ −309° (c 1.3, methanol)]; uv λ_{max} 285 nm (ε 3740); nmr (CD_3OD) δ 3.11 (s, 3, NCH_3), 3.94 (s, 1, CHAr), 6.07–7.8 (m, 8, ArH).

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.8; H, 4.6; N, 9.0. Found: C, 66.1; H, 4.8; N, 9.2.

Dimethylcyclopenol (VIc).—A solution of 200 mg of cyclopenol (VIb) in cold methanol was treated with a 4 *M* excess of ethereal diazomethane for 18 hr. The solution was filtered, evaporated to dryness, and chromatographed on silica gel to yield 62 mg of dimethylcyclopenol: mp 168–168.5° (lit.[6] mp 167–169°).

Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.4; H, 5.4; N, 8.3; mol wt, 338. Found: C, 67.4; H, 5.2; N, 8.1; mol wt, 338 (mass spectroscopy).

Ethyl o-Nitrobenzoylsarcosinate.—A suspension of 15.35 g (0.1 mol) of ethyl sarcosinate hydrochloride[33] in 150 ml of chloroform was stirred vigorously at 0° while 18.5 g (0.1 mol) of *o*-nitrobenzoyl chloride[34] in 20 ml of chloroform was added slowly. Stirring was continued for 21 hr at room temperature followed by successive washings with water, 0.1 *N* hydrochloric acid, 0.01 *N* sodium hydroxide, and water. Drying and removal of solvent gave a residue which was short path distilled at 110° (50 μ) to afford 26.6 g (75% yield) of ethyl *o*-nitrobenzoylsarcosinate.

Anal. Calcd for $C_{12}H_{14}N_2O_5$: C, 54.1; H, 5.3; N, 10.6. Found: C, 53.7; H, 5.1; N, 10.7.

3,4-Dihydro-4-methyl-1H-1,4-benzodiazepine-2,5-dione (Xb).—A solution of 15 g (56 mmol) of ethyl *o*-nitrobenzoylsarcosinate (XIa) in 120 ml of ethanol containing 600 mg of platinum oxide was hydrogenated at 40 psi for 45 min. The residue from filtration and evaporation of the mixture was recrystallized from methanol to give 6.7 g (63% yield) of Xb: mp 241–243° (lit.[18] mp 246–247°), uv λ_{max} 215 nm (ε 32,140), 291 (2180); ir (Nujol) 5.88 (CONH), 6.10 μ ($CONCH_3$); nmr (d_6-DMSO) δ 7–7.9 (m, 4, ArH), 3.83 (s, 2, CH_2), 3.11 (s, 3, NCH_3).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.1; H, 5.3; N, 14.7; mol wt, 190. Found: C, 63.0; H, 5.2; N, 14.5; mol wt, 190 (mass spectroscopy).

3,4-Dihydro-1,4-dimethyl-1H-1,4-benzodiazepine-2,5-dione (Xc).—A solution of 190 mg (1 mmol) of Xb in 30 ml of methanol was treated with 50 ml of ethereal diazomethane (5 mmol) and the solution was stored at 0° overnight. Evaporation of solvent gave 140 mg of product which contained some Xb. Fractional recrystallization from an ethanol–water solution gave 40 mg of Xc: mp 142–143° (lit.[15] mp 146–147°); uv λ_{max} 288 nm (ε 1970); nmr δ 3.4 (s, 3, NCH_3), 3.52 (s, 3, NCH_3).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.7; H, 5.9; N, 13.7; mol wt, 204. Found: C, 64.8; H, 5.9; N, 13.7; mol wt, 204 (mass spectroscopy).

Decarboxylation of 3,4-Dihydro-4-methyl-1H-1,4-benzodiazepine-2,5-dione (Xb).—A suspension of 380 mg (2 mmol) of Xb in 30 ml of 2 *N* hydrochloric acid was boiled in a stream of carbon dioxide free nitrogen. The effluent gas was passed through two bubblers containing carbon dioxide free 0.1 *N* sodium hydroxide for 3 hr. Addition of saturated barium chloride solution to the bubblers gave a precipitate of barium carbonate (40 mg) indicating that ~10 mol % of the theoretical amount of carbon dioxide had been evolved. The hydrolysis solution was evaporated to dryness and a small portion of the residue was examined by paper chromatography. Sarcosine, *o*-aminobenzoylsarcosine, and *o*-methylaminoacetylaminobenzoic acid were identified by comparison with authentic samples using 1-butanol–acetic acid–water (4:1:5) as the chromatographic solvent.

1-Acetyl-3-*trans*-benzylidine-3,4-dihydro-4-methyl-1H-1,4-benzodiazepine-2,5-dione (XIe).[35]—A mixture of 2.66 g (14 mmol) of Xb, 2.2 g (10.8 mmol) of benzaldehyde, and 125 g

(33) W. Staudt, *Z. Physiol. Chem.*, **146**, 286 (1925).
(34) E. W. Parnell, *J. Chem. Soc.*, 2369 (1959).
(35) *cis* and *trans* designations are based on the cinnamate portion of the molecule.

(15.2 mmol) of sodium acetate in 4 ml of acetic anhydride was heated with stirring at 140° for 2 hr. Water was added, the solution was stirred, and the aqueous phase was decanted. The oily residue was trituated with ether and unreacted Xb was removed by filtration. The filtrate was evaporated. The residue was dissolved in chloroform, washed successively with sodium bisulfite and water, dried, and evaporated to a red viscous liquid which deposited 0.9 g of XIe: mp 177–179° from methanol solution; uv λ_{max} 245 nm (ϵ 14,500), 283 (13,320); nmr ($CDCl_3$) δ 7.5 (m, 9, ArH), 7.16 (s, 1, =CH), 3.3 (s, 3, NCH_3), 2.68 (s, 3, $NCOCH_3$).

Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.2; H, 5.0; N, 8.7. Found: C, 71.0; H, 5.0; N, 8.7.

3-*trans*-Benzylidine-1-chloro-3,4-dihydro-4-methyl-1H-1,4-benzodiazepine-2,5-dione (XIf).—A solution of 0.192 g (0.6 mmol) of N-acetyl compound XIe in 2 ml of dioxane and 1 ml of 5.25% sodium hydrochlorite solution was stirred at room temperature for 5 min. The solution was diluted with water and extracted with chloroform and the combined extracts were washed with water, dried, and evaporated to a residue. The residue was recrystallized from chloroform–petroleum ether to give 0.131 g of XIf: mp 129–130°; uv λ_{max} 213 nm (ϵ 40,000), 243 (16,300), 283 (13,570).

Anal. Calcd for $C_{17}H_{13}N_2O_2Cl$: C, 65.3; H, 4.2; N, 9.0. Found: C, 65.2; H, 4.3; N, 9.0.

3-*trans*-Benzylidine-3,4-dihydro-4-methyl-1H-1,4-benzodiazepine-2,5-dione (XIc) from XIf.—Potassium iodide in 1 ml of 3% aqueous acetic acid was added in portions to a solution of 0.131 g of XIf in 1 ml of dioxane followed by decolorization with 0.1 *M* sodium thiosulfate solution. The reaction mixture was extracted with chloroform. The extract was dried and evaporated to a semicrystalline residue, which was recrystallized from chloroform–petroleum ether solution to yield 0.11 g of XIc: mp 201–202°.

3-*cis*- and -*trans*-Benzylidine-3,4-dihydro-4-methyl-1H-4-benzodiazepine-2,5-diones (XIc and XId).—A solution of Xb (5.32 g) in 8 ml of acetic anhydride was treated with 2.5 g of fused sodium acetate and 4.4 g of benzaldehyde. The mixture was heated at gentle reflux temperature for 2 hr and evaporated to a semisolid mass, and the residue was repeatedly concentrated from toluene, then suspended in water. The oily precipitate was extracted into methylene chloride, washed with 5% sodium bicarbonate, dried, and evaporated and the residue was placed onto a column of 60 g of activity III Woelm alumina. Elution with benzene gave 0.87 g of *trans* XIc, mp 201–205°, and further elution with benzene–methylene chloride (3:1) gave *cis* XId, mp 185°.

Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.4; H, 5.1; N, 10.1. Found for XIc: C, 73.0; H, 5.4; N, 10.2. Found for XId: C, 73.1; H, 5.0; N, 10.1.

α-(N-Methyl-N-*o*-nitrobenzoyl)aminocinnamic Acid (XIIIa).—A mixture of 3.33 g (14 mmol) of *o*-nitrobenzoylsarcosine,[36] 2.2 g (20.8 mmol) of benzaldehyde, and 1.25 g (15.2 mmol) of sodium acetate in 4 ml of acetic anhydride was heated for 4 hr. Ice–water was added to the stirred solution, the aqueous layer was decanted, and the residual oil was dissolved in 5% sodium bicarbonate solution and washed with methylene chloride. The aqueous layer was acidified to pH 2 and extracted with chloroform. The extract was dried and evaporated and the residue was recrystallized from methanol–petroleum ether to yield 3.96 g of XIIIa: mp 182–183°; uv λ_{max} 264 nm (ϵ 20,100); nmr δ 7.3–8.5 (m, 10, ArH and =CHAr), 3.59, 3.06 (d, 3 H, NCH_3).

Anal. Calcd for $C_{17}H_{14}N_2O_5$: C, 62.6; H, 4.3; N, 8.5. Found: C, 62.7; H, 4.1; N, 8.6.

α-(N-Methyl-N-*o*-acetylaminobenzoyl)aminocinnamic Acid (XIIIb).—A solution of XIe (50 mg) in 5 ml of methanol was treated with 0.5 ml of 2 *N* sodium hydroxide and 1 ml of water and the solution was heated at reflux for 10 min. The solution was diluted with water and acidified with 5% H_3PO_4, forming a precipitate which was filtered and dried to yield 38 mg of XIIIb. Recrystallization from ethyl acetate–hexane gave material of mp 231–232° dec; uv λ_{max} 280 nm (sh) (ϵ 13,600), 245 (16,400); nmr (d_6-DMSO) δ 6.8–8.1 (m, 10, ArH, =CHAr), 3.13, 2.79 (d, 3, NCH_3), 2.12, 1.97 (d, 3, CH_3CON).

***dl*-Cyclopenin (XIIa).**—A solution of XIc (0.176 g) in 10 ml of methylene chloride was treated with 85% *m*-chloroperbenzoic acid (1.06 g) and the solution was stored at 25° for 17 days. The suspension was diluted with methylene chloride to dissolution of suspended material and washed successively with 2% sodium thiosulfate, 2% sodium bicarbonate, and sodium chloride solutions. The methylene chloride phase was dried and evaporated to a viscous residue which afforded 70 mg of *dl*-cyclopenin: mp 189–191° after crystallization. Pure *dl*-cyclopenin was obtained by recrystallization from ether–hexane solution: mp 193–195°.

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.4; H, 4.8; N, 9.5; mol wt, 294. Found: C, 69.6; H, 4.8; N, 9.5; mol wt, 294 (mass spectroscopy).

***dl*-Isocyclopenin (XIIb).**—A solution of XId (30 mg) in methylene chloride was treated with 85% *m*-chloroperbenzoic acid (200 mg) and the solution was allowed to stand at 25° for 30 days. It was then washed successively with sodium thiosulfate, sodium bicarbonate, and sodium chloride solutions. Drying and evaporating the methylene chloride gave a residue from which 10 mg of *dl*-isocyclopenin (XIIb) was obtained after two crystallizations from ether–hexane solution. The melting point was very sensitive to the rate of heating and at 10°/min was 210–213°.

Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.4; H, 4.8; N, 9.5; mol wt, 294. Found: C, 69.3; H, 5.0; N, 9.5; mol wt, 294 (mass spectroscopy).

Conversion of *dl*-Cyclopenin (XIIa) into Viridicatin (Ia).—A suspension of 0.054 g of *dl*-cyclopenin in 5 ml of 2 *N* hydrochloric acid was heated at 87° for 3 hr. The suspension was cooled and the crystalline precipitate was filtered to yield 0.042 g (97% yield) of crude product. Recrystallization from ethanol gave viridicatin: mp 265° (lit.[5] mp 269°); uv λ_{max} 329 nm (ϵ 8300), 317 (11,200), 307 sh (9100), 285 (9100), 220 (42,800).

Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.9; H, 4.7; N, 5.9. Found: C, 76.1; H, 4.7; N, 6.1.

Conversion of *dl*-Isocyclopenin (XIIb) into Viridicatin (Ia).—A suspension of 1.0 mg of XIIb in 1 ml of 2 *N* hydrochloric acid and 1 ml of ethanol was heated at reflux temperature for 3 hr. Evaporation of solvent and washing of the residue with water afforded viridicatin.

Reaction of Cyclopenin with Thiourea.—A solution of 5 mg of cyclopenin and 2.5 mg of thiourea in 2 ml of absolute butanol-1 was heated at 80–90° for 7 days. The solvent was evaporated and the residue was chromatographed by preparative tlc. The uv fluorescent band was eluted with methanol and evaporation of the methanol gave a white crystalline product (XIa–XIb): mp 232–235°; uv λ_{max} 230 sh, 267, and 319 nm; nmr (d_6-DMSO) δ 7.1–7.8 (m, 10, ArH and NH), 2.83 (d, 3, NCH_3).

Anal. Calcd for $C_{16}H_{16}N_4O_2S$: C, 61.3; H, 4.6; N, 15.9; mol wt, 352. Found: C, 60.9; H, 4.8; N, 16.6; mol wt, 352 (mass spectroscopy).

Phenylglycidanilide.—To 1 g (4.48 mmol) of *trans*-cinnamanilide[18] in 75 ml of chloroform was added 1.72 g (10 mmol) of *m*-chloroperbenzoic acid and the solution was allowed to stand at room temperature for 18 hr. The reaction mixture was extracted several times with 50 ml of 5% sodium bicarbonate solution followed by one extraction with 50 ml of water. The resultant red organic phase was dried over sodium sulfate and filtered, and the solvent was removed by evaporation. This left a red oil which was dissolved in a minimum of warm ethanol; water was added until the solution became cloudy. Cooling produced crystals and several crops were obtained by the further addition of water to give a total of 0.5 g (47%) of the epoxide: mp 142° (lit.[37] mp 142°).

Reaction of Phenylglycidanilide and Thiourea.—A mixture of 100 mg (0.7 mmol) of phenylglycidanilide, 53.6 mg (0.7 mmole) of thiourea, and 10 ml of absolute ethanol was heated on a steam bath for 4 hr. Water was added until the solution became cloudy, and storage in a refrigerator gave crystals, 84 mg (90%), mp 151–152°, identical with *trans*-cinnamanilide.

Registry No.—VIc, 19581-62-5; Xa, 5118-94-5; Xb, 3415-35-8; Xc, 1015-77-6; XIa, 19581-63-6; XIb, 19553-21-0 XIc, 19113-24-7; XId, 19553-22-1; XIe, 19553-23-2; XIf, 19614-24-5; *l* XIIa, 10088-76-3; *dl* XIIa, 19357-57-4; *dl* XIIb, 19553-26-5; XIIIa, 19543-44-3; XIIIb, 19600-43-2; ethyl *o*-nitrobenzoylsarcosinate, 19543-45-4.

(36) L. H. Sternbach, U. S. Patent 2,893,992 (July 7, 1959).

(37) S. Bodforss, *Ber.* **52**, 142 (1919).

Plant Antitumor Agents. II. The Structure of Two New Alkaloids from *Camptotheca acuminata*[1,2]

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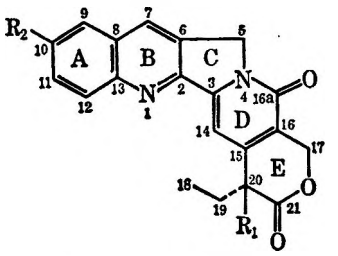
Further fractionation of *C. acuminata* has yielded two new alkaloids, hydroxycamptothecin (2) and methoxycamptothecin (3). The former could be methylated to give a methyl ether identical with 3. In order to establish the position of the hydroxyl group in ring A, nmr spectra of deuterated methoxycamptothecin and of the model compounds 7–10 have been obtained. The syntheses of model compounds have been described.

The isolation and structure of camptothecin 1, an alkaloid with a novel ring system exhibiting potent antileukemic and antitumor activities, has been reported from our laboratory.[2] Further fractionation of *C. acuminata* has resulted in the isolation of two minor and related components hydroxycamptothecin (2) and methoxycamptothecin (3) both possessing good antileukemic activity in L-1210 (Chart I[3]). This report is on the characterization of these two alkaloids.

CHART I



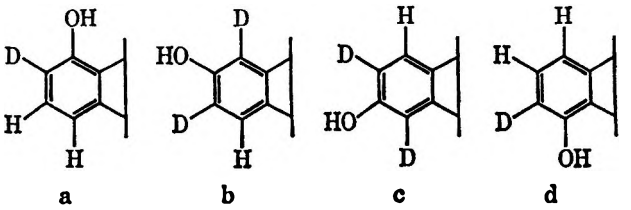
1, R_1 = OH; R_2 = H
2, R_1 = R_2 = OH
3, R_1 = OH; R_2 = OCH_3
4, R_1 = OH; R_2 = O_2CCH_3
5, R_1 = R_2 = O_2CCH_3

The molecular composition of 2 ($C_{20}H_{16}N_2O_5$) as determined by mass spectrometry suggested that it might be a monohydroxy derivative of 1 ($C_{20}H_{16}N_2O_4$). This hypothesis was further supported by the formation of mono (4) and diacetate (5) derivatives. The ultraviolet spectra of compounds 4 and 5 were similar to that of 1 thereby suggesting the presence of the same camptothecin chromophore in these compounds. The phenolic nature of the hydroxyl function was evidenced by the positive ferric chloride test and bathochromic shifts in the ultraviolet spectrum of 2 in the presence of dilute base. Treatment of 2 with diazomethane gave a compound identical with 3 obtained from natural sources. Hence, methoxycamptothecin is the methyl ether of hydroxycamptothecin.

The phenolic nature of the additional hydroxyl function in 2 meant it could be present in only one of the three rings, A, B, or D. The nmr spectra of 1 and 2 were quite similar except for some differences in the aromatic region. In the aromatic region of 1 and 2, the one proton singlet at δ 8.38 has been assigned to the C-7 proton *para* to the quinoline nitrogen.[4] The other one proton singlet at δ 7.22 must therefore be due to the C-14 proton *meta* to the pyridone nitrogen.[5] These assignments are further supported by the nmr spectra of tricyclic model compounds 7–10 (see Figure 1) in which the singlet due to the C-9[6] proton appears around δ 8.20 while the other singlet around δ 7.20 is absent. Therefore, the phenolic hydroxyl in 2 cannot be located at C-7 or C-14 and consequently its location is narrowed to one of the four possible positions in ring A.

In order to determine the exact position of the hydroxyl group in ring A, it was decided to study the deuterium exchange reaction of 2. It is well known that protons adjacent to a phenolic hydroxyl group can be replaced by deuterium under base catalysis.[7] The four possibilities in the present case are shown by partial structures a, b, c, and d (Chart II). The nmr spectra of b and c would show only a one-proton singlet in the aromatic region, whereas a and d would show two-proton doublets in this region.

CHART II



a b c d

In our studies, deuterated hydroxycamptothecin was prepared by treatment with aqueous sodium deuterioxide and converted into the corresponding methyl ether for reasons of solubility. In the nmr spectrum of the deuterated methoxycamptothecin (*cf.* Figure 1) the signals due to the C-7 and C-14 protons in the aromatic region appeared unaltered as expected. However, the multiplets centered at δ 8.0 and 7.44 in the undeuterated sample were replaced by a pair of doublets located precisely as in the undeuterated sample, suggesting partial structure a or d. The results of deuteration therefore tend to favor position 9 or 12 for the location of the hydroxyl (methoxy in 3) group in 2.

A priori it was felt that the aromatic regions of the nmr spectra of model compounds having methoxy

(1) This investigation was conducted under Contract SA-43-ph 4322, Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health. Presented in part before the Organic Division at the 19th Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967.

(2) Previous paper in this series: Plant Antitumor Agents. I: M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, **88**, 3888 (1966).

(3) The numbering system is based on the probable relationship of camptothecin to indole alkaloids, particularly those of the ajmalicine type; *cf.* M. Shamma, *Experientia*, **24**, 107 (1968).

(4) W. Seiffert, *Angew. Chem. Intern. Ed. Engl.*, **1**, 215 (1962); Varian Spectra Catalog, Vol. 2, Spectrum No. 579.

(5) J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.*, 859 (1961).

(6) The numbering system for the model compounds is different from that of 1 and is based on similar compounds reported in the literature; *cf.* G. Kempter and S. Hirschberg, *Chem. Ber.*, **98**, 419 (1965).

(7) G. W. Kirby and L. Ogunkoya, *J. Chem. Soc.*, 6914 (1965).

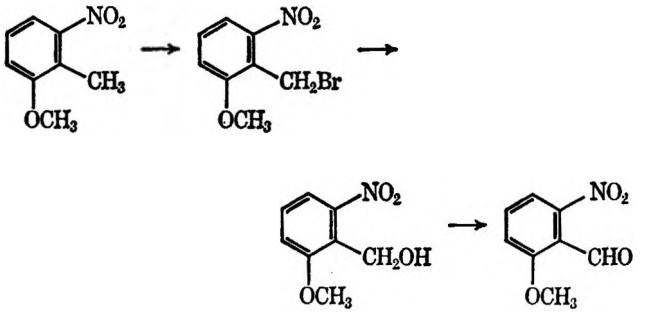
groups at the two positions suggested by deuterium-exchange reactions should be significantly different. A comparison of the nmr spectra of these compounds with that of **3** should therefore allow one to choose between the two possible positions suggested by deuteration studies.

With this objective, pyrroloquinolines **7** and **8** with a methoxy group at positions 5 and 8 of ring A were synthesized (see below) using procedures already developed in our laboratory in connection with studies on the total synthesis of camptothecin.[8] The aromatic regions of the nmr spectra of **7** and **8** were indeed different; however, these did not bear any resemblance with that of **3** (*cf.* Figure 1). Therefore, the remaining two methoxypyrroloquinolines **9** and **10** were also synthesized (see below). A comparison of their spectra with that of **3** (*cf.* Figure 1) left no doubt as to the identity of the splitting patterns of **9** and **3**, thereby establishing beyond any reasonable doubt that the methoxy group in methoxycamptothecin and therefore the hydroxy group in hydroxycamptothecin must be located at position 10 as shown in formulas **3** and **2**, respectively. Such a placement is in accord with biogenetic considerations.[9,10]

In view of the above findings, the deuteration of **2** was repeated under base and also acid catalysis using drastic conditions. However, no deuterium exchange at the other *ortho* position was observed. It appears therefore that the 11 position in pyrroloquinolines like the 3 position in 2-naphthol is inert toward electrophilic substitution.

Synthesis of Pyrroloquinolines.—The isomeric 3-, 4-, and 5-methoxy-2-nitrobenzaldehydes[11-13] were synthesized using methods reported in the literature. The fourth isomer 2-nitro-6-methoxybenzaldehyde was prepared from 2-nitro-6-methoxytoluene as shown in Chart III. Bromination of the latter with N-bromo-

CHART III



succinimide gave 2-nitro-6-methoxybenzyl bromide which on boiling with aqueous sodium carbonate solution gave the corresponding alcohol. Oxidation of the alcohol with potassium dichromate and sulfuric acid yielded the desired aldehyde.

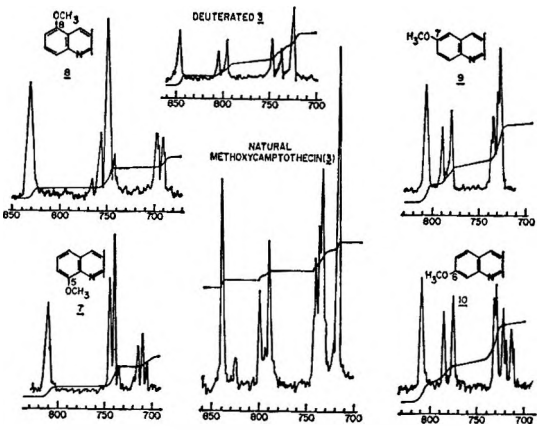
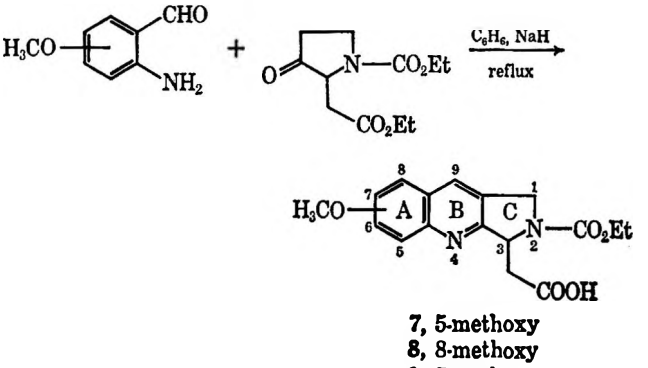


Figure 1.—Aromatic regions of the 100-MHz nmr spectra of **3**, **7**, **8**, **9**, **10**, and deuterated **3** run in DMSO-d_6-TMS.

Reduction[14] of the methoxy-2-nitrobenzaldehydes gave the corresponding methoxy-2-aminobenzaldehydes.

Base-catalyzed Friedlander condensations of the methoxy-2-aminobenzaldehydes with ethyl 1-ethoxycarbonyl-3-oxopyrrolidin-2-ylacetate[15] (**6**) gave the corresponding methoxypyrroloquinolines **7**–**10** (Chart IV) isolated as carboxylic acids.

CHART IV



7, 5-methoxy
8, 8-methoxy
9, 7-methoxy
10, 6-methoxy

Experimental Section[16]

Isolation of Hydroxycamptothecin (2).—Compound **2** was present in the material that was eluted after methoxycamptothecin during the large-scale isolation of camptothecin from *C. acuminata* by the Squibb group. This material was further fractionated by a second adsorption chromatography on a silicic acid column (300 g). A solution of the mixture (500 mg) in 5% methanol in chloroform (75 ml) was applied to the column. The column was eluted with 5% methanol in chloroform. All fractions were investigated by means of tlc using chloroform–acetone–methanol (7:2:1) as the solvent system. Compound **2** (85 mg) was crystallized by the dropwise addition of ethyl acetate to a boiling solution of **2** in 20% methanol–chloroform until turbidity was observed at which point it was allowed to cool slowly: mp 268–270°; ir (KBr) 3480 (OH), 1740–1755 cm^{-1} (lactone C=O);

(8) J. A. Kepler, M. C. Wani, M. E. Wall, and S. G. Levine, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., 1968, Paper No. ORGN 027.

(9) E. Wenkert, K. G. Dave, R. G. Lewis, and P. W. Sprague, *J. Amer. Chem. Soc.*, **89**, 6741 (1967).

(10) E. Wenkert, *ibid.*, **84**, 98 (1962).

(11) P. Friedlander and O. Schenck, *Ber.*, **47**, 3040 (1914).

(12) R. B. Woodward, F. Bader, H. Bickel, A. Frey, and R. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(13) H. H. Hodgson and H. G. Beard, *J. Chem. Soc.*, 147 (1926).

(14) L. I. Smith and J. W. Opie, *Org. Syn.*, **28**, 11 (1948).

(15) J. W. Clark-Lewis and P. I. Mortimer, *J. Chem. Soc.*, 191 (1961).

(16) Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 221 spectrophotometer. Ultraviolet spectra were determined in methanol on a Cary Model 14 spectrophotometer. Nuclear magnetic resonance spectra were obtained in deuteriochloroform or dimethyl sulfoxide-d_6 with TMS as an internal standard on a Varian HA-100 apparatus; results are expressed in parts per million on a δ scale. Mass spectra were determined with A. E. I. MS-902 mass spectrometer through the valued assistance of Dr. David Rosenthal of our laboratory. Thin layer chromatography was performed on silica gel HF plates.

uv max 222 mμ (ε 50,300), 267 (27,400), 330 (12,100), 382 (28,000); nmr (DMSO-d_6) δ 0.88 (t, 3, C-18), 1.85 (m, 2, C-19), 5.15 (s, 2, C-5), 5.35 (s, 2, C-17), 6.40 (s, 1, C-20, OH), 7.22 (s, 1, C-14), *ca.* 7.28 (m, 2, C-11 and C-12), 7.96 (d, 1, C-9), 8.38 (s, 1, C-7), 10.3 (s, br, C-10, OH).

Anal. Calcd for $C_{20}H_{16}N_2O_5 \cdot H_2O$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.97; H, 4.55; N, 7.29. *Anal.* Calcd for $C_{20}H_{16}N_2O_5$: *m/e* 364. Found: *m/e* 364.

Isolation of methoxycamptothecin (3) was accomplished by the fractional crystallization of the material that was eluted immediately after camptothecin during the large-scale isolation of camptothecin from *C. acuminata* by the Squibb group. The material (12.5 g) was dissolved in a mixture of hot acetonitrile (1000 ml) and methanol (300 ml). Traces of insoluble brown material were removed by filtration and the solution was slowly cooled to about −10° to give precipitate A (1.61 g) and filtrate B.

A tlc of precipitate A on Eastman Chromagram (Type K 301R, silica gel) in benzene–acetone–methanol (18:2:0·5) indicated the presence of **1** as the major impurity in **3**. It was triturated with hot 20% ethanol in acetonitrile (100 ml). The insoluble material was extracted with hot 50% ethanol in acetonitrile (80 ml). Evaporation of the filtrate gave **3** (140 mg) identical with the one obtained by the methylation of **2**. Concentration of filtrate B to about 500 ml gave precipitate C (300 mg). Precipitate C was processed in a manner analogous to precipitate A to yield an additional 60 mg of **3**.

Compound **3** was crystallized in the same manner as **2**: mp 254–255°; ir (KBr) 3330 (OH), 1750 cm^{-1} (lactone C=O); uv max 220 mμ (ε 49,900), 264 (29,800), 293 (5700), 312 (8600), 328 (12,000), 365 sh (27,500), 379 (31,500); nmr (DMSO-d_6) δ 3.96 (s, 3, OCH_3), 7.38 (m, 2, C-11 and C-12), 7.94 (d, 1, C-9). Rest of the spectrum was similar to that of **2**.

Anal. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.80; N, 7.40. Found: C, 66.41; H, 4.88; N, 7.16.

Hydroxycamptothecin Monoacetate 4.—To a suspension of **2** (75 mg) in 50 ml of dry benzene was added 0.4 ml of acetic anhydride and 0.3 ml of pyridine and the reaction mixture was refluxed for 24 hr. The solvent and excess reagents were removed under vacuum at 50°. The product was crystallized from methanol: mp 255–257°; ir (Nujol) 3470 (OH), 1750 cm^{-1} (lactone C=O); uv max 218 mμ (ε 24,400), 253 (17,500), 290 (4500), 365 (13,400).

Anal. Calcd for $C_{22}H_{18}N_2O_6$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.26; H, 4.48; N, 6.77.

Hydroxycamptothecin diacetate 5 was prepared in the same manner as **4** by using a large excess of acetic anhydride and pyridine and increasing the reflux period to 3 days: mp 270–273°; ir (Nujol) absence of OH, 1750 cm^{-1} (lactone C=O); uv similar to that of **4**.

Anal. Calcd for $C_{24}H_{20}N_2O_7$: *m/e* 448. Found: *m/e* 448.

2-Nitro-6-methoxybenzyl Bromide.—To a solution of 1 g of 2-nitro-6-methoxytoluene in 75 ml of carbon tetrachloride were added 2.13 g of N-bromosuccinimide and 30 mg of benzoyl peroxide. The reaction mixture was refluxed for 18 hr, cooled to 0°, and filtered. The product (1.05 g, 71%) from the filtrate was crystallized from ether–hexane, mp 68–69°.

Anal. Calcd for $C_8H_8NO_3Br$: C, 39.46; H, 3.27. Found: C, 39.44; H, 3.37.

2-Nitro-6-methoxybenzyl Alcohol.—2-Nitro-6-methoxybenzyl bromide (5.59 g) was added to a solution of 3.03 g of sodium carbonate in 240 ml of water. The reaction mixture was refluxed for 16 hr, cooled, and extracted with chloroform. The product (3.17 g, 76%), obtained from the dry chloroform extract, was crystallized from ether–hexane, mp 72–73°.

Anal. Calcd for $C_8H_9NO_4$: C, 52.46; H, 4.95. Found: C, 52.62; H, 5.00.

2-Nitro-6-methoxybenzaldehyde.—A solution of 2.63 g of sodium dichromate dihydrate in 22 ml of 20% sulfuric acid was added during 1 hr to 3.17 g of 2-nitro-6-methoxybenzyl alcohol. The reaction mixture was then heated at 60–65° for 3 hr, cooled, and quenched with 25 ml of water. The product (2.41 g, 77%) was crystallized from ether–benzene, mp 101–103°.

Anal. Calcd for $C_8H_7NO_4$: C, 53.04; H, 3.90. Found: C, 53.14; H, 3.93.

Table I gives the melting points and literature references to the preparation of **3-, 4-, and 5-methoxy-2-nitrobenzaldehydes.**

Preparations of 3-, 4-, 5-, and 6-methoxy-2-aminobenzaldehydes from the corresponding nitro compounds were carried out following a procedure[14] reported for the preparation of O-aminobenzaldehyde. These were obtained in 67, 81, 29, and 45% yield, respectively. Owing to the tendency of the O-aminobenzaldehydes to undergo self-condensation,[14] these were used without further characterization.

TABLE I

Compd	Mp, °C	Ref
3-Methoxy	102	11
4-Methoxy	95–96	12
5-Methoxy	83	13

1,3-Dihydro-2-ethoxycarbonyl-3-carboxymethyl-5-methoxy-2H-pyrrolo[3,4-*b*]quinoline (7).—A solution of 1.69 g of 2-amino-3-methoxybenzaldehyde and 2.38 g of **6**[15] in 100 ml of benzene was refluxed until no more water collected in the Dean–Stark trap. It was cooled to 45° and 420 mg of 56% sodium hydride in mineral oil added. The reaction mixture was allowed to stand overnight at room temperature. A 50-ml portion of water was added and the mixture shaken vigorously for 10 min. The water layer was acidified to pH 5 with 1 *N* hydrochloric acid, saturated with sodium chloride, and extracted several times with ethyl acetate. The product (1.03 g, 28%) was crystallized from ethyl acetate: mp 213–215°; ir (KBr) 3450 (OH), 1750 (monomeric carboxyl C=O), 1690 cm^{-1} (N-carbethoxy C=O); uv max 253 mμ (ε 35,500), 321 (5500); nmr (DMSO-d_6) δ 1.28 (t, 3, CH_2CH_3), 3.06 (s, br, 2, $>CHCH_2CO_2H$), 3.94 (s, 3, OCH_3), 4.16 (q, 2, CH_2CH_3), 4.74 (q, 2, C-1), 5.17 (t, 1, C-3), 7.14 (m, 1, C-7), 7.24 (m, 2, C-6 and C-8), 8.19 (s, 1, C-9).

Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.79; H, 5.64; N, 8.42.

1,3-Dihydro-2-ethoxycarbonyl-3-carboxymethyl-8-methoxy-2H-pyrrolo[3,4-*b*]quinoline (8) was prepared in exactly the same manner as **7** from 2-amino-6-methoxybenzaldehyde and **6** in 37% yield: mp 202–204°; ir (KBr) 3450 (OH), 1750 (monomeric carboxyl C=O), 1690 cm^{-1} (N-carbethoxy C=O); uv max 232 mμ (ε 31,700), 321 (4600); nmr (DMSO-d_6) δ 6.96 (m, 1, C-6), *ca.* 7.56 (m, 2, C-5 and C-7). The rest of the spectrum was similar to that of **7**.

Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.66; H, 5.57; N, 8.21.

1,3-Dihydro-2-ethoxycarbonyl-3-carboxymethyl-7-methoxy-2H-pyrrolo[3,4-*b*]quinoline (9) was prepared in exactly the same manner as **7** from 2-amino-5-methoxybenzaldehyde and **6** in 38% yield: mp 198–200° (with prior softening); ir (KBr) 3450 (OH), 1725 (carboxyl C=O), 1710 cm^{-1} (N-carbethoxy C=O); uv max 217 mμ (41,500), 242 sh (21, 800), 330 (6300); nmr (DMSO-d_6) δ 7.29 (m, 2, C-6 and C-8), 7.86 (d, 1, C-5). The rest of the spectrum was similar to that of **7**.

Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.88; H, 5.48; N, 8.42.

1,3-Dihydro-2-ethoxycarbonyl-3-carboxymethyl-6-methoxy-2H-pyrrolo[3,4-*b*]quinoline (10) was prepared in exactly the same manner as **7** from 2-amino-4-methoxybenzaldehyde and **6** in 84% yield: mp 198–202° (with previous softening around 186°); ir (KBr) 3450 (OH), 1725 (carboxyl C=O), 1705 cm^{-1} (N-carbethoxy C=O); uv max 224 mμ (ε 33,900), 335 (8700); nmr (DMSO-d_6) δ 7.18 (m, 1, C-8), 7.34 (d, 1, C-5), 7.82 (d, 1, C-7). Rest of the spectrum was similar to that of **7**.

Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.64; H, 5.62; N, 8.73.

Deuterated Methoxycamptothecin. Base Catalysis.—A solution of 40 mg of **2** in 1 ml of 1 *N* sodium deuterioxide was heated at 100° in a nitrogen-filled sealed tube for 9 days. Traces of insoluble material were removed by filtration and the deep orange filtrate was acidified to pH 4 under cooling. The suspension was freeze dried and the residue was extracted thrice with 10 ml of 20% methanol–chloroform. The solution was treated with excess diazomethane solution in ether. The product (33 mg) was crystallized from chloroform–ethyl acetate: nmr (DMSO-d_6) δ 7.45 (d 1, C-11), 8.0 (d, 1, C-12). The rest of the spectrum was similar to that of **3**.

Deuterated Hydroxycamptothecin. Acid Catalysis.—A solution of 20 mg of **2** in 0.3 ml of DMSO-d_6 containing 2 drops of 1 *N* deuterium chloride was heated at 100° for 24 hr in a nmr tube. The progress of the reaction was followed by nmr spectroscopy: (DMSO-d_6–DCl) δ 7.45 (d, 1, C-11), 8.05 (d, 1, C-12). The rest of the spectrum was similar to that of **2**.

Registry No.—**2**, 19685-09-7; **3**, 19685-10-0; **4**, 19685-11-1; **5**, 19685-12-2; **7**, 19713-66-7; **8**, 19713-67-

8; **9**, 19689-84-0; **10**, 19689-85-1; 2-nitro-6-methoxybenzyl bromide, 19689-86-2; 2-nitro-6-methoxybenzyl alcohol, 19689-87-3; 2-nitro-6-methoxybenzaldehyde, 19689-88-4.

Acknowledgments.—We wish to thank Messrs. G. S. Abernethy, Jr., and H. L. Taylor for their help in the isolation of alkaloids and Mr. J. B. Thompson for technical assistance.

Thurberin, a New Pentacyclic Triterpene from Organ Pipe Cactus

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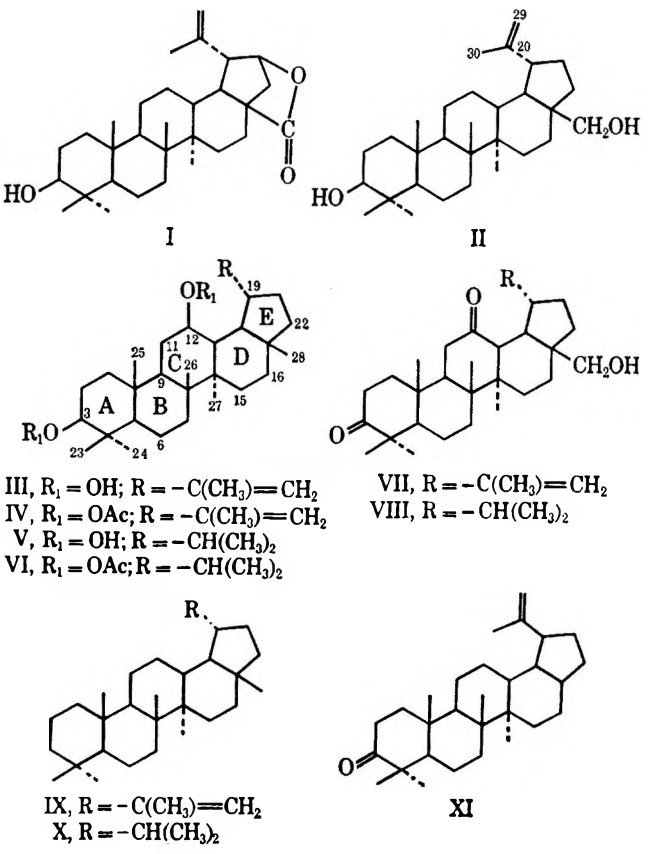
A chemical analysis of the alcoholic extract of the fresh cortical (pulp) portion of the Organ Pipe cactus (*Lemaireocereus thurberi*) affords, besides thurberogenin (I), two more triterpenes, betulin (II) and a new triterpene, thurberin (III), hitherto unidentified in this species. The new triterpene belongs to the lupeol class and is an isomer of betulin. Based on the mass, nmr, spectral, and optical rotatory dispersion (ORD) data, the hydroxyl groups are assigned to positions 3 and 12.

In the course of our studies of the biosynthesis of wound tissue formation in giant cacti,[1,2] we examined the ethanol extract of the Organ Pipe cactus (*Lemaireocereus thurberi*) cortex. Acid hydrolysis of the extract yielded a neutral fraction, which had a very high lipid and steroid content. From this fraction, we isolated three crystalline compounds by column chromatography on alumina. The first was identified as thurberogenin (I), previously found by Djerassi[3] in Organ Pipe. The second compound was betulin (II), hitherto undetected in this species. The third substance (mp 206–208°) had the same molecular formula as betulin $C_{30}H_{50}O_2$, gave a positive tetranitromethane test and had an ir spectrum almost identical with that of betulin. It appeared to be a new triterpene of the lupane class, and was given the trivial name, thurberin (III). Evidence to support the structural assignment (III) is given below.

Thurberin formed a diacetate (IV) and absorbed 1 mol of hydrogen (PtO_2) to yield dihydrothurberin (V), which also could be converted into a diacetate (VI). Oxidation of thurberin with CrO_3–pyridine led to the diketone, thurberindione (VII), which on catalytic reduction (H_2/PtO_2) yielded dihydrothurberindione, VIII. When VII was submitted to Wolff–Kishner conditions, α-lupene (IX) was formed; under identical conditions VIII gave rise to lupane (X).[4]

These transformations established that thurberin is a lupenediol, isomeric with betulin (II). The two hydroxyl groups were assigned the positions C-3 and C-12 on the basis of ir, nmr, mass, and ORD spectral studies, as outlined in the following sections.

Nmr Measurements.—The nature of the two hydroxyl groups was deduced from the 100-Mc CAT nmr spectra of thurberin (III) and its diacetate (IV). The spectrum of III contained a one-proton quartet centered at τ 6.76 with splitting of 10 and 4.5 cps (X component of ABX system), characteristic of the C-3 proton resonance, adjacent to an OH moiety. This



pattern is almost identical in the spectrum of the diacetate, IV, but is displaced downfield to τ 5.6. This evidence also substantiates the equatorial orientation of the C-3 hydroxyl group.

Information regarding the second OH group also was obtained from the above spectra, which showed a C–X proton quartet centered at τ 6.37 (characteristic of an axial proton attached to an OH-substituted carbon atom).[5] Similar results with appropriate downfield shifts (τ 5.2) were observed in the spectrum of the diacetate, IV. Since the ir spectrum of thurberindione, VII, showed only a single band at 5.88 μ, indicating no cyclopentanone moiety[5] or aldehyde moiety, the nmr data confirm the existence of a second OH group in one of the cyclohexane rings.

(1) C. Steelink, M. Young, and R. L. Caldwell, *Phytochem.*, **6**, 1435 (1967).

(2) C. Steelink, E. Riser, and M. J. Onore, *ibid.*, **7**, 1673 (1968).

(3) (a) C. Djerassi, L. E. Geller, and A. J. Lemin, *J. Amer. Chem. Soc.*, **75**, 2254 (1953); (b) C. Djerassi, E. Farkas, L. H. Liu, and G. H. Thomas, *ibid.*, **77**, 5330 (1955); (c) M. Marx, J. Leclercq, B. Tursch, and C. Djerassi, *J. Org. Chem.*, **32**, 3150 (1967).

(4) We are gratefully indebted to Professor C. Djerassi, Department of Chemistry, Stanford University, Stanford, Calif., for his generous supply of these specimens for our work.

(5) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 47.

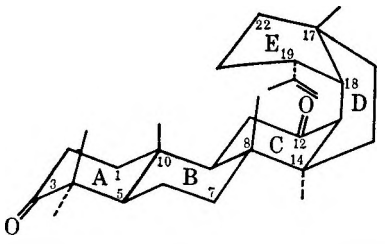


Figure 1.—Conformational model of thurberin-3,12-dione (VII) based on stereochemistry of lupane skeleton.

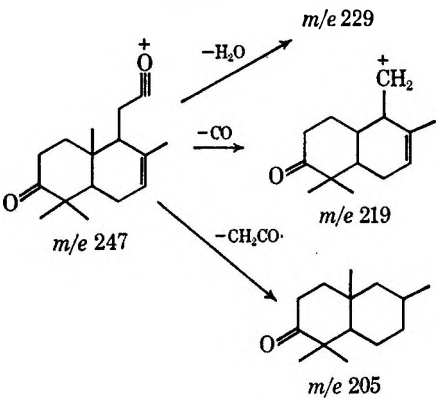
Evidence for the presence of an isopropenyl group was also obtained from the spectra of III and IV, which displayed a three-proton singlet at τ 8.24 (τ 8.34 in IV) due to the C-29 methyl resonances of a side chain isopropenyl group and a doublet centered at τ 5.34 (τ 5.44 in IV), indicative of C-30 protons. Further proof for the presence of the isopropenyl group was afforded by the spectrum of dihydrothurberin diacetate (VI) which exhibited no olefinic proton signal, but rather two three-proton singlets at τ 9.08 and 9.13. This is characteristic of an isopropyl group.[6] All other signals in VI were identical with IV. The location of the isopropenyl group at C-19 was unequivocally established by the previous conversion of VII into lupane and lupene.

Mass Spectral Measurements.—Prominent peaks in the mass spectra of thurberin (III) were *m/e* 442 (25.3), 424 (8.16), 399 (9.12), 234 (34.5), 216 (10.9), 207 (74.1), 189 (100), 147 (81.0), 107 (74.13); diacetate IV *m/e* 526 (3.0), 466 (34.5), 423 (7.15), 276 (7.5), 249 (9.5), 216 (18.5), 189 (100), 135 (60.0), 107 (60.5). These spectra were very similar to those of betulin (II) and its diacetate. This, together with the characteristic peaks at 207 and 189, established the basic structure of the A and B rings as being derived from a 3-hydroxypentacyclic triterpene.[7] A striking feature of the spectrum of III was the *absence* of a strong fragment at 411 (M − 31), which is *prominent* in the spectrum of betulin. This suggests the absence of a $-CH_2OH$ group in III. The low intensity of the M − 43 peak in II and III is consistent with the presence of an isopropenyl moiety.[7]

The possible location of the second OH group was inferred from the mass spectrum of thurberindione (VII): *m/e* 438 (61.5), 395 (6.0), 382 (12.0), 247 (91.5), 229 (47.5), 219 (8.0), 205 (27.5), 23 (100). The spectrum of the dihydro derivative (VIII) also contained prominent peaks at 247, 229, 219 and 205. By assuming carbonyl functions at C-3 and C-12, one can rationalize these results by Scheme I.

ORD Measurements.—Three compounds were used to establish the position of the second OH group: thurberindione (VII), $[\phi]_{300}$ +1408°, lupen-3-one (XI), $[\phi]_{310}$ +3080°, and dihydrothurberindione (VIII), $[\phi]_{310}$ −1412°, all in methanol. Since both VII and XI absorb in essentially the same region of the spectrum and there is no vicinal interaction between the two carbonyl chromophores in VII, the C–X chromophore must have a negative cotton effect. This partially cancels the strong positive cotton effect of the C-3

SCHEME I



ketone group. Such a negative effect will be exhibited by a C-12 carbonyl function and not by a C-11 function, as close examination of a conformational model of the lupane-3,12-dione skeleton (chair–chair–chair–boat–chair)[8] and application of the octant rule reveal[9] (see Figure 1).

Confirmation of this assumption was obtained from the spectrum of dihydrothurberindione (VIII) which exhibited a strong *negative* cotton effect. The isopropenyl moiety at C-19 is able to exert this pronounced effect on the carbonyl function, only if the latter is uniquely situated at C-12 (Figure 1).

Conclusion

Thurberin is shown to be Δ-20,30-lupene-3,12-diol. The presence of an oxygen function at C-12 is unique among cactus triterpenes; its isolation from Organ Pipe represents the first report of its occurrence in nature.

Experimental Section

A. General.—Melting points are uncorrected. Unless otherwise stated, all infrared spectra were recorded on KBr pellets using a Perkin-Elmer Infracord. Model 137 and/or Perkin-Elmer grating Infracord, Model 337. Ultraviolet absorption spectra were determined in methanol using a Cary recording spectrophotometer, Model 14. Nuclear magnetic resonance spectra were run in deuteriochloroform using a Varian HR-100 nmr spectrometer. Chemical shifts are reported in parts per million (τ) from TMS as internal standard. Mass spectra were taken using a Hitachi Perkin-Elmer double-focusing spectrometer (all-glass inlet system), Model RMU-6E. Specific rotations and optical rotatory dispersion measurements were performed in methanol using a Cary recording spectropolarimeter, model 60. Vpc analysis were carried out using 3% QF-1 Chrom W as stationary phase.

Purification of all triterpene derivatives (isolates or synthetates) was routinely carried out by chromatography on dry packed neutral alumina (grade III) followed by repeated crystallization from methanol–chloroform solutions.

B. Extraction of Triterpenes.—The specimens employed in the present investigation were collected on Oct 5, 1967, at the Organ Pipe National Monument, Organ Pipe, Ariz. Wet, cortical (pulp) tissue of mature *Lemaireocereus thurberi* (15 kg) was macerated in a Waring Blendor in hot 95% ethanol. The ethanol extract, after filtration, was concentrated to half volume. Enough concentrated HCl was added to make the solution 0.4 *N*, and the mixture was refluxed for 24 hr. The cooled solution was neutralized with NH_3 to pH, 7; the ethanol was removed under vacuum; and the resulting aqueous layer was repeatedly ex-

(6) A. I. Cohen, D. Rosenthal, G. W. Karkower, and J. Fried, *Tetrahedron*, **21**, 3179 (1965); D. Lavie, Y. Shvo, and E. Glotter, *ibid.*, **19**, 2255 (1963).

(7) H. Budzikiewicz, J. M. Wilson, and C. Djerassi, *J. Amer. Chem. Soc.*, **85**, 3688 (1963).

(8) T. G. Halsall, E. R. H. Jones, and G. D. Meakins, *J. Chem. Soc.*, 2862 (1952), and references cited therein.

(9) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 178.

tracted with ether. The ethereal solution was washed with 10% KOH and dried. From this neutral solution, the triterpenes were isolated.

C. Isolation and Identification of Individual Triterpenes—The ethereal solution (above) was concentrated to dark, viscous oil, dissolved in a small amount of chloroform, and chromatographed on dry-packed acid-washed alumina with eluents listed in Table I, in descending order.

TABLE I

CHROMATOGRAPHY OF NEUTRAL FRACTION FROM THE HYDROLYSIS OF ETHANOL EXTRACT OF THE CORTICAL PORTION OF *Lemaireocereus thurberi*

Fractions	Solvent	Compds isolated	Amount, g
A	Benzene–chloroform (4:1 v/v)	Thurberogenin	1.47
B	Benzene–chloroform (2:1 v/v)	Thurberin + betulin	9.82
C	Chloroform	Betulin	0.19
D	Ether	Betulin	0.033

Thurberogenin (I).—The residue from fraction A, after removal of lipids with hexane and extensive rechromatography, yielded colorless needles from methanol: mp 288–290° (acetate mp 247–249°), undepressed by admixture with an authentic sample.[4]

Betulin (II).—The viscous oily material from fractions C and D was rechromatographed on neutral alumina with ligroin–chloroform (3:2 v/v), followed by benzene–chloroform (2:1 v/v) to yield colorless tiny needles from methanol, mp 249–251° (acetate, 217–219°), containing 1 mol of solvent of crystallization. These were identical with authentic samples.[10]

Thurberin (III).—Although we experienced little difficulty in isolating this material betulin was always a minor contaminant. Only thin layer chromatography on silica with benzene–ethyl acetate (8:2 v/v) could separate betulin from thurberin; this could not be duplicated on a preparative scale. For derivatives and other chemical degradations, the crude material (III) was used without purification.

For analysis and spectroscopic measurements, a small sample of pure thurberin was isolated using the invert dry column technique[11] followed by alumina (grade III) column chromatography. Crystallization from methanol yielded colorless needles: mp 206–208°, $[\alpha]^{25}D$ +12° (*c* 0.001, methanol); λ_{max} 2.88, 6.1, 6.99, 7.22 μ; nmr (deuteriochloroform) τ 8.24 (singlet, 3 H), 6.76 (quartet, 1 H), 6.37 (quartet, 1 H), 5.34 (doublet, 2 H). The compound gave a positive tetranitromethane (TNM) test, showed no selective uv absorption, and contained 1 mol of methanol.

Anal. Calcd for $C_{30}H_{50}O_2 \cdot CH_4O$: C, 78.43; H, 11.46; mol wt, 442. Found: C, 78.56; H, 11.48; *m/e* 442.

The diacetate had mp 191–192°; $[\alpha]^{25}D$ +47° (*c* 0.000428, methanol); λ_{max} 5.8, 6.02 μ.

Anal. Calcd for $C_{34}H_{54}O_4$: C, 77.52; H, 10.33; mol wt, 526. Found: C, 77.84; H, 10.29; *m/e* 526.

Dihydrothurberin (V).—A solution of crude thurberin (200 mg) in ethanol (10 ml) was hydrogenated over PtO_2 (15 mg) at room temperature. After the usual purification (part a), 37 mg of product was obtained: mp 259–261°; $[\alpha]^{25}D$ −62° (*c* 0.00122, methanol). No band at 6.0–6.1 μ in the ir spectrum was observed, and a negative TNM test was obtained.

Anal. Calcd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79; mol wt, 444. Found: C, 80.89; H, 11.66; *m/e* 444.

The diacetate had mp 241–243°; $[\alpha]^{25}D$ +9° (*c* 0.0011, methanol); λ_{max} 5.75, 5.80 μ.

Anal. Calcd for $C_{34}H_{56}O_4$: C, 77.22; H, 10.67; mol wt, 528. Found: C, 76.89; H, 10.73; *m/e* 528.

Thurberin-3,12-dione (VII).—A cold solution of crude thurberin (1.2 g) in pyridine (25 ml) was added portionwise to a stirred solution of chromic anhydride (2.0 g) in water (1.2 ml) and pyridine (40 ml) maintained below 0° and left overnight. The reaction was worked up in the usual way, yielding 750 mg of colorless flakes, mp 168–169°, which contained minor impurities. An analytical sample of VII was isolated by rechromatography on alumina and several recrystallizations from methanol–chloroform: mp 182–183°; $[\alpha]^{25}D$ +22° (*c* 0.001, methanol); $\lambda_{max}^{CHCl_3}$ 5.88 and 6.1 μ; λ_{max} 290 mμ; and gave a positive TNM test. It exhibited the following ORD spectrum (*c* 0.001, methanol): $[\phi]_{589}$ +97°, $[\phi]_{305}$ +1364° (shoulder), $[\phi]_{300}$ +1408° (peak), $[\phi]_{270}$ +44 (trough).

Anal. Calcd for $C_{30}H_{46}O_2$: C, 82.14; H, 10.57; mol wt, 438. Found: C, 82.42; H, 10.71; *m/e* 438.

Dihydrothurberin-3,12-dione (VIII).—Hydrogenation of crude VII, as described above, yielded after chromatograpy and crystallization from methanol–chloroform a colorless solid: mp 263–266°; $[\alpha]^{25}D$ −32° (*c* 0.0012, methanol); λ_{max} 5.88 μ; λ_{max} 290 mμ; and gave negative TNM test. ORD data (*c* 0.0012, methanol) were as follows: $[\phi]_{589}$ −18°, $[\phi]_{315}$ −1412° (peak), $[\phi]_{305}$ −1356° (shoulder), $[\phi]_{275}$ −37° (trough).

Anal. Calcd for $C_{30}H_{48}O_2$: C, 81.76; H, 10.98; mol wt, 440. Found: C, 81.69; H, 11.12; *m/e* 440.

Lupane (X) **from Dihydrothurberindione** (VIII).—A mixture of pure dihydrothurberin-3,12-dione (80 mg), diethylene glycol (6 ml), KOH (0.5 g), and hydrazine hydrate (1.0 ml, 99%) was heated under reflux for 20 hr in an atmosphere of nitrogen. Dilution with water, followed by extraction with ether, afforded a solid material. Purification in the usual manner (part A) yielded colorless needles (35 mg), mp 184–186°, of lupane, identical with an authentic sample.[4] In the same manner, α-lupene (IX) was obtained from thurberin-3,12-dione (VII), mp 161–163°, identical with a sample prepared from lupeol[12] by chromic oxidation and Wolff–Kishner reduction.

Registry No.—III, 19769-92-7; III (diacetate), 19769-93-8; V, 19769-94-9; V (diacetate), 19769-95-0; VII, 19806-63-4; VIII, 19769-96-1.

Acknowledgment.—We wish to acknowledge the generous support of the National Institute of Health (GM-12288) for this work. Also, we are indebted to Dr. R. B. Bates of this department for his helpful interpretation of the nmr spectra, as well as to Mr. G. Edmundson of this department for ORD measurements, and Professor Carl Djerassi, Stanford University, for his constructive comments. We thank the National Park Service for permission to take samples at Organ Pipe National Monument.

(10) We are grateful to Dr. J. Knight, Department of Chemistry, Arizona State University, Tempe, Ariz., for the gift of this material.

(11) V. K. Bhalla, U. R. Naik, and S. Dev, *J. Chromatog.*, **26**, 54 (1967).

(12) We are grateful to Professor J. R. Cole, Department of Pharmacy, University of Arizona, Tucson, Ariz., for providing us with this sample.

The Ozonolysis of Tetrahydrochromans. Formation of Glycols and Normal Ozonolysis Products[1]

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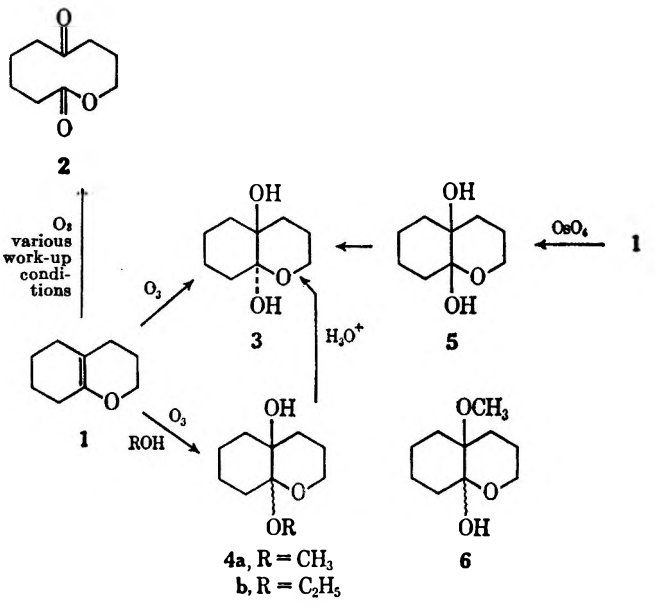
The ozonolysis of tetrahydrochromans followed by work-up with zinc and acetic acid gives varying amounts of 6-ketononanolides, the expected product, and *trans*-9,10-dihydroxyhexahydrochromans, depending on reaction conditions. Ozonolysis in methanol gives 9-methoxy-10-hydroxyhexahydrochroman as the principal product. It is postulated that ozonolysis of enol ethers such as tetrahydrochromans can give either ozonides and/or peroxidic products which are converted into the expected dicarbonyl products or epoxy ethers which are solvolyzed to give dihydroxy or alkoxyhydroxy ethers. Electronic factors leading to epoxy ether formation in ozonolysis and the problem of the assignment of stereochemistry to the isolated dihydroxy and alkoxyhydroxy ethers are discussed.

It has been suggested by Bailey and Lane[4] that the interaction of ozone with olefins can involve two distinct and competing processes proceeding from the formation of a π complex: (a) a concerted 1,3-dipolar cycloaddition of ozone which leads to the formation of an initial ozonide (a 1,2,3-trioxolane or "molozonide") which is converted to a "normal" ozonide (1,2,4-trioxolane) and derived normal ozonolysis products, and (b) conversion to a σ complex which loses molecular oxygen to give an epoxide and its derived products.

Epoxide formation has been observed in the ozonolysis of olefins which are substituted by bulky groups[4-6] and an argument based on steric hindrance to 1,3-dipolar addition of ozone has been advanced.[4] The "electrophilic trend" in the rates of ozone attack on olefins has been reemphasized recently[7] and it has been suggested that epoxide formation and related oxygen-transfer reactions are related to the ease of formation of stable carbonium ions.[4,7]

We now report that the ozonolysis of tetrahydrochromans such as **1**[8,9] can lead to the normal ozonolysis products, 6-ketononanolides **2**, and also to several products which can be rationalized as arising from epoxy ether intermediates: *trans*-dihydroxy ethers **3** and alkoxyhydroxy ethers **4** (Scheme I).

SCHEME I



Results

Table I summarizes our results on the ozonolysis of **1**. Ozonolysis of **1** at −78° (Dry Ice–acetone) or at room temperature followed by rapid reductive work-up in acid (runs 1–3) gives **2** as the major product (54–70%) as well as small yields of 9,10-dihydroxyhexahydrochroman **3**. These reactions were analyzed *via* gas chromatography on crude mixtures which were silanized.[10] The glycol **3** has been previously obtained by us in the treatment of **1** with moist perphthalic acid[8] or with osmium tetroxide followed by a reductive work-up with sulfite. The latter reaction presumably first gives the *cis*-glycol **5** which is readily isomerized to the *trans* isomer **3** at its anomeric center.[11] We have previously shown that **3** and the related **11** are most likely *trans* substituted.[9]

Runs 1–3 represent the best conditions for converting **1** to **2** by ozonolysis. Other runs (4–6) were unsuccessful. The best yield of glycol **3** (run 8) was reproducibly obtained by a 0° reductive work-up of a low-temperature ozonolysis mixture which had been allowed to remain at −78° for 12 hr.[12] Ozonolysis of **1** in methanol with a trimethyl phosphite work-up gave 9-methoxy-10-hydroxyhexahydrochroman (**4a**) (23% isolated, 46% by vpc). In order to clarify the origin of the methoxy group in **4a**, **1** was ozonized in methanol with no work-up (run 10) to give **4a** (34%). Thus **4a** can be formed without the presence of trimethyl phosphite. A similar reaction of **1** in ethanol with triethyl phosphite work-up gave **4b** (run 11). As a check, treatment of **1** with oxygen gave no reaction. The structure of **4a** follows from its facile conversion to **3** with dilute acetic acid, another example of rapid solvolysis at an anomeric center. If **4a** had the positions of the hydroxy and

(1) This investigation was supported by Public Health Service Research Grant AI 06303 from the National Institute of Allergy and Infectious Diseases. This is part V of the series, Medium-Ring Compounds.

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(3) Taken from the Ph.D. Thesis of R. D. Rapp, Lehigh University, 1967.

(4) P. S. Bailey and A. G. Lane, *J. Amer. Chem. Soc.*, **89**, 4473 (1967), and cited references; R. W. Murray, *Accounts Chem. Res.*, **1**, 313 (1968).

(5) P. D. Bartlett and M. Stiles, *J. Amer. Chem. Soc.*, **77**, 2806 (1955).

(6) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

(7) D. G. Williamson and R. J. Cvetanovic, *J. Amer. Chem. Soc.*, **90**, 4248 (1968).

(8) I. J. Borowitz, G. Gonis, R. Kelsey, R. Rapp, and G. J. Williams, *J. Org. Chem.*, **31**, 3032 (1966).

(9) I. J. Borowitz, G. J. Williams, L. Gross, and R. Rapp, *ibid.*, **33**, 2013 (1968).

(10) C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).

(11) For related arguments on anomeric center reactions, see ref 9.

(12) First performed by George Gonis, Lehigh University.

TABLE I

THE OZONOLYSIS OF TETRAHYDROCHROMAN

Run No.	Reaction conditions	Reducing agent	Reduction temp, °C	Yields, % Keto-lactone	Dihydroxy ether	Alkoxyhydroxy ether	Other
1[a]	Methylene chloride, 25°	Zn–HOAc	Reflux	70	3		
2[a]	Methylene chloride, −78°	Zn–HOAc	−78	54	6		
3[a]	Methylene chloride, −78°	Zn–HOAc	Reflux	68	4		
4	Ether, −78°	BuMgI	−78				c
5	*n*-Hexane, −78°	$(CH_3O)_3P$	−78				c
6	Methanol, −78°	Ph_3P	−78				Polymer
7[b]	Methylene chloride, −78°; 12 hr at −78°	Zn–HOAc	25		14.5		
8[b]	Methylene chloride, −78°; 12 hr at −78°	Zn–HOAc	0		39		
9	Methanol, −78°	$(CH_3O)_3P$	−78	15[a]	3[a]	23,[b] 46[a] (4a)	
10[a]	Methanol, −78°	CH_3OH	25			34 (4a)	
11[a]	Ethanol, −78°	$(C_2H_5O)_3P$	−78			11 (4b)	

[a] Yields by vpc on silanized reaction mixtures. [b] Isolable yields. [c] Undefined products.

TABLE II

THE OZONOLYSIS OF SUBSTITUTED TETRAHYDROCHROMANS

Run no.	Reaction conditions	Reducting agent	Reduction Temp, °C	Yields, %[a] Keto-lactone	Dihydroxy ether	Alkoxy hydroxy ethe
1	Methylene chloride, −78°, on **7**	1. HOAc 2. Zn–HOAc	Reflux	53		
2	Methylene chloride, −78°, on **7**	1. HOAc 2. Zn–HOAc	Reflux	56		
3	Methylene chloride, −78°, on **8**	Zn–HOAc	Reflux	4	20 (11)	
4	Methanol, −78°, on **8**	$(CH_3O)_3P$	−78	*b*	*b*	*c*

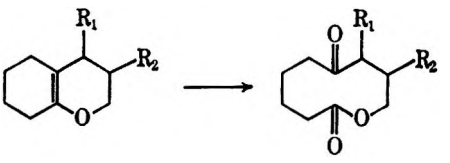
[a] Isolable yields. [b] Present by tlc. [c] Small yield (*ca.* 6%) present; nmr (CCl_4) consistent with presumed structure but not conclusive; could not be purified to analytical purity.

methoxy groups reversed, as in **6**, no conversion to **3** would be expected with dilute acid.

The assignment of the stereochemistry of **4a** presents difficulty. Infrared studies suggest that **4a** is intramolecularly hydrogen bonded (see Experimental Section) with ν_{OH} 3600 cm^{-1} at 0.005 *M* in carbon tetrachloride. While such bonding is only possible between the hydroxy and methoxy groups in the *cis* isomer, it is also possible between the hydroxyl and the ring oxygen in both the *cis* and *trans* isomers.[13] The observed ν_{OH} and $\Delta\nu_{OH}$ (from cyclohexanol) is such that we cannot distinguish between these types of intramolecular hydrogen bonding for **4a**. Thus our stereochemical assignment must remain in doubt. The actual stereochemistry of **4a** may not be very informative mechanistically, in any case, since the methoxyl in **4a** is at an anomeric center. Thus the relative stereochemistry of **4a** as isolated may not be the same as that of the form initially obtained in the ozonolysis of tetrahydrochroman.

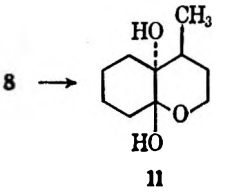
The ozonolysis of 3-methyltetrahydrochroman **7** and the 4-methyl isomer **8** are given in Table II. Reasonable yields of 8-methyl- and 7-methyl-6-ketononanolides **9** and **10** were obtained if the initial ozonolysis mixtures were treated with acetic acid at reflux before reductive work-up with zinc–acetic acid (Scheme II). Omission of the acetic acid treatment in the ozonolysis of **7** resulted in a low yield of **9** (run 3).

SCHEME II



7 $R_1 = H, R_2 = CH_3$ **9**

8 $R_1 = CH_3, R_2 = H$ **10**



11

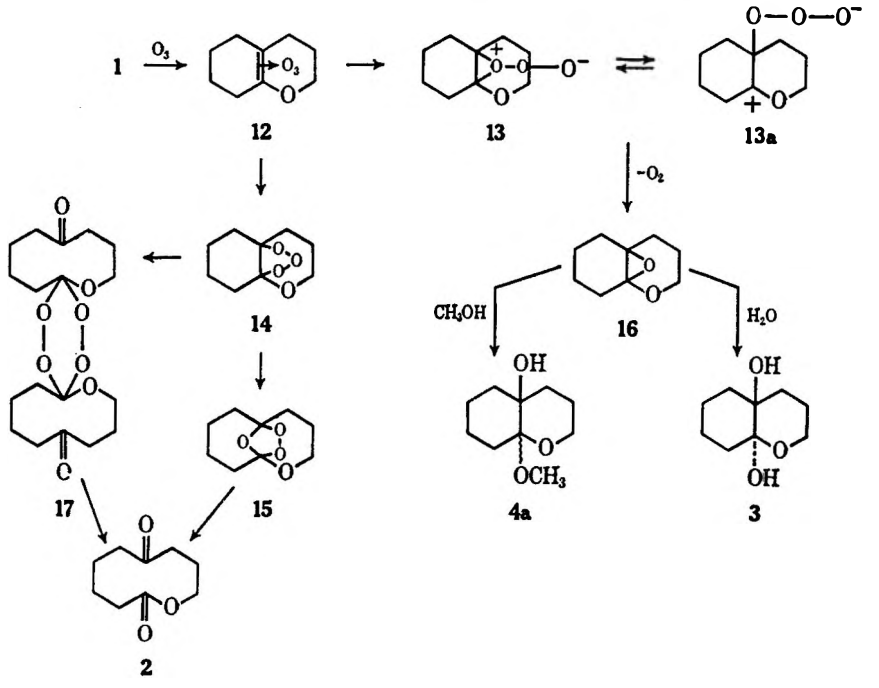
Discussion

Our results suggest that the ozonolysis of tetrahydrochromans may occur *via* two pathways. The normal pathway, leading to 6-ketononanolides, can be visualized as in Scheme III. It may involve the formation of the "normal" ozonide **15** and, more probably, the dimeric ketoperoxide (**17** and isomers) as is found in the ozonolysis of 9,10-decalin and other tetrasubstituted olefins.[6,14] The alternate pathway may involve epoxy ether formation. We suggest that epoxide formation may be important in tetrahydrochroman ozonolysis

(13) M. Tichy, *Advan. Org. Chem.*, **5**, 115 (1965).

(14) R. Criegee, *Ann.*, **583**, 1 (1953), and references therein.

SCHEME III



because of the stabilization of positive charge in intermediates such as **13a** by the ring oxygen.[15] The epoxy ether **16** is not isolable, in keeping with the known high reactivity of epoxy ethers toward nucleophiles.[16] Thus conversion of **16** to **3** with water or to **4a** with methanol should occur readily.[17]

Our data suggest the following possibilities. Ozonolysis of **1** in the polar solvent methanol may encourage formation of the dipolar species **13** and/or **13a** with the resultant production of **16** and then **4a**.[18] Reaction in less polar solvents, such as methylene chloride, may allow the formation of molozonide **14** to predominate, albeit slowly. It is clear from our data that treatment of an ozonized mixture with acetic acid enhances ketolactone formation while formation of the glycol **3** is enhanced by "aging" the ozonized mixture before work-up. Our data is probably insufficient to fully explain these effects. We suggest, however, that the addition of acetic acid might cause protonation of **13**–**13a** and thereby slow down the formation of **4a** more than it influences the formation of **14** or **17**. This argument assumes that species such as **13** and/or **13a** are present after ozonolysis so that they can be influenced during work-up. This possibility is speculative and other factors which influence the formation of **2** *vs.* **3** may have to be considered. It has been suggested that the function of acetic acid is to make the reduction of species such as **17** more likely.[19] While this might explain the high yields of **2** in runs 1–3 (Table I), it does not explain the product differences noted in runs 7–11. It would appear that the initial competition between the formation of **16** and **14** (or **17**) is influenced by a number of factors including the nature of the solvent and the reaction conditions.

Since ozonolysis in methanol gives only a small amount of **2**, the difference due to the use of triphenylphosphine or triethyl phosphite in the subsequent work-up (runs 6,9) is not readily defined. It is of some interest that work-up with triphenylphosphine,[20] or butylmagnesium iodide,[21] both of which have been used in other ozonolysis work-ups, is totally unsuccessful in our work. In relation to our runs **4** and **5** we note that Criegee has previously found that the ozonolysis of tetrasubstituted olefins in nonpolar solvents (methyl chloride or petroleum ether) gives polymeric peroxides.[14]

Experimental Section

Gas chromatograms were recorded on a Varian Aerograph A-700 gas chromatograph employing stainless steel columns packed with 20% DEGS or 1–20% SE-30 on Chromosorb W as noted. Other instrumental and experimental techniques as well as the preparation of tetrahydrochromans have been previously described.[9]

General Ozonolysis Procedure.—A Welsbach T-23 ozonizer was used with 67-V potential on the primary coils and an oxygen pressure of 8 psi. The oxygen was dried by a potassium hydroxide tower before entering the ozonizer. Ozone concentration, determined by bubbling the gas stream through a 5% solution of aqueous potassium iodide for a measured period of time and titrating the liberated iodine with standard thiosulfate solution, was *ca.* 0.15 mmol/min. Ozonolysis was performed in a reaction flask followed by an after bubbler containing KI solution to detect ozone coming through the reaction flask. Ozone uptake was usually quantitative. The ozonizer was then turned off and oxygen was passed through the ozonizer and reaction flask for 15 min to remove excess ozone. The reduction of the ozonide thus formed was done as described below.

Silanization of Ozonolysis Reaction Mixtures.[10]—To a vial containing the reaction mixture resulting from ozonolysis work-

(15) The structures **13** and **13a** may also be considered to be related to σ complexes. These have been recently emphasized in certain ozonolyses: P. R. Story, R. W. Murray, and R. D. Youssefyeh, *J. Amer. Chem. Soc.*, **88**, 3144 (1966).

(16) C. L. Stevens and J. Tazuma, *ibid.*, **76**, 715 (1954), and references cited therein.

(17) The possibility that conversion of **2** into **3** occurs under reductive work-up was eliminated *via* a control experiment which showed that the ketolactone **2** is recovered (92%) after treatment with zinc and acetic acid in CH_2Cl_2 at reflux.

(18) It is possible that **4a** is directly formed from **13**–**13a**, as is suggested by Professor Robert Murray.

(19) Suggested by a referee.

(20) L. Horner in "Newer Methods of Preparative Organic Chemistry," Vol. 2, W. Foerst, Ed., Academic Press, New York, N. Y., 1963, pp 163–212.

(21) F. L. Greenwood, *J. Org. Chem.*, **29**, 1321 (1964).

up (10 mg) in dry pyridine (0.20 ml) was added hexamethyldisilazane (0.20 ml) and trimethylchlorosilane (0.10 ml). The capped vial was shaken for 30 sec, the precipitated salt was allowed to settle, and a sample (15 μl) of the supernatant liquid was used in vpc analysis on a 1% SE-30 column. The relative amounts of various components present was estimated by the use of calibration curves for the pure components.

The Ozonolysis of Tetrahydrochroman 1. A. Reduction with Trimethyl Phosphite in Methanol.—The ozonolysis of **1** (2.76 g, 0.020 mol) in methanol (100 ml) at −78° (Dry Ice–acetone) by the above procedure (run 9, Table I) was followed by the addition of trimethyl phosphite (3.97 g, 0.0320 mol) at −78° over a 15-min period. The mixture was stirred an additional 30 min before being brought to room temperature. Removal of methanol *in vacuo*, addition of ether, washing the ether solution with water, drying, and removal of solvent gave an oil (2.30 g). The oil deposited 9-methoxy-10-hydroxyhexahydrochroman (**4a**) (0.85 g, 0.0046 mol, 23%): mp 86.5–87.0°[c]; nmr ($CDCl_3$), τ 6.45 (m, 2, CH_2O), 6.82 (s, 3, OCH_3), 7.61 (s, 1, OH), 8.0 (m, 2, CH_2CH_2OH), and 8.45 (m, 10, CH_2); mass spectrum (70 eV),[22] *m/e* 186 (M^+) (calcd 186), 168 (M − H_2O), 154 (M − CH_3OH).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.60; H, 9.83.

In another run the oil resulting from the above work-up was silanized and analyzed by vpc at 150° to contain **4a** (1.7 g, 0.0091 mol, 46%), **2** (0.5 g, 0.003 mol, 15%), and **3** (0.1 g, 0.0006 mol, 3%). A similar reaction in ethanol with triethyl phosphite–ethanol work-up gave the presumed **4b** (11%), mp 108–113°, which had **3** as a persistent impurity (by vpc) and could not be prepared analytically pure by recrystallization or sublimation (run 11).

B. In Methanol.—Similar ozonolysis in methanol (100 ml) at −78° and removal of the solvent *in vacuo* at room temperature gave an oil which slowly deposited **4a** (1.27 g, 0.0068 mol, 34%), mp 80–84°, mmp 84–85° with the above sample (run 10).

C. Reduction with Zinc–Acetic Acid at 0°.—Ozonolysis of **1** (0.020 mole) in methylene chloride (100 ml) at −78° was followed by storage at −78° for 12 hr. The mixture was then brought to 0°; zinc dust (3.9 g, 0.059 g-atom) and acetic acid (8.3 ml) were added. The mixture was stirred for 2 hr, the zinc and the solvent were removed by filtration and evaporation, respectively, and the residue was dissolved in hot carbon tetrachloride. Upon cooling, **3** (1.33 g, 0.0077 mol, 39%), mp 112–121° and mmp 122–124° with genuine sample of mp 125–127°, precipitated.

D. Reduction with Zinc–Acetic Acid at Other Temperatures.—Ozonolysis of **1** followed by addition of zinc–acetic acid at −78° for 2 hr gave a mixture which was brought to room temperature, filtered, washed with 2% potassium carbonate and water, dried, and evaporated to give an oil (2.04 g) which contained (vpc on a silanized sample) **2** and **3** (runs 1–3, 7, Table I). Ozonolysis at −78 or 30° followed by immediate work-up with zinc–acetic acid in methylene chloride at reflux (40°) gave **2** and **3** as shown in Table I.

E. Other reduction methods are indicated in Table I and were unsatisfactory for the conversion of **1** to **2** (runs 4–6).

The Ozonolysis of Substituted Tetrahydrochromans. A. Best Conditions.—Ozonolysis of **7** or **8** (0.020 mol) followed by addition of acetic acid (8.3 ml), a reflux period of 12 hr, addition of zinc dust (3.9 g, 0.059 g-atom), and a further reflux period of 36 hr gave **9**, bp 105–110° (0.15 mm), or **10**, bp 100–110° (0.1 mm), ir and nmr spectra identical with those of genuine samples[9] (Table II).

B. Formation of the Glycol 11 from 4-Methyltetrahydrochroman 8.—Ozonolysis of **8** at −78° was followed by bringing the reaction mixture to room temperature and the addition of zinc–acetic acid (amounts as in section A). The mixture was then heated at reflux overnight (work-up as in D above) to give 4-methyl-9,10-dihydroxyhexahydrochroman **11** (0.74 g, 0.0040 mol, 20%): mp 151–152°; ir (CCl_4), 3600 cm^{-1}.

(22) Kindly performed by David Baugher of PAR Associates on a modified CEC mass spectrometer Model 21-103C utilizing a Micro-Teck high-temperature inlet system.

Anal. Found for $C_{10}H_{18}O_3$: C, 64.60; H, 9.71.

Distillation of the residual oil gave **10** (0.16 g, 0.00087 mol, 4%), ir spectrum (neat) identical with that of genuine 7-methyl-6-ketononanolide.[9] Work-up on an ozonolysis of **8** in MeOH with $(CH_3O)_3P$ gave the results indicated in Table II, run 4.

Infrared Studies[23] on 4a and 11.—The model compound 2,5-dimethylcyclohexanol (1.0 *M* in CCl_4 in a 0.1-mm NaCl cell) showed a sharp band at 3620 (free OH) and a broad band at 3390 cm^{-1} (intermolecular H-bonded OH); a 0.1 *M* solution showed increased absorption at 3620 and none at 3390 cm^{-1}. A dilute solution of cyclohexanol (CCl_4) gave a sharp peak at 3630 cm^{-1} (lit.[24] 3625 cm^{-1} for free OH). Infrared spectra of *trans*-2-methoxy-1-cyclohexanol[25–27] taken at 1.0, 0.1, and 0.05 *M* concentrations (CCl_4) with cell path lengths of 0.1, 1.0, and 1.0 mm, respectively, gave, at 1.0 *M*, a broad band at 3480 and a sharp peak at 3600 cm^{-1} (equal intensity); at 0.1 *M*, 3480 (weak) and 3600 cm^{-1} (strong); at 0.05 *M*, only 3600 cm^{-1}. The 3600-cm^{-1} peak is the intramolecular H-bonded OH (lit.[28] 3594 cm^{-1}) while the 3480 peak is the intermolecular H-bonded OH.

Spectra of a saturated and a 1:10 saturated solution of **4a** (CCl_4) showed a sharp peak at 3600 and a broad band at 3510 cm^{-1}. On further dilution to 0.0077 and 0.005 *M* solutions, **4a** showed only the 3600-cm^{-1} peak. The 3510-cm^{-1} peak was assigned to an intermolecular H-bonded OH since it disappeared upon dilution.[13,24b] The 3600-cm^{-1} peak is probably due to an intramolecular H-bonded OH. Since both the *cis* and *trans* forms of **4a** can have intramolecular H-bonding (see Discussion) no stereochemical assignment could be made.

The stereochemistry of **11** was assigned the *trans* configuration as already published.[9]

The Hydrolysis of 9-Methoxy-10-hydroxyhexahydrochroman 4a to the Glycol 3.—A solution of **4a** (0.1 g) in methanol (10 ml), glacial acetic acid (0.5 ml), and water (3 ml) was kept at room temperature overnight and then heated at reflux for 3 hr. Analysis (tlc on silica gel using 25% MeOH–C_6H_6 for development) showed that **3** was mainly present with only a trace of starting material: product mp 115–120°, mmp 119–124° with a genuine sample of **3** of mp 121–125°.

The Reaction of Tetrahydrochroman with Osmium Tetroxide.—To a solution of **1** (0.136 g, 0.000983 mol) and pyridine (0.156 g, 0.00197 mol) in isooctane (15 ml) was added osmium tetroxide (0.250 g, 0.000983 mol) in isooctane (20 ml). A brown precipitate formed immediately. The reaction mixture was stirred at room temperature for 48 hr, and the precipitated osmate ester was collected, washed with isooctane, and hydrolyzed with sodium sulfite (25 g) in 50% aqueous ethanol (50 ml). After 30 min the reaction mixture was filtered and extracted with CH_2Cl_2, and the organic layer was dried and evaporated to give *trans*-9,10-dihydroxyhexahydrochroman (**3**), mp 126–127°, mmp 127–128° with genuine **3** of mp 125–127°; the ir of the product (Nujol mull) was identical with that of genuine **3**.

Registry No.—**1**, 7106-07-2; **4a**, 19689-90-8; **11**, 19685-08-6.

Acknowledgment. We wish to thank the National Science Foundation for funds used in purchasing the Varian A-60 nmr spectrometer at Lehigh University. We also wish to thank Professor Robert Murray for useful discussions, Dr. George Gonis for preliminary ozonolysis studies, and Dr. Eric Lord for stimulating discussions and infrared studies.

(23) Determined on Beckman IR-8 and Perkin-Elmer 227 grating infrared spectrophotometers, using variable-thickness NaCl cells.

(24) (a) B. Casu, M. Reggiari, G. G. Gallo, and A. Viginani, *Tetrahedron*, **22**, 3061 (1966); (b) L. P. Kuhn, *J. Amer. Chem. Soc.*, **74**, 2492 (1952).

(25) Synthesized from cyclohexene oxide and sodium methoxide[26] (35%), bp 87–92° (13 mm), lit.[27] bp 72–73° (10 mm), or from cyclohexene oxide, methanol, and *p*-toluenesulfonic acid (52%), bp 94–96° (35 mm).

(26) P. Bedos and M. C. Moreau, *Compt. Rend.*, **183**, 750 (1926).

(27) S. Winstein and R. B. Henderson, *J. Amer. Chem. Soc.*, **65**, 2196 (1943).

(28) K. W. Buck, A. B. Foster, A. Labib, and J. M. Webber, *J. Chem. Soc.*, 2846 (1964).

Electron Impact Fragmentation of Steroidal Ethylene Hemithioketals and Ethylene Dithioketals[1]

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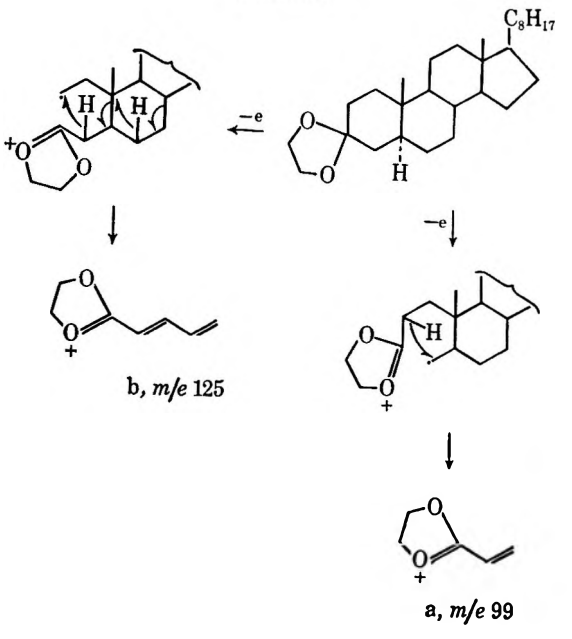
The mass spectra of the 3-ethylene dioxy ketal, hemithioketal, and dithioketal derivatives of cholestane and cholestan-4-one are compared. The hemithioketal is found to be a poor derivative for characterizing steroidal 3-ketones because its fragmentation generates ions resembling the ionized 3-keto compound. The 3-dithioketal is also found to undergo primary fragmentation in the dithiolane ring. Introduction of a carbonyl group at C-4 changes the fragmentation of the dioxy ketal very little, but alters the patterns of the sulfur-containing compounds a great deal. Alteration of configuration at C-5 in the cholestan-4-one derivatives has essentially no effect on the fragmentation pattern.

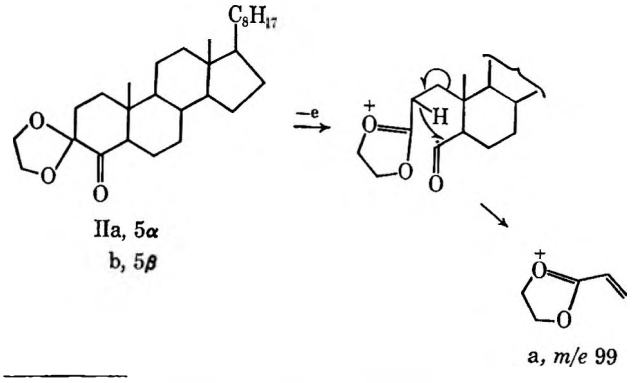
The mass spectra of steroidal ethylene ketals and ethylene thioketals were compared by Djerassi and coworkers[2] several years ago. The fragmentation of ethylene ketals was found to be simpler and more specific than that of the thioketals and this derivative has been recommended[3] for mass spectral characterization of steroidal ketones. In this report the spectra of ethylene dioxy, hemithio-, and dithioketal derivatives of cholestan-3-one are compared with each other and with their α-carbonyl analogs, in an effort to probe the reasons for the simpler fragmentation of the ethylene dioxy ketals. A number of stereoisomers were also investigated.

Results

It has been pointed out[2-4] that the spectra of ethylene ketal derivatives of 3-keto steroids are dominated by two peaks irrespective, to a considerable extent, of other functional groups in the system. Formation of the diagnostic ions[2,3] a and b require α cleavage on either side of the ketal group accompanied by hydrogen transfer, as shown in Scheme I. When no hydrogen is available on C-2 and C-4, the corresponding ion is not formed. This is the case for the epimeric 3-ethylenedioxy derivatives (II)[5] of 5α-cholestan-4-one and 5β-cholestan-4-one. The spectra of this epimeric pair are nearly identical. The largest peak (Table I) is contributed by the diagnostic ion of mass 99. The absence of hydrogen on C-4 accounts for the absence of a peak at *m/e* 125 for the second diagnostic ion, b. No other peak has a relative intensity greater than 20% (Table I) when the spectrum is obtained under the conditions reported. Thus, while the presence of the α-carbonyl group precludes hydrogen transfer from C-4 and genesis of one of the diagnostic ions, it introduces no equally facile new fragmentation.

SCHEME I





In the spectrum of 3-(ethylene-1′-oxy-2′-thio)cholestane (III) the sulfur-containing peaks analogous[4] to diagnostic ions a and b have relative intensities of 37 and 18%, respectively. The key to the fragmentation of this compound appears to be the primary elimination of ethylene sulfide from the oxathiolane ring, generating ions of mass 60 and 386 (Table I). The base peak in the spectrum is at *m/e* 231. Major peaks are found at this mass in the spectra[6] of many ketocholestanes. The ion of mass 231 is generated in the fragmentation of cholestan-3-one, for example, by loss of carbons 15, 16, and 17 and the side chain, with transfer of one

(1) This work was supported in part by U. S. Public Health Service Grant HE 08913 (to C. H. R.), U. S. Public Health Service Grant FR 4378, National Science Foundation Grant GB 7866, and National Institutes of Health Program Grant GM-16492.

(2) G. v. Mutzenbecher, Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *Steroids*, **2**, 475 (1963).

(3) C. Djerassi, *Pure Appl. Chem.*, **9**, 159 (1964), and references therein.

(4) H. Audier, J. Bottin, A. Diara, M. Fetizon, P. Foy, M. Golfier, and W. Vetter, *Bull. Soc. Chim. Fr.*, 2292 (1964).

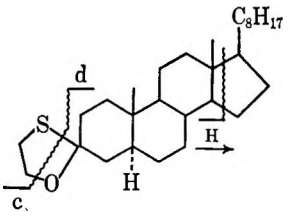
(5) (a) C. H. Robinson and L. Milewich, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, No. O-67; (b) C. H. Robinson, L. Milewich, G. Snatzke, W. Klyne, and S. R. Wallis, *J. Chem. Soc., C*, 1245 (1968); (c) C. H. Robinson and L. Milewich, manuscript in preparation.

(6) H. Budzikiewicz and C. Djerassi, *J. Amer. Chem. Soc.*, **84**, 1430 (1962).

TABLE I
INTENSITIES OF MAJOR PEAKS IN THE MASS SPECTRA OF COMPOUNDS I–VI

Compd no.	M+ RI[b]	M+ TI[c]	M − 28 RI	M − 28 TI	M − 56 RI	M − 56 TI	M − 60 RI	M − 60 TI	M − 88 RI	M − 88 TI	m/e 231 RI	m/e 231 TI	Diagnostic ions: Type a RI	Type a TI	a + 1[a] RI	a + 1[a] TI	Type b RI	Type b TI	Ion k RI	Ion k TI	m/e 60 RI	m/e 60 TI
I	<1	2.78											100	27.85	17	4.74	40	11.14				
II	<1	0.56	2	1.12									100	55.87	15	8.37						
III	11	0.85	1	0.08			49	3.78			100	7.72	37	2.86	23	1.78	18	1.40			32	2.47
IV	10	1.54	13	2.00	10	1.54			25	3.85			100	15.38	45	6.92			10	1.54	6	0.92
V	80	3.48	24	1.04			32	1.39					25	1.10	26	1.13	16	0.70			100	4.35
VI	14	0.98	5	0.35	49	3.46			3	0.21			100	7.06	78	5.51			33	2.33	6	0.42

[a] Corrected for ^{13}C. [b] RI = per cent relative intensity. [c] TI = per cent total ionization, Σ_{29}.

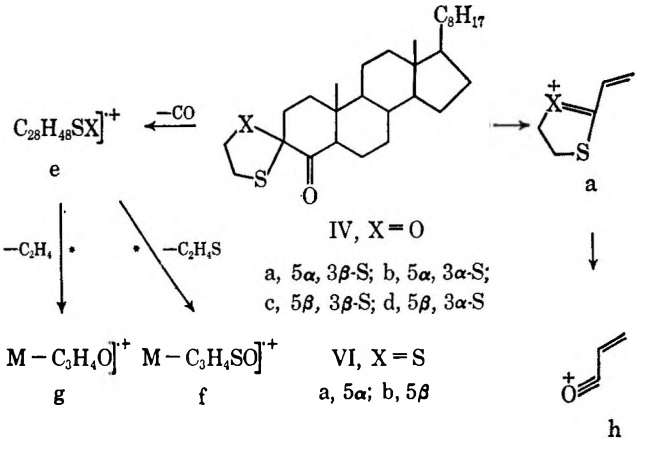


IIIa, 3β-S, 3α-O
b, 3α-S, 3β-O

hydrogen atom.[6,7] In the hemithioketal system III the ion appears to result from loss of ethylene sulfide from one end of the molecule followed by loss of carbons 15, 16, and 17, the side chain, and a transferred hydrogen atom. An intermediate d resembling ionized cholestan-3-one might be postulated because the rest of the spectrum resembles that[6] of cholestan-3-one.

In the spectra of the 4-keto analogs[5] (IVa–d) of this hemithioketal, the base peak is again generated by the diagnostic ion a (mass 115), and the spectra of all four epimers are indistinguishable. An M − 28 ion e is present in this system and is identified in the complete high-resolution spectrum of compound IV as formed by the loss of carbon monoxide from the molecular ion (Table I). This differs from the pattern of the α-keto dioxy ketal (II) and suggests that the carbonyl group exerts more influence on fragmentation in the α-keto hemithioketal compound. The primary elimination of carbon monoxide (*m/e* 432) is followed by fragmentation in the 1,3-oxathiolane ring. (See Scheme II).

SCHEME II



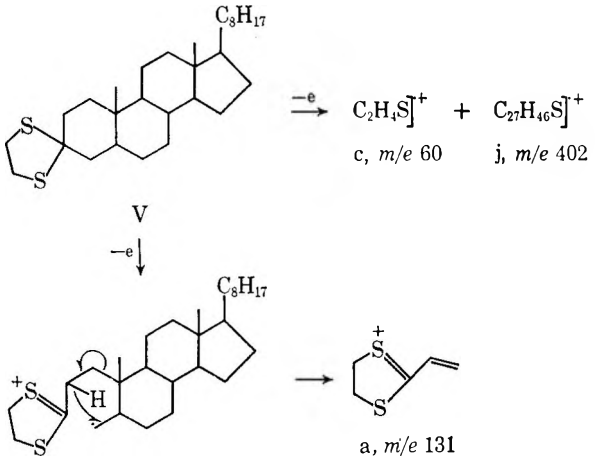
Secondary elimination of C_2H_4S leads to the M − 88 ion f (*m/e* 372) whose composition is $C_{26}H_{44}O$. A flattop metastable peak is observed in the region *m/e* 320–323, supporting this sequence (m − 28 → m − 88) as one route to the mass 372 ions. Elimination of carbon monoxide may also be followed by loss of ethylene, perhaps from the 1,3-oxathiolane ring, generating the only other prominent peak in the high-mass half of the spectrum, M − C_3H_4O, *m/e* 404. In the low-mass range the peak at *m/e* 55 has a relative intensity of 20%. This ion is thought to be formed by secondary decomposition of the mass 115 ion.

Thus the base peak (*m/e* 231) in the spectra of both cholestan-4-one[6] and 3-(ethylene-1′-oxy-2′-thio)cholestane (III) requires fragmentation characteristic of the

(7) L. Tökés, G. Jones, and C. Djerassi, *J. Am. Chem. Soc.*, **90**, 5465 (1968).

hydrocarbon skeleton. When these two functional groups are present together in ring A (IV), this peak occurs to only a few per cent (Table I), and scission of the doubly activated 3,4 bond becomes the major primary process. This leads to generation of the base peak corresponding to diagnostic ion a.

The loss of ethylene sulfide is again an important primary process in the fragmentation of the cholestan-3-one dithioketal V. The base peak (ion c) occurs at *m/e* 60 (Table I). Ethylene is also eliminated from the molecular ion. The molecular ion has a relative intensity of 80%, the peak at *m/e* 131 (corresponding to



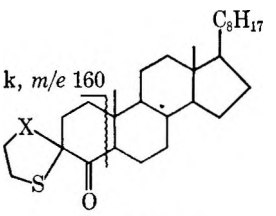
diagnostic ion a) has a relative intensity of 25%, and the second diagnostic peak (*m/e* 157) has a relative intensity of only 16%. The intensity of the peak at *m/e* 132 (26%) is comparable with that of the peak at *m/e* 131 and the mass 132 ion is probably formed with the same C–C bond scissions without hydrogen transfer from C-2, or with a reciprocal transfer. Here, as in the case of the hemithioketals, the diagnostic mass 131 ion has a higher relative intensity in the fragmentation of the α-carbonyl thioketal VI than in the fragmentation of the thioketal itself.

The fragmentation of the C-5 epimers of the 3-ethylene thioketal derivative of cholestan-4-one (VI)[5] leads to nearly identical spectra in which the diagnostic peak has a relative intensity of 100%. A prominent peak (49%) in these spectra occurs at M − 56, *m/e* 420. Accurate mass measurements confirm these mass 420 ions g to have the composition $C_{26}H_{44}S_2$, and a metastable peak at 393.9 suggests that they are formed by sequential loss of carbon monoxide and ethylene. Ethylene is probably lost from the dithiolane ring, such loss having precedent in the fragmentation of tetrahydrothiophene.[8]

Here, as in the α-carbonyl hemithioketal IV, the possibility cannot be eliminated that the diagnostic ion a is formed from the M − CO ion e in addition to, or instead of, the molecular ion.

A moderately intense ion (33%) of mass 160 may be composed of carbons 1–4 and the functional groups. The occurrence of this ion k suggests that not all initial bond cleavage occurs between the thioketal and the carbonyl group. The analogous $C_6H_8O_2S$ ion (mass 144) is present to a small extent (Table I) in the spectrum

(8) A. M. Duffield, H. Budzikiewicz, and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 2920 (1965).



VIa, 5α
b, 5β

of the α-keto hemithioketal IV, and the corresponding mass 128 ion is absent in the spectrum of the α-keto dioxy ketal.

Discussion

One of the most severe limitations of electron impact fragmentation is its inability to distinguish between stereoisomers. The virtual identity of spectra among each of the four sets of epimers discussed here accords with the majority of cases reported.

In the fragmentation of the dioxy ketal I the two most facile α cleavages are those in the A ring which lead to diagnostic ions a and b. When oxygen is replaced by sulfur in the cyclic ketal, scission of C–S bonds (α to the second heteroatom) completes favorably, and primary fragmentation occurs in the oxathiolane or dithiolane ring as well as in the steroid A ring. A larger variety of ions is formed; species arising from scission of C–S bonds contribute the base peaks.

The introduction of a carbonyl group at C-4 facilitates α scission of the 3,4 bond relative to the C–S bond, and in all three of the α-keto ketals the base peak again represents diagnostic ions whose formation involves this A-ring scission. Fission in the oxathiolane and dithiolane rings appears only in secondary processes in these compounds, following elimination of carbon monoxide.

Experimental Section

The ethylene dioxy, hemithio-, and dithioketals described in this paper were prepared by standard procedures, using a benzene solution of the appropriate ketone together with excess ketalizing reagent (ethylene glycol, 2-mercaptoethanol, or ethane-1,2-dithiol) and *p*-toluenesulfonic acid as catalyst. The mixture was refluxed under a Dean–Stark water separator until the reaction was judged complete from tlc of aliquots of the reaction mixture.

All compounds were homogeneous as judged by tlc, and each had infrared and nuclear magnetic resonance spectra consistent with its structure.[9]

The ethylene dioxy ketal I of 5 α-cholestan-3-one had mp 114–115° (lit.[10] mp 115.5–116°), and the corresponding ethylene dithioketal V had mp 143–144° (lit.[11] mp 146.5–147.5°). The known 3-ethylenedithio-5β-cholestan-4-one (VI) had mp 131–132° (lit.[12] mp 128°). The isomeric 3-hemithioketals (IIIa and b) derived from 5α-cholestan-3-one had mp 100–101° (IIIa) and mp 143–145° (IIIb). The high-melting isomer IIIb has been described[13] as existing in two polymorphic modifications of mp 135–136° or 144–145°. We observed only the higher melting modification. In the case of the isomer IIIa, described[13] as showing mp 112–113°, we attribute the difference in melting

(9) All new compounds (IIa, IIb, IVa–d, VIa) gave satisfactory combustion analyses, and a detailed account of the preparation and characterization of these ketals will be given in a forthcoming publication[5] dealing with some of their chemical reactions.

(10) Z. Pelah, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *ibid.*, **86**, 3723 (1964).

(11) L. F. Fieser, *ibid.*, **76**, 1945 (1954).

(12) R. Stevenson and L. F. Fieser, *ibid.*, **78**, 1409 (1956).

(13) E. L. Eliel, L. A. Pilato, and V. G. Badding, *ibid.*, **84**, 2377 (1962).

point of our sample (mp 100–101°) to polymorphism, as our sample was chromatographically homogeneous (in particular, free from starting material and the isomeric IIIb) and had the expected nmr spectrum. All melting points are corrected and determined on a Kofler block.

Low-resolution mass spectra reported in Table I were obtained on an Hitachi RMU 6 mass spectrometer using 80-eV ionization energy with source and direct-inlet temperatures of 180–200°. The complete high-resolution mass spectrum of compound IV was obtained on a CEC-110 mass spectrometer. Individual exact ion masses were determined using the RMU 7 high-resolution instrument.

Registry No.—IIa, 18897-72-8; IIb, 18897-73-9; IIIa, 2760-91-0; IIIb, 2760-93-2; IVa, 18897-78-4; IVb, 17021-85-1; IVc, 18897-79-5; IVd, 18897-77-3; VIa, 18897-74-0; VIb, 18897-75-1.

Acknowledgment.—The assistance of Mr. W. R. Landis of the National Institutes of Health and of the Purdue University Mass Spectrometry Center is most gratefully acknowledged. We also thank Miss M. Pyles for her skillful assistance.

Intramolecular Catalysis in the Acetylation of Methyl Cholate[1]

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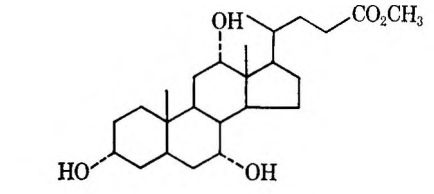
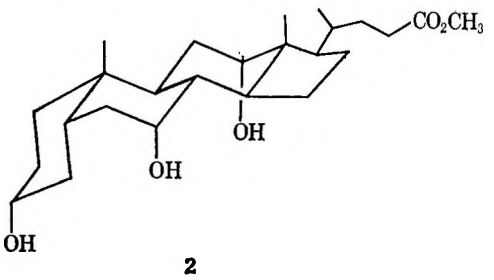
Received November 27, 1968

The hydroxyl groups of methyl cholate decrease in reactivity toward acetic anhydride in the order 3 > 12 > 7 when they are present in compounds free of intramolecular influences. In methyl cholate, however, the 7-hydroxyl is acetylated in preference to the 12-hydroxyl as a result of three interactions: (1) deactivation of the 12-hydroxyl by the side chain, (2) enhancement of 7-hydroxyl reactivity by a 3-acetoxy group, and (3) enhancement of 7-hydroxyl reactivity by the 12-hydroxyl. Preferential acetylation at the 7-hydroxyl occurs also in the absence of a 3-acetoxy group, as in methyl 3α,7α-dihydroxycholanate.

The order of reactivity of the hydroxyl groups of methyl cholate (1) toward acylating agents is established as 3 > 7 > 12, based in part on its acetylation to the 3,7-diacetate by acetic anhydride and pyridine.[2] On conformational grounds, however, the reverse order of reactivity for the 7- and 12-hydroxyls might have been predicted. From inspection of structure 2, it is evident that the 7-hydroxyl is surrounded axially by two hydrogens and a methylene group, while merely three hydrogens surround the 12-hydroxyl, giving rise to less steric inhibition. Some possible explanations for this anomaly include (a) an indirect route for acylation at C-7, (b) inhibition of reactivity of the 12α-hydroxyl, and (c) enhancement of 7α-hydroxyl group reactivity.



1



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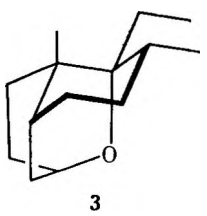

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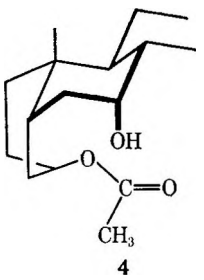


4

An indirect route *via* acetyl migration from the 3 position is conceivable. When the A ring assumes a chair conformation (as in 2), the 3- and 7-hydroxyls are relatively remote. In the conformational equilibrium some portion of the molecules could exist in a boat conformation, however (as is required in the 3,9-oxide 3[3]), producing a structure 4 which could permit acetyl migration from the more reactive 3 position. Acetyl migration does *not* occur, however, under the conditions which produce the 3,7-diacetate of methyl cholate.[4]

In the work reported here we confirm the reactivity sequence predicted on conformational grounds, and examine the latter two explanations of the methyl cholate anomaly. Relative reactivities of 3α-, 7α-, and 12α-hydroxyl groups were assessed by comparing yields of acetate produced under identical conditions with methyl lithocholate (5), methyl 7α-hydroxycholanate (6), and 5β-pregnan-12α-ol (7). Inhibition of the reactivity of the 12-hydroxyl by the bile acid side chain was assessed by comparing 5β-pregnan-12α-ol (7) with methyl 12α-hydroxycholanate (8). The acetylation of methyl 7α-12α-dihydroxycholanate (9) was studied in order to determine whether a 3α-acetoxy group influences the course of the reaction, and acetylation yields of other bile acid derivatives were compared for the purpose of detecting enhancement of 7α-hydroxyl group reactivity, should it exist.

In order to test the prediction that the inherent relative reactivity is 3 > 12 > 7 when these three hydroxyl groups are free of influence by any other group in the molecule, we chose compounds in which

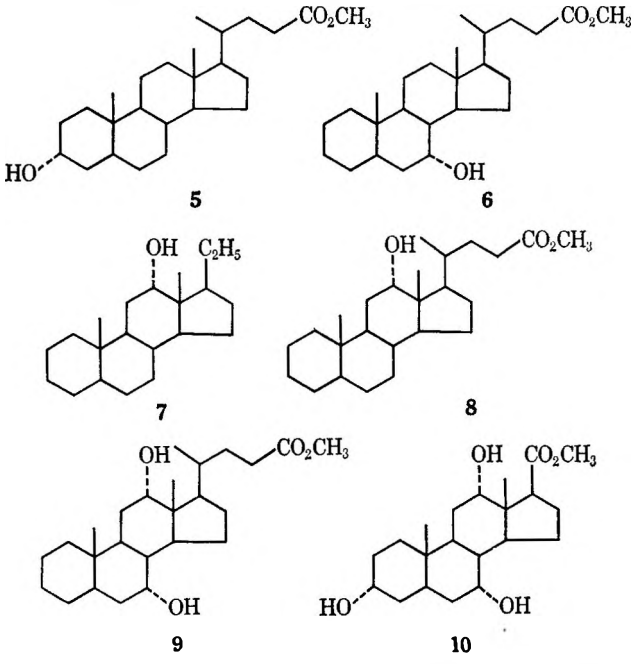
(1) Taken in part from the M.S. thesis of B. Orwig, Indiana University, Indianapolis, Ind., 1967.

(2) L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.*, **72**, 5530 (1950).

(3) V. R. Mattox, *et al.*, *J. Biol. Chem.*, **164**, 569 (1946); R. B. Turner, *et al.*, *ibid.*, **166**, 345 (1946).

(4) R. T. Blickenstaff and B. Orwig, *J. Org. Chem.*, **32**, 815 (1967).

the side chain was either too far from (5 and 6) or too short to reach (7) the hydroxyl. So that the results



would be pertinent to methyl cholate, the three monohydroxy steroids were treated with acetic anhydride and pyridine under conditions similar to those which convert methyl cholate into the 3,7-diacetate.[2] The yields presented in Table I confirm the sequence 3 > 12 > 7, illustrating the sensitivity of this reaction to neighboring conformational factors.

TABLE I

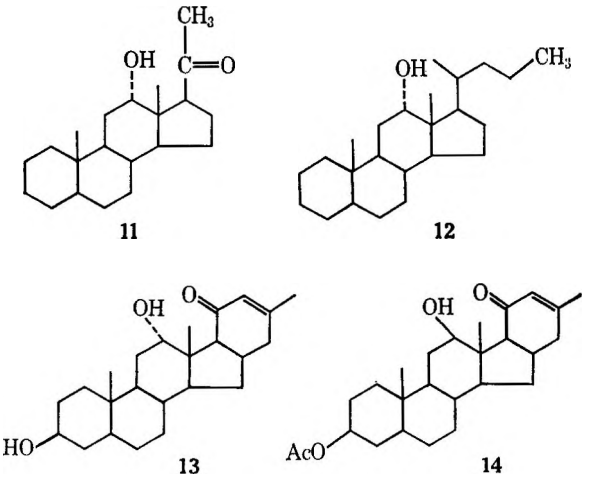
ACETYLATION OF HYDROXY STEROIDS WITH ACETIC ANHYDRIDE AND PYRIDINE[a]

Compd no.	Name	Yield of acetate, %
5	Methyl lithocholate	77
6	Methyl 7α-hydroxycholanate	3–7
7	5β-Pregnan-12α-ol	45–50
8	Methyl 12α-hydroxycholanate	5–8
9	Methyl 7α,12α-dihydroxycholanate	56
11	5β-Pregnan-12α-ol-20-one	18–21
12	12α-Cholanol	5–10
17	Methyl 3α-acetoxy-7α,12α-dihydroxycholanate	60–70
18	Methyl 3α-acetoxy-7α-hydroxycholanate	19

[a] Steroid (0.37 mmol), Ac_2O (0.1 ml), pyridine (0.1 ml), and benzene (0.84 ml), room temperature, 24 hr.

Inhibition of 12α-hydroxyl group reactivity by side-chain shielding has been evoked to explain 3,7 diacetylation of methyl cholate (1) in contrast to 3,12 diacetylation of methyl etiocholate (10).[5] In this comparison the difference in results could, however, have been attributed to a difference in reaction conditions. The diacetylation of methyl cholate was carried out with acetic anhydride and pyridine in benzene,[6] while the diacetylation of methyl etiocholate was achieved by letting a solution of the steroid in glacial acetic acid containing anhydrous HCl stand at room temperature for 5 days.[7,8] The mechanism for acid-catalyzed esterifications is well known,[9] but, even if one accepts that alcoholysis follows the same mechanism as hydrolysis of anhydrides,[10] it is unlikely that steric requirements in the two transition states (in the acetic acid and the acetic anhydride reactions) would be identical. Consequently, it seemed advisable to compare methyl 12α-hydroxycholanate (8) with 5β-pregnan-12α-ol-20-one (11), models for methyl cholate and methyl etiocholate, under the same conditions in order to eliminate any possible ambiguity.[11] The observation that the latter gives about four times as high a yield of acetate as methyl 12α-hydroxycholanate clearly implicates the side chain (Table I). 5β-Pregnan-12α-ol (7) gives an even higher yield, suggesting some indirect influence by the 20-carbonyl of 11.

The Fieser postulate, shielding by the bile acid side chain, is, thus, confirmed, although the detailed chemical nature of that shielding remains to be clarified. It is tempting to relate shielding to hydrogen bonding of the hydroxyl to the side chain, for Wall, *et al.*, found that the 12α-hydroxy compound 13, which cannot H bond intramolecularly, is easily acetylated under conditions that leave the 12β-hydroxy compound 14, which is strongly H bonded, untouched.[12] Indeed,



the infrared spectra of methyl 12α-hydroxycholanate in carbon tetrachloride indicate intramolecular hydrogen bonding (Table II), whereas spectra of 5β-pregnan-12α-ol-20-one and 5β-pregnan-12α-ol indicate only intermolecular hydrogen bonding. As both of the latter are acetylated in higher yield than methyl 12α-hydroxycholanate, it might be inferred that, if comparable molecular associations take place in benzene–pyridine–acetic anhydride solution, the intramolecular H bonding of methyl 12α-hydroxycholanate is responsible for its low reactivity. This interpretation

(5) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 222.

(6) L. F. Fieser, S. Rajogopalan, E. Wilson, and M. Tishler, *J. Amer. Chem. Soc.*, **73**, 4133 (1951).

(7) A. Lardon, *Helv. Chim. Acta*, **30**, 597 (1947).

(8) The argument that the difference in acetylation results could be due to the difference in experimental conditions is somewhat muted by the observation that methyl cholate is converted into its 3,7-diacetate by acetic acid and acetyl chloride: H. Wieland and W. Kapitel, *Z. Physiol. Chem.*, **212**, 269 (1932).

(9) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p 321.

(10) A. R. Butler and V. Gold, *J. Chem. Soc.*, 4362 (1961).

(11) Our short side chain is one atom shorter than Lardon's [-C(=O)CH_3 *vs.* -C(=O)OCH_3], and inspection of models shows that both are too short to reach the 12α-hydroxyl.

(12) M. E. Wall, F. I. Carroll, and G. S. Abernethy, Jr., *J. Org. Chem.*, **29**, 604 (1964).

TABLE II

INFRARED EVIDENCE FOR HYDROGEN BONDING

Compd no.	Name	4% solution	8% solution
8	Methyl 12α-hydroxycholanate	2.70, 2.8–2.9 (sh)[a]	2.70, 2.8–2.9 (sh)[a]
6	Methyl 7α-hydroxycholanate	2.70	2.70, 2.9 (sh)
7	5β-Pregnan-12α-ol	2.70	2.70, 2.90
11	5β-Pregnan-12α-ol-20-one	2.70	2.70, 2.85
12	12α-Cholanol	2.70	2.70, 2.8–2.9 (sh)

[a] $\lambda_{max}^{CCl_4}$ in μ; in 0.2-mm (4%) and 0.1-mm (8%) cells.

is faulty, however, for both 12α-cholanol (**12**) and methyl 7α-hydroxycholanate (**6**) also exhibit low reactivity, but neither hydrogen bonds intramolecularly. Consequently, although the side chain surely deactivates the 12α-hydroxyl, the manner in which this is accomplished is unknown, and other factors may also be important in the diacetylation of methyl cholate.

A 3α-acetoxy group, for example, although shown not to migrate to the 7 position, might conceivably influence the course of the reaction by directing acetylation toward the 7-hydroxyl. In that event, a compound lacking a functional group at carbon 3 might react differently toward acetic anhydride than does methyl cholate. For the purpose of testing this possibility, methyl 7α,12α-dihydroxycholanate (**9**), prepared by reduction of methyl 7α,12α-dihydroxy-3-oxocholanate,[13] was acetylated under conditions that convert methyl cholate into the 3,7-diacetate. The structure of product **15** was indicated by its oxidation to **16**, which along with methyl 3α,7α-diacetoxy-12-oxocholanate exhibits a positive Cotton effect (Scheme I).[14] Confirmation of the 12-oxo structure was obtained by Wolff–Kishner reduction of **16** to 7α-hydroxycholanic acid, which was converted with diazomethane into methyl 7α-hydroxycholanate (**6**). Selective acetylation of 7,12-diol **9** at the 7-hydroxyl proves that the presence or absence of a 3-acetoxy group does not materially influence the course of the reaction.

It is of some interest to note, however, that the yield obtained in this reaction, 56%, is a slightly less than the 66–70% yield of 3,7-diacetate obtained from methyl 3α-acetoxy-7α,12α-dihydrocholanate (**17**) under the same conditions. A similar enhancement of reactivity of the 7-hydroxyl by a 3α-acetoxy group is observed by comparing yields of 7-acetate produced from methyl 7α-hydroxycholanate (**6**), 3–7%, and methyl 3α-acetoxy-7α-hydroxycholanate (**18**), 19%. A much larger effect, however, is obtained in the enhancement of 7-hydroxyl reactivity by the 12α-hydroxyl group: compare **6** (3–7%) with **9** (56%) and **18** (19%) with **17** (66–70%). The significance of compound **17** is that it surely is the intermediate in the diacetylation of methyl cholate. The full explanation of the methyl cholate anomaly, then, must take into account not only 12-hydroxyl deactivation by the side chain, but also 7-hydroxyl enhancement by both the 3-acetoxy group and the 12-hydroxyl group. Bifunctional intramolecular catalysis of a possibly similar nature has been observed by Kupchan, *et al.*, in the acetylation of several perhydrobenzoquinolizine derivatives.[15,16]

(13) F. Nakada, *Steroids*, **2**, 45 (1963).

(14) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960, p 44.

(15) S. M. Kupchan, J. H. Block, and A. C. Isenberg, *J. Amer. Chem. Soc.*, **89**, 1189 (1967). One of the mechanisms proposed by these authors, the general acid–general base mechanism, is readily adaptable to methyl cholate 3-acetate. The adaptation is not wholly adequate, however, for neither does it embrace the role of the side chain, nor does it explain why an analogous process does not occur in which the side-chain ester carbonyl and the 7-hydroxyl combine to enhance reactivity of the 12-hydroxyl.

Experimental Section[17]

Methyl 7α-hydroxycholanate (**6**) was prepared by the action of diazomethane on 7α-hydroxycholanic acid, obtained by Wolff-Kishner reduction of methyl 7α-acetoxy-3,12-dioxocholanate, mp (**6**) 78.5–80.0° (lit.[18] mp 78–79°).

The **acetate** crystallized out of MeOH–H_2O, mp 95–96.2°.

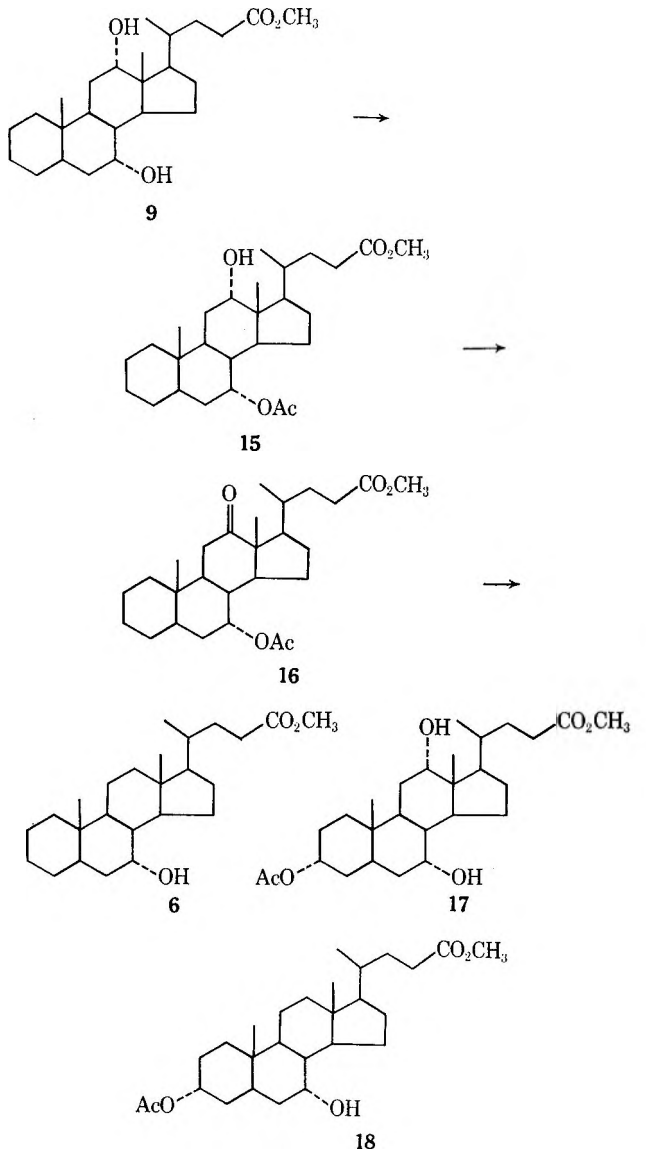
Anal. Calcd for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 75.06; H, 10.43.

(16) The results in Table I for methyl 7α- and 12α-hydroxycholanate are not precise enough either to confirm or conflict with our preliminary finding that (under slightly different conditions) the 12-hydroxy compound reacts at a faster rate than its 7-hydroxy isomer (R. T. Blickenstaff and A. Sattar, Second International Congress on Hormonal Steroids, Milan, 1966, Abstract No. 391). It is interesting to note that a comparable difference in rates for the trimethylsilylation of these two isomers was observed recently [T. Briggs and S. R. Lipsky, *Biochim. Biophys. Acta*, **97**, 579 (1965)].

(17) Melting points were taken on a Unimelt apparatus and are uncorrected. Infrared spectra were determined in CCl_4 solution or as mineral oil mulls with an Infracord. Optical rotatory dispersion spectra were determined on a Rudolph prototype at Eli Lilly and Co. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(18) P. D. Ray, E. A. Doisy, Jr., J. T. Matschiner, S. L. Hsia, W. H. Elliott, S. A. Thayer, and A. E. Doisy, *J. Biol. Chem.*, **236**, 3158 (1961).

SCHEME I



5β-Pregnan-12α-ol (7) was prepared by Wolff–Kishner reduction of 2 g of 5β-pregnan-12α-ol-3,20-dione. The crude product (1.8 g) was recrystallized in MeOH–H_2O to give 1.3 g of **7**: mp 100–101°; λ_{max}^{Nujol} 2.81 (OH), 9.33, 9.49, 9.70 μ.

Anal. Calcd for $C_{21}H_{36}O$: C, 82.83; H, 11.92. Found: C, 83.14; H, 11.87.

The acetate crystallized from MeOH–H_2O, mp 56.0–56.8°.

Anal. Calcd for $C_{23}H_{38}O_2$: C, 79.71; H, 11.05. Found: C, 80.01; H, 11.44.

Methyl 12α-hydroxycholanate (8) was prepared by hydrogenation of the Δ^3 analog, obtained from dehydrotosylation of methyl deoxycholate 3-monotosylate, mp (**8**) 117–118° (lit.[19] mp 120–121°).

Methyl 7α,12α-Dihydroxycholanate (9).—Methyl cholate (**1**) was oxidized with aluminum isopropoxide and acetone to methyl 7α,12α-dihydroxy-3-oxocholanate,[20] which was then reduced by the Wolff–Kishner method to 7α,12α-dihydroxycholanic acid. The latter was converted with refluxing methanolic HCl into methyl 7α,12α-dihydroxycholanate (**9**), mp 153–154° (lit.[18] mp 155–156°).

5β-Pregnan-12α-ol-20-one (11).—3α,12α-Diacetoxy-5β-pregnan-20-one (2.00 g) was hydrolyzed by heating it in a mixture containing 1.6 g of KOH, 8 ml of MeOH, and 8 ml of H_2O near reflux temperature for 15 min. The cooled mixture was diluted with 40 ml of H_2O and filtered; the precipitate was washed with H_2O and vacuum dried. The crude diol was further dried by axeotropic distillation of benzene; then without additional purification, it was tosylated with 2.0 g of *p*-toluenesulfonyl chloride in 14 ml of pyridine. After 3 hr at room temperature, the solution was poured on crushed ice, causing a gum to separate. Trituration of the gum in dilute HCl formed a solid, which was filtered, washed with H_2O and dried, 2.81 g. Crystallization from methanol gave **3α-tosyloxy-5β-pregnan-12α-ol-20-one**, mp 145–146°.

Anal. Calcd for $C_{28}H_{40}O_5S$: C, 68.82; H, 8.25; S, 6.56. Found: C, 68.77; H, 8.24; S, 6.28.

First and second crops (2.30 g) were combined for dehydrotosylation in 18 ml of collidine. The solution was refluxed 3 hr, cooled, diluted with ice, and acidified with H_2SO_4. Slowly a brown solid formed, which was filtered, washed with H_2O, and dried, 1.45 g. Two crystallizations from aqueous acetone gave the analytical sample of **5β-pregna-3-en-12α-ol-20-one**: mp 184–149°; λ_{max} 2.80 (OH) and 5.91 μ (C=O).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.50; H, 10.20.

Hydrogenation of the olefin in absolute ethanol with 5% Pd/C at 50 psi for 30 min gave **5β-pregnan-12α-ol-20-one (11)**, after two crystallizations from aqueous acetone: mp 132–133°; λ_{max} 2.79 (OH) and 5.90 μ (C=O).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.75. Found C, 79.02; H, 10.51.

The acetate crystallized from MeOH–H_2O, mp 84–86°.

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.06. Found: C, 76.52; H, 10.27.

12α-Cholanol (12).—Reduction of methyl 12α-hydroxycholanate (**8**) with lithium aluminum hydride gave 12α,24-cholanediol, different preparations melting variously at 113–119, 119–124, 126–128, and 129–131°, but with similar ir spectra (lit.[21] mp 113–115°); λ_{max}^{Nujol} 2.91, 9.45, 9.68, 9.82 μ. Selective mesylation with methanesulfonyl chloride in pyridine gave 12α-hydroxycholan-24-yl mesylate: mp 89–95° (lit.[22] mp 97.4–98.6°); λ_{max}^{Nujol} 2.73, 8.55, 10.60, 10.90 μ. Reduction of the monomesylate with lithium aluminum hydride, under the conditions used for the reduction of 3α-hydroxycholan-24-yl tosylate to 3α-cholanol,[23] and chromatography on alumina gave 12α-cholanol (**7**), mp 102–103° (lit.[24] mp 100.9–103.3°).

The acetate crystallized out of MeOH–H_2O, mp 63.5–64.0°.

Anal. Calcd for $C_{26}H_{44}O_2$: C, 80.35; H, 11.41. Found: C, 80.54; H, 11.46.

Acetylation of Methyl 7α,12α-Dihydroxycholanate (9).—A warm solution of 1.00 g of **9** in 5.6 ml of benzene and 0.64 ml of pyridine was cooled to room temperature, and acetic anhydride (0.64 ml) was added. After 24 hr the solution was poured into 35 ml of H_2O, the flask was rinsed with 10 ml of ether, and the combined organic layer was washed with three 15-ml portions of water and evaporated to dryness: 1.06 g of crude product, mp 108–132°. An identical product was obtained with 1.00 g of **9**, 11.5 ml of benzene, 0.9 ml of pyridine, and 0.9 ml of acetic anhydride. Crystallization of 2.12 g of the crude product from benzene–petroleum ether (bp 30–60°) gave a mixture (1.20 g, mp 124–142°) which was chromatographed on alumina. Benzene–ether 33:1 eluted 0.47 g of methyl 7α-acetoxy-12α-hydroxycholanate (**15**), and ether–methanol 1:1 eluted unreacted **9**. Recrystallization of the first fraction from benzene–petroleum ether gave pure **15**: mp 138–139°; λ_{max}^{Nujol} 2.80 (OH), 5.79, and 5.85 μ (C=O).

Anal. Calcd for $C_{27}H_{44}O_5$: C, 72.28; H, 9.88. Found: C, 72.04; H, 9.91.

It is likely that the mother liquor from the original crystallization contained additional product, for a small-scale acetylation (150 mg) of **9** in which the total crude steroid mixture was chromatographed as described above provided 93 mg (56%) of **15**, 40 mg (27%) of **9**, and no other products (thin layer chromatography), except that in one run a trace of fast moving component was observed, possibly diacetate.

Methyl 7α-Acetoxy-12-oxocholanate (16).—A solution of 252 mg of $Na_2Cr_2O_7 \cdot 2H_2O$ in 5.34 ml of glacial acetic acid was added to a solution of 377 mg of **15** in 5.34 ml of acetic acid.[25] After 20 min at room temperature, the solution was diluted with water to turbidity and refrigerated overnight. Filtering, washing with H_2O, and drying the solid product gave 352 mg of crude

(19) J. Barnett and T. Reichstein, *Helv. Chim. Acta*, **21**, 926 (1938).
(20) S. Kuwada and S. Morimoto, *Bull. Chem. Soc. Jap.*, **17**, 147 (1942).
(21) G. V. Rao and C. C. Price, *J. Org. Chem.*, **27**, 205 (1962).
(22) F. C. Chang, *J. Pharm. Sci.*, **53**, 1014 (1964).
(23) R. T. Blickenstaff and F. C. Chang, *J. Amer. Chem. Soc.*, **80**, 2726 (1958).
(24) R. T. Blickenstaff and F. C. Chang, *ibid.*, **81**, 2835 (1959).
(25) L. F. Fieser, *ibid.*, **75**, 4377 (1953).

material that was satisfactory for the subsequent steps. Two crystallizations from acetone–H_2O gave the analytical sample of **16**: mp 172–173°; λ_{max}^{Nujol} 5.78 and 5.90 μ (C=O).

Anal. Calcd for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.81; H, 9.62.

Methyl 7α-acetoxy-12-oxocholanate was hydrolyzed by heating a mixture of 99 mg of **16**, 0.1 g of KOH, 0.3 ml of H_2O, 3 ml of acetone, and 5 ml of MeOH at reflux for 5 hr. The crude product was crystallized twice from methanol–water to give an analytical sample of **7α-acetoxy-12-oxocholanic acid**: mp 154–155°; λ_{max}^{Nujol} 2.8–2.9 (OH of carboxyl), 5.75 (ester and acid C=O), 5.87 (ketone C=O), 8.04, 9.80 μ.

Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 71.95; H, 9.52.

Methyl 7α-acetoxy-12-oxocholanate gave a positive Cotton effect curve, $[\alpha]_{314\ m\mu}$ 790 (1.85%, dioxane). Methyl 3α,7α-diacetoxy-12-oxocholanate, mp 177–178.5° (lit.[6] mp 179–181°), prepared by dichromate oxidation of methyl cholate 3,7-diacetate, also gave a positive Cotton effect curve, $[\alpha]_{306\ m\mu}$ 785 (1.68%, dioxane).

Reduction of Methyl 7α-Acetoxy-12-oxocholanate.—A mixture of 304 mg of **16**, 3.34 ml of diethylene glycol, and 1.61 ml of 100% hydrazine hydrate was refluxed 1.5 hr, then heated to 240° with the condenser removed. Potassium hydroxide (0.6 g) was added and, after more H_2O had boiled off, the condenser was replaced and the mixture refluxed 4.5 hr. It was then cooled, diluted with H_2O, and acidified with HCl to pH 2. The resulting white precipitate was filtered, washed with H_2O, and dried over P_2O_5, yield 287 mg. The crude hydroxy acid was esterified by treatment of its methanolic solution with ethereal CH_2N_2. The crude product, an oil, was chromatographed twice on alumina and the fractions eluted by ether and by methanol were crystallized twice from acetone–H_2O to give methyl 7α-hydroxycholanate (**6**), mp 74–76.5°, ir same as that derived from methyl 7α-acetoxy-3,12-dioxocholanate.

Methyl cholate 3-acetate (**17**) is the sample described in ref 4; methyl lithocholate (**5**) was prepared from commercial lithocholic acid and methanolic HCl.

Methyl 3α-Acetoxy-7α-hydroxycholanate (**18**).—Chenodeoxycholic acid was converted into the methyl ester with diazomethane, but the product failed to crystallize even after chromatography. As it showed only one spot on tlc, it was acetylated as the oil by the method for preparation of methyl cholate 3-acetate.[26] The crude product crystallized with difficulty out of acetone–petroleum ether (bp 30–60°) to give fine needles of **18**: mp 57–58°; λ_{max}^{Nujol} 2.77, 5.72, 8.1, 8.60, 8.80, 9.28, 9.75, 10.20 μ.

(26) R. Grand and T. Reichstein, *Helv. Chim. Acta*, **28**, 344 (1945).

Anal. Calcd for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89. Found: C, 72.31; H, 10.00.

Acetylation Procedure.—These conditions are similar to those under which methyl cholate is converted into the 3,7-diacetate. A solution of the steroid (0.37 mmol), acetic anhydride (0.10 ml), and dry (KOH) pyridine (0.10 ml) in 0.84 ml of benzene was kept at room temperature (25°) for 24 hr. Ether (3.2 ml) was used to transfer the reaction mixture to a separatory funnel containing 2.5 ml of water. The ethereal layer was washed with three portions (2.5 ml) of water and evaporated *in vacuo* to dryness. The residue was chromatographed on 30 times its weight of alumina in an 8-mm column, eluted by appropriate combinations of petroleum ether, benzene, ether, and ethanol, separations being followed by tlc. Plates were developed in 3–7% methanol in benzene, then sprayed with 50% H_2SO_4 and heated. In general, compounds lacking free hydroxyl groups (acetates of monohydroxy steroids) were eluted from the column with petroleum ether (bp 30–60°)–benzene mixtures, monohydroxy steroids with benzene–ether mixtures, and dihydroxy steroids with ether–ethanol mixtures. (In a few instances of incomplete separation of ROAc and ROH, the mixture was further separated on thin layer silica gel plates.) Appropriate cuts from the column were combined into acetate and unreacted steroid fractions, weighed, and identified by ir. The yields, based on weights of the acetate fractions, are given in Table I; 84–94% of the starting steroid was accounted for.

Registry No.—**1**, 1448-36-8; **6** (acetate derivative), 19684-60-7; **7**, 6618-40-2; **7** (acetate derivative), 19684-62-9; **11**, 19684-63-0; **11** (acetate derivative), 19684-64-1; **12** (acetate derivative), 19684-29-8; **15**, 19684-66-3; **16**, 19684-67-4; **18**, 19684-68-5; 3α-tosyloxy-5β-pregnan-12α-ol-20-one, 19684-40-3; 5β-pregna-3-en-12α-ol-20-one, 19684-69-6; 12α-hydroxycholan-24-yl mesylate, 1253-86-7; 7α-acetoxy-12-oxocholanic acid, 19684-30-1.

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Alicyclic Carbohydrates. XXXVI. Participation by Neighboring Methoxyl in a Displacement of Hydroxyl by Halogen. Conversion of (−)-Inositol into *meso*-(1,3,5/2,4)-Cyclohexanepentol[1,2]

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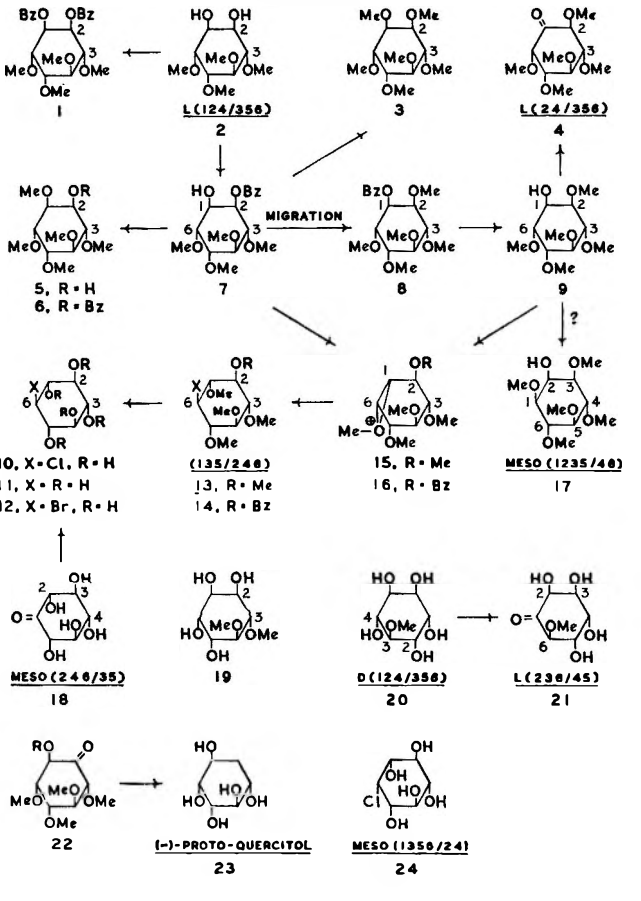
A neighboring methoxyl group appears to participate in the reaction of phosphorus pentachloride with the one free hydroxyl group in (−)-inositol 2,3,4,5,6-pentamethyl ether (**9**). The reaction product was the all-*trans* diastereomer (**13**, X = Cl) of chloropentamethoxycyclohexane identified by conversion into the previously known cyclohexanepentol ("*scyllo*-quercitol") (**11**), and to the chloropentol (**10**) pentaacetate. Tetramethyl ether **2** derived from (−)-inositol was selectively benzoylated at the (equatorial) position 2. The resulting tetramethyl ether monobenzoate (**7**) reacted with methyl iodide and silver oxide to give a mixture consisting mainly of 1-monobenzoate pentamethyl ether **8**, owing to acyl migration.[4,5] Similar reaction of tetramethyl ether monobenzoate **7** with phosphorus pentachloride gave chloropentol tetramethyl ether monobenzoate **14**, which was identified by conversion into the same chloropentol (**10**).

Recently we reported a synthesis of levorotatory form **23** of quercitol or *proto*-quercitol.[2] This synthesis was effected by oxidation of hexol pentamethyl ether **5**, a derivative of (−)-inositol (**3**, Me = H), to the ketopentol or inosose derivative, **22**.[6] Indirect conversion of the carbonyl group to methylene, followed by ether cleavage, gave the desired cyclohexanepentol stereoisomer, **23**.[7]

In the course of this research we also prepared diastereomeric hexol pentamethyl ether **9**. Efforts were made to replace the free hydroxyl group of this compound by halogen, which probably could easily be replaced by hydrogen to give a diastereomeric quercitol derivative (**9**, OH = H). However, the halogenation of **9** with phosphorus pentachloride gave quite unexpected and interesting results, which will now be described.[8]

Hexol pentamethyl ether **9** was prepared from the previously reported[2] tetramethyl ether **2** (Scheme I). This intermediate reacted selectively with benzoyl chloride under suitable conditions to give the equatorial monobenzoate **7**. When this derivative was methylated in the presence of silver oxide, the benzoyl group migrated from position 2 to axial position 1, so that the predominant product was the diastereomeric pentamethyl monobenzoate **8** instead of **6**. Intermediate **8** was readily hydrolyzed to hexol pentamethyl ether **9**. On reaction with excess benzoyl chloride, hexol tetramethyl ether **2** was converted into tetramethyl dibenzoate **1**, as expected.

Scheme I



Hexol pentamethyl ether **9** was treated with phosphorus pentachloride in benzene for 6 hr at 80° under anhydrous conditions. The product, a colorless syrup, was shown by microanalysis and infrared spectroscopy to be a chlorocyclohexanepentol pentamethyl ether (**13** or stereoisomer, X = Cl). In order to characterize this product further, it was demethylated with hydrogen bromide, giving a colorless crystalline compound, mp 236–237°, whose microanalysis and ir spectrum

(1) Presented in part to the International Conference on Cyclitols and Phosphoinositides at the N. Y. Academy of Sciences, New York, N. Y., Sept 1968.

(2) For preceding paper, see G. E. McCasland, M. O. Naumann, and L. J. Durham, *J. Org. Chem.*, **33**, 4220 (1968); see also G. E. McCasland, M. O. Naumann, and L. J. Durham, *Carbohyd. Res.*, **4**, 516 (1967).

(3) To whom any correspondence should be addressed at the University of San Francisco.

(4) For recent studies indicating that acyl migration may be more common than often realized, see S. J. Angyal and G. J. H. Melrose, *J. Chem. Soc.*, 6494, 6501 (1965).

(5) For an example of acyl migration during methylation, see L. Anderson and A. M. Landel, *J. Amer. Chem. Soc.*, **76**, 6130 (1954).

(6) Hexol pentamethyl ether **9** on oxidation in a similar manner with sodium metaperiodate (catalyzed by ruthenium dioxide) gave a ketopentol (inosose) pentamethyl ether, presumably **4**, as a syrup. From this syrup was prepared a (not completely pure) 2,4-dinitrophenylhydrazone, yellow needles, mp 210° (*Anal.* Calcd for $C_{17}H_{24}N_4O_8$: C, 47.66; H, 5.64. Found: C, 41.37; H, 5.62). Material is not available at present for further characterization.

(7) For procedures used for oxidation of secondary alcohol groups, see (a) V. M. Parikh and J. K. N. Jones, *Can. J. Chem.*, **43**, 3452 (1965); (b) W. Sowa and G. H. S. Thomas, *ibid.*, **44**, 836 (1966); (c) J. Parrick and J. W. Rasburn, *ibid.*, **43**, 3453 (1965).

(8) At the time this work was started, we erroneously believed that hexol pentamethyl ether **9** had configuration **5**, so that the expected product of halogenation and dehalogenation would have been the pentamethyl ether of (−)-*proto*-quercitol **23**.

were consistent with its chlorocyclohexanepentol[9] structure (**10** or stereoisomer). The configuration of **10** was determined by dehalogenation in the usual manner[10b] to the previously known *meso*(135/24) or "*scyllo*" diastereomer of cyclohexanepentol (quercitol), **11**. The identity of **11** was confirmed by comparisons with authentic samples of "*scyllo*-quercitol" [10] and its pentaacetate[10] and pentabenzoate. Cyclohexanepentol **11** previously was prepared from ketopentol ("*scyllo*-inosose") **18** or bromopentol **12**.[10]

The ir spectra of the pentol and its pentaacetate and pentabenzoate contained characteristic absorption peaks at about 853 cm^{-1} (methylene C–H rock), and did not contain any peaks at about 873 cm^{-1} which could indicate the presence of equatorial HOC-H, or equatorial RCOOC–H. Thus no axial functional groups were present.[11]

Although epimeric chloropentol **24** presumably also would give cyclohexanepentol **11** on dehalogenation, configuration **24** is highly improbable for mechanistic reasons. Also the infrared spectra of our chloropentol and its pentaacetate and pentamethyl ether indicated it is the all-equatorial diastereomer **10**.

The spectra each contained peaks due to C–Cl stretching absorption at about 780 cm^{-1} (lit.[11] ranges, axial 646–730 and equatorial 736–856 cm^{-1}). Peaks corresponding to equatorial ClC–H rock, or equatorial HOC–H rock (lit.[11] about 873 cm^{-1}), were absent. The nmr spectrum of **10** has not been fully interpreted. However, by use of proton magnetic double resonance (see below) on its pentaacetate derivative, the all-equatorial or "scyllo" configuration was definitely established.

The over-all result in the reaction of hexol pentamethyl ether **9** with phosphorus pentachloride thus consisted of (1) inversions of configuration at positions 1 and 6, formula **9**; (2) migration of a methoxyl group from position 6 to 1; (3) replacement of position 6 functional group by chlorine. The most reasonable interpretation of these results, we believe, is participation by the neighboring methoxyl group at position 6 in the reaction with phosphorus pentachloride, giving the bicyclic methoxonium ion **15** (not isolated), which on nucleophilic attack by chloride ion with inversion, at position 6, would give chloropentol pentamethyl ether **13**.

The departing group, perhaps $-OPCl_4$, presumably is displaced by the neighboring *trans*-methoxyl to give methoxonium ion **15**. The *trans*-diaxial conformation of the groups at positions 1 and 6 (formula **9**) should be favorable to such an internal displacement.

Other possible mechanisms, *e.g.*, the direct epimerization of the position 6 methoxyl group to give diastereomer **17**, followed by displacement of a hydroxyl (or possibly, phosphate ester) group at position 2 (formula **17**) seem much less probable.

Thus the reaction here described is one of a growing number of instances in which a supposedly "inert" methoxyl or alkoxyl group serves as a participating neighboring group in a displacement reaction.

For example, previous studies[12] have shown that a neighboring methoxyl group may participate in certain solvolyses of alkyl arylsulfonates, and in certain substitution reactions of alkyl halides with silver acetate. This participation leads to kinetic effects (anchimeric assistance) and in some cases to otherwise unexpected configurational inversions or retentions, racemization, methoxyl migration, or demethylation. There have been few, if any, examples reported of such participation by neighboring methoxyl in the displacement of *hydroxyl by halogen*.

Hexol tetramethyl ether monobenzoate **7** was treated with phosphorus pentachloride in a similar manner. The product, a colorless syrup, was shown by microanalysis and infrared spectroscopy to have the constitution of a chlorocyclohexanepentol tetramethyl ether monobenzoate (**14** or stereoisomer, X = Cl). The nmr spectrum has not been fully interpreted, but apparently is that of a mixture containing other stereoisomers or by-products as well as **14**. However, when this syrup was cleaved with hydrogen bromide, the only product isolated was a chlorocyclohexanepentol, mp 234–236°, shown to be identical with diastereomer **10** above. The over-all yield, based on **7** (not **14**), was 27%.

Although the tetramethyl ether monobenzoate may react in more than one manner with phosphorus pentachloride, these preliminary results suggest that the (*trans*) neighboring methoxyl at position 6 (formula **7**) has a greater tendency to "participate" than the (*cis*) neighboring benzoyloxy group at position 2.

In the course of our synthetic work, we also prepared hexol tetramethyl ether dibenzoate **1**. Also, we converted the diacetone ketal of (+)-pinitol (**20**) into the corresponding ketopentol (inosose) monomethyl ether **21**. Also, we prepared samples of the previously reported[13] 3,4-dimethyl ether **19** of (−)-inositol and its 1,2:5,6-diacetone ketal.[14] These various compounds were used for proton magnetic resonance studies (see below).

Proton Magnetic Resonance Studies.—Proton magnetic resonance spectroscopy at 60 and 100 MHz was used to establish or confirm the constitution and configuration of most of the products and intermediates here reported (for details, see the Experimental Section).

The special reagent, trichloroacetyl isocyanate,[15] was added directly to the sample tube in the case of the hexol pentamethyl ether **9**, causing cancellation of the –OH and HOCH signals and the appearance of new signals, for the RNHCOOCH and -NH– protons. The

(9) During the period 1907–1915, Müller, and Griffin and Nelson, by reaction of *myo*-inositol with hot acetyl chloride (or its hexaacetate with hydrogen chloride) prepared 6-chlorocyclohexanepentol pentaacetate samples of mp 247 and 250°, respectively, which probably were identical with each other, and with our isomer of mp 248° (**10**, pentaacetate). No samples of their products are available for comparison. See (a) *J. Chem. Soc.*, **91**, 1790 (1907); **101**, 2383 (1912); (b) *J. Amer. Chem. Soc.*, **37**, 1552 (1915).

(10) (a) T. Posternak, *Helv. Chim. Acta*, **24**, 1045 (1941); (b) G. E. McCasland and E. C. Horswill, *J. Amer. Chem. Soc.*, **75**, 4020 (1953).

(11) For discussions of axial–equatorial effects in the ir spectra of substituted cyclohexanes, see (a) S. A. Barker, E. J. Bourne, R. Stephens, and D. H. Whiffen, *J. Chem. Soc.*, 4211 (1954); (b) A. R. H. Cole, P. R. Jeffries, and G. T. A. Muller, *ibid.*, 1222 (1959); (c) M. Larnaudie, *J. Phys. Radium*, **15**, 650 (1954); (d) D. H. R. Barton, J. E. Page, and C. W. Shoppee, *J. Chem. Soc.*, 331 (1956).

(12) See for examples (a) B. Capon, *Quart. Rev.* (London), **18**, 48 (1964); (b) S. Winstein, *et al.*, *J. Amer. Chem. Soc.*, **65**, 2196 (1943); **74**, 1160 (1952); **75**, 145, 155 (1953); **79**, 3278 (1957); *Tetrahedron*, **3**, 1 (1958); (c) D. S. Noyce, *et al.*, *J. Amer. Chem. Soc.*, **82**, 884, 1246 (1960).

(13) L. Anderson, R. Takeda, S. J. Angyal, and D. J. McHugh, *Arch. Biochem. Biophys.*, **78**, 518 (1958).

(14) (a) S. J. Angyal, C. G. Macdonald, and N. K. Matheson, *J. Chem. Soc.*, 3321 (1953); (b) S. J. Angyal and C. G. Mcdonald, *ibid.*, 686 (1952); (c) M. Pitman, M.S. Thesis (with Professor S. J. Angyal), University of N. S. W., Sydney, Australia, 1957.

(15) V. W. Goodlett, *Anal. Chem.*, **37**, 431 (1965).

use of trichloroacetyl isocyanate also permitted all five of the methoxyl groups to be observed as well-resolved individual three-proton singlets.

The spectrum of free chloropentol **10** was found difficult to interpret, even when recorded at 220 MHz with the superconducting solenoid pmr spectrometer.[16] However, the 100-MHz spectrum of the corresponding pentaacetate was successfully interpreted by means of spin decoupling (double resonance). The Cl–CH signal was thus demonstrated to be a triplet centered at 4.00 ppm, with the sum of its coupling constants (J) equal to at least 20 Hz. The Cl–CH proton must then be axial and have two axial neighboring protons, so that the all-equatorial conformation and configuration **10** is correct.

The spectrum of *meso*-(1,3,5/2,4)- or *scyllo*-quercitol[10] was recorded (apparently for the first time), using deuterium oxide at 60 MHz. The equatorial methylene proton produced a pair of triplets, due to coupling with the geminal proton (J = 12 Hz), and the two neighboring axial protons (J = 4 Hz). The axial methylene proton produced a quartet further upfield, due to approximately equal coupling (J = 12 Hz) with the geminal and two neighboring axial protons. The remaining five, very similar (all axial) ring protons produced a complicated narrow multiplet in the region 3.1–3.8 ppm.

In the course of this work, the spectra of the previously known (−)-inositol dimethyl ether **19** and its diacetone ketal, and of the new inosose monomethyl ether **21** were observed.

Experimental Section[17]

All melting points have been corrected, and were measured on a Nalge–Axelrod micro hot stage. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. Optical rotations were measured with a Rudolph Model 62 laboratory polarimeter. Infrared spectra were recorded on Perkin-Elmer Model 137 and 437 spectrometers. Darco G-60 brand[18] of decolorizing charcoal was used. Petroleum ether of boiling point 60–80° was used.

Proton magnetic resonance spectra at 60 MHz were recorded and integrated with Varian A-60 and A-60D spectrometers, and at 100 MHz were recorded with Varian HR-100 and HA-100 spectrometers. The HA-100 was operated in the frequency-sweep mode. Unless otherwise noted, each spectrum was run both at 60 and 100 MHz. For spectra in chloroform-*d*, tetramethylsilane (TMS) was used as internal reference. For spectra in deuterium oxide, sodium 2,2-dimethyl-2-silapentanesulfonate (DSS) was used as internal reference. Chemical shifts are reported in parts per million (δ) from the TMS or DSS reference taken as zero. Field-swept double-resonance experiments on the HR-100 spectrometer were conducted according to the method of Johnson.[19] Modulation was provided by the fixed oscillator of the Varian V-3521-A nmr integrator (operated on its lower side band), and a Hewlett–Packard hp-200-J audiooscillator (monitored by a Hewlett–Packard 521-C frequency counter), for fixed and variable modulation, respectively. Triple-resonance experiments were conducted with additional modulation from a Hewlett–Packard 200-CD oscillator.

L(1,2,4/3,5,6) Stereoisomer of 3,4,5,6-Tetramethoxy-1,2-cyclohexanediol 2-Monobenzoate [Tetra-O-methyl-(−)-inositol Monobenzoate], 7.—To a 2.36-g portion of tetramethyl ether 2,[2] mp 90–92°, in 15 ml of pyridine was added 1.5 ml of benzoyl chloride dropwise at room temperature. The mixture after standing for 24 hr was slowly poured with stirring into 100 ml of ice–water. The resulting mixture was extracted with two 50-ml portions of ethyl acetate and the extract processed in the usual manner. After three recrystallizations from light petroleum, the product was obtained as colorless needles: 2.1 g (62%); mp 120–121°; $[\alpha]^{25}D$ −94.1° (c 3, CCl_4); ir (Nujol) 720, 1100, 1275, 1615, 1725, and 3750 cm^{-1}; nmr (60 MHz, $CDCl_3$); δ 8.08 (m, 2, aromatic *ortho*), 7.3–7.6 (m, 3, *meta* plus *para*), 5.27 (m, 1, poorly resolved, sum of J = 18 Hz, H-2), 4.38 (m, 1, sum of J = 10 Hz, H-1, collapses to three-line pattern on adding D_2O), 3.2–3.9 (m, partially obscured by methoxy singlets, 4, H-3, H-4, H-5, H-6), 3.63 (s, 3, -OMe), 3.54 (s, 6, -OMe), 3.52 (s, 3, -OMe), 2.42 (d, 1, J = 3.5 Hz, -OH, disappears upon addition of D_2O). On the addition of D_2O, a large singlet appeared at 4.63 ppm (HDO).

Anal. Calcd for $C_{17}H_{24}O_7$: C, 59.99; H, 7.11. Found: C, 59.90; H, 7.35.

L(1,2,4/3,5,6) Stereoisomer of 3,4,5,6-Tetramethoxy-1,2-cyclohexanediol Dibenzoate [Tetra-O-methyl-(−)-inositol Dibenzoate], 1. A. From the Tetramethyl Ether.—To a solution of 0.24 g of tetramethyl ether 2 (mp 90–92°) in 3.0 ml of pyridine was added 0.35 ml of benzoyl chloride. After 50 hr the mixture was slowly poured into 25 ml of ice-cold 2% sodium bicarbonate solution, with stirring. After 12 hr of stirring, the mixture was extracted with two 25-ml portions of ethyl acetate. The ethyl acetate extract was processed in the usual manner, giving 0.36 g (80%) of the once-recrystallized (from petroleum ether) product, colorless prisms: mp 106–108°; $[\alpha]^{25}D$ −111.1° (c 7, CCl_4); ir (Nujol) 715, 1110, 1265, 1610 and 1730 cm^{-1}; nmr (60 MHz, $CDCl_3$) δ 7.85–8.15 (m, 4, aromatic *ortho*), 7.3–7.8 (m, 6, *meta* plus *para*), 5.89 (t, 1, J = 3.5 Hz, H-1). 5.51 (m, 1, sum of J = 13 Hz, H-2), 3.5–4.0 (m, partially obscured by methoxy singlets, 4, H-3, H-4, H-5, H-6), 3.71, 3.63, 3.58, and 3.54 (singlets, total 12 H, -OMe), spectrum unchanged by addition of a little D_2O.

Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 65.15; H, 6.33.

B. From the Tetramethyl Ether Monobenzoate.—When monobenzoate **7** (mp 121°) was treated in a similar manner (using less benzoyl chloride), the dibenzoate, mp 106–108°, was obtained in 85% yield, and shown by ir spectrum and mixture melting point to be identical with the product above.

L(1,2,4/3,5,6) Stereoisomer of 2,3,4,5,6-Pentamethoxycyclohexanol [Penta-O-methyl-(−)-inositol], 9.—A 2.0-g portion of tetramethyl ether monobenzoate **7** (mp 121°) was methylated in the manner previously described,[2] giving 0.51 g (24%) of the crystallized (from *n*-heptane) product, 2-O-benzoyl-1,3,4,5,6-penta-O-methyl-(−)-inositol, **6**, resulting from methylation *without* acyl migration, mp 88–90°.

The *n*-heptane mother liquor on evaporation yielded a larger amount of the 1-O-benzoyl-2,3,4,5,6-penta-O-methyl-(−)-inositol, **8**, in the form of a colorless syrup: ir (liquid film) 715, 925, 1110, 1150, 1275, 1610, 1730, and 2900 cm^{-1}. This product is the result of acyl migration during methylation.

This syrup was hydrolyzed with hot aqueous ethanolic sodium hydroxide in the usual manner, giving 0.48 g (52%) of crystallized (from *n*-heptane) hexol pentamethyl ether, **9**: mp 65–66°; colorless prisms; $[\alpha]^{25}D$ −37.2° (c 4, CCl_4); ir (Nujol) 1020, 1100, 1150, 1190, and 3640 cm^{-1}; nmr (chloroform-*d*, 60 and 100 MHz) δ 4.15 (m, 1, poorly resolved, H-1), 3.2–3.8 (partially obscured by methoxyl singlets, 5, H-2, H-3, H-4, H-5 and H-6), 3.59, 3.60 (s, 6, -OMe, three each, OMe, not resolved at 60 MHz), 3.51 (s, 6, -OMe), 3.48 (s, 3, -OMe), 2.92 (d, poorly resolved, 1, -OH) [at 100 MHz after addition of a little trichloroacetyl isocyanate,[15] δ 8.77 (s, 1, -NH–), 5.45 (t, 1, J =

(16) F. A. Nelson and H. E. Weaver, *Science*, **146**, 223 (1964).

(17) (a) In Scheme I, each perspective formula of a (−)-inositol derivative is numbered to correspond with the Maquenne configurational prefix "L(124/356)," and so oriented that position 2 will be in the upper right hand corner, with numbering running from right to left around the front. For consistency in the present article, ring carbon 2 in each of these formula is so chosen that it corresponds to ring carbon 2 in the *starting material*, compound **2**. (b) For each such (−)-inositol derivative, an alternative numbering is possible, in which positions 1, 2, 3, 4, 5, and 6 become, respectively, 6, 5, 4, 3, 2, and 1, without invalidating the prefix "L(124/356);" *e.g.*, consider compound **3**. (c) Since *Chemical Abstracts* index names typically are based on constitution *without regard to configuration*, the *Chemical Abstracts* numbering may differ from that used here (see Experimental Section). For example, *Chemical Abstracts* presumably would designate compound **9** (or **5**) "2,3,4,5,6-pentamethoxycyclohexanol" (*Chemical Abstracts* assigns alkoxyl groups higher numbers than hydroxyl groups when a choice must be made; thus the name 1,2,3,4,5-pentamethoxy-6-cyclohexanol presumably would not be used).

(18) The reagents mentioned are products of the following companies: (a) Darco Division, Atlas Powder Co., Wilmington, Del.; (b) Resinous Products Division, Rohm and Haas Co., Philadelphia, Pa.

(19) L. F. Johnson, "Varian Associates Technical Information Bulletin," Vol. 3, No. 3, Varian Associates, Palo Alto, Calif., 1963, pp. 5–7, 11–13.

2.5, RNHCOOCH, H-1), 3.61, 3.59, 3.54, 3.51, and 3.48 (singlets, total 15 H, -OMe)].

The ratio of migrated to nonmigrated product in the methylation is about 2:1.

Anal. Calcd for $C_{11}H_{22}O_6$: C, 52.78; H, 8.86. Found: C, 53.03; H, 8.80.

L(1,2,4/3,5,6) **Stereoisomer of Hexamethoxycyclohexane [Hexamethyl Ether of (−)-Inositol], 3.**—A mixture of 5.0 g of tetramethoxycyclohexanediol monobenzoate **7** (mp 121°), 5.0 ml of methyl iodide, 5.0 g of KOH, and 30 ml of dry benzene was boiled under reflux for 2 hr with vigorous stirring. The cooled mixture was filtered, and the filtrate washed with sodium bicarbonate solution and with water. The dried solution was evaporated, giving the hexamethyl ether, 3.00 g (77%), as an almost colorless syrup: nmr (chloroform-*d*, 60 and 100 MHz, HA-100 frequency sweep) δ 3.80 (m, broad low, 2, equatorial, H-1 and H-6), 3.30–3.75 (singlets, total 4 H, partially obscured, chemical shifts nearly identical, axial H-2, H-3, H-4, and H-5), 3.60 (s, 6, -OMe), 3.50 (s, 12, -OMe). For analysis, the syrup was distilled, bp 110–112° (2 mm).

Anal. Calcd for $C_{12}H_{24}O_6$: C, 54.53; H, 9.15. Found: C, 54.21; H, 9.12.

meso-(1,3,5/2,4,6) **Diastereomer of 6-Chloro-1,2,3,4,5-cyclohexanepentol (Chlorodeoxyinositol), 10. A. From Inositol Pentamethyl Ether.**—A solution of 0.25 g of hexol pentamethyl ether **9** (mp 66°) in 2.0 ml of dry benzene was heated with 0.30 g of phosphorus pentachloride for 6 hr at 80° under anhydrous conditions. After cooling, the mixture was stirred with 20 ml of ice-cold water, extracted with two 20-ml portions of chloroform, and the chloroform–benzene extract was washed with two 15-ml portions of saturated sodium bicarbonate and water (15 ml). The separated and dried organic phase on evaporation gave a syrup.

Microanalysis indicated that this syrup was the nearly pure chloropentol pentamethyl ether (containing a little phosphorus impurity).

Anal. Calcd for $C_{11}H_{21}ClO_5$: C, 49.16; H, 7.82; Cl, 13.26; P, 0.00. Found: C, 49.51; H, 7.69; Cl, 13.42; P, 0.32.

The ir spectrum of the syrup was recorded (Nujol) at 720, 780, 1030, 1070–1200 (broad, C–O str), 1400, 1480 (C–H bend), 3050 cm^{-1} (C–H str).

To the syrup was added 5.0 ml of a 32% solution of hydrogen bromide in anhydrous acetic acid, and the mixture boiled under reflux for 1 hr, then evaporated. The residue was taken up in 10 ml of water, and the resulting solution treated with charcoal, and evaporated, giving a syrupy residue. The residue was crystallized from 95% ethanol, giving 60 mg (30%) of chloropentol **10**: colorless needles; mp 234–237° dec; ir (Nujol) 778, 985, 1090, and 3450 cm^{-1}.

Anal. Calcd for $C_6H_{11}ClO_5$: C, 36.28; H, 5.58; Cl, 17.85. Found: C, 35.99; H, 5.59; Cl, 17.69.

B. From Tetramethoxycyclohexanediol Monobenzoate.—A 2.0-g portion of tetraether monobenzoate **7** (mp 121°) in 4.0 ml of benzene was treated with 2.4 g of phosphorus pentachloride, and the crude product isolated in the form of a syrup. Microanalysis indicated that this syrup was the nearly pure chloropentol tetramethyl ether monobenzoate (**14**) (containing a little phosphorus impurity).

Anal. Calcd for $C_{17}H_{23}ClO_6$: C, 56.90; H, 6.41; Cl, 9.62; P, 0.00. Found: C, 56.59; H, 6.40; Cl, 9.75; P, 0.49.

The ir spectrum of the syrup was recorded (Nujol) at 710, 760, 1100 (broad), 1260, 1450, 1730 (C=O str), 3050 cm^{-1} (CH str). The nmr spectrum indicated more than one compound was present. The syrup was cleaved with hydrogen bromide, in a manner similar to that described above. The crude chloropentol was taken up in 25 ml of ice-cold water, and the mixture extracted with three 20-ml portions of ethyl acetate. The aqueous phase was treated with charcoal and evaporated. The residue was crystallized and recrystallized from 95% ethanol, giving 0.32 g (27%) of the chloropentol as colorless needles, mp 234–236°. The product was shown by its spectrum and mixture melting point to be identical with the above.

meso-(1,3,5/2,4,6) **Diastereomer of 6-Chloro-1,2,3,4,5-cyclohexanepentol Pentaacetate (Chlorodeoxyinositol Pentaacetate).**—A mixture of 20 mg of chloropentol **10** (mp 234–237° dec) with 5 ml of acetic anhydride and 100 mg of fused sodium acetate was boiled under reflux for 2 hr. The product, isolated in the usual manner, was recrystallized from 95% ethanol, giving 26 mg (64%) of the pentaacetate: colorless needles; mp 247–248° (sealed capillary tube); ir (Nujol) 795, 1220, 1260, and 1750 cm^{-1}; nmr (chloroform-*d*, 60 and 100 MHz) δ 5.15–5.40 (overlapping multiplets, total 5 H, poorly resolved, AcOCH protons H-1, H-2, H-3, H-4, and H-5), 4.00 (t, 1, sum of *J* about 20 Hz, H-6, collapses to singlet on simultaneous irradiation of H-1 and H-5), 2.08 (s, 6, acetate methyl), 2.00 (singlet, 9, acetate methyl).

Anal. Calcd for $C_{16}H_{21}ClO_{10}$: C, 47.01; H, 5.18; Cl, 8.67. Found: C, 47.28; H, 5.17; Cl, 8.92.

meso-(1,3,5/2,4) **Diastereomer of 1,2,3,4,5-Cyclohexanepentol (*scyllo*-Quercitol, Deoxyinositol), 11.**—To a solution of 80 mg of chloropentol **10** (mp 234–237° dec) in 10 ml of water was added 1.0 g of moist Raney nickel catalyst and 1.0 g of moist Amberlite IR-45, anion-exchange resin.[18] The mixture was hydrogenated (3 atm, 25°, 24 hr). The filtrate was evaporated and the residue crystallized from 95% ethanol, giving 55 mg (83%) of pentol **11**: colorless needles; mp 242–243° (lit.[10] mp 235°); ir (Nujol) 945, 999, 1040, 1110, and 3750 cm^{-1}; nmr (D_2O, 60 MHz) δ 4.58, 3.1–3.8 (m, 5, H-1, H-2, H-3, H-4, and H-5), 2.28 and 2.08 (pair of triplets, total area 1 H, J_{gem} = 12 Hz; $J_{1,6e} = J_{5,6e} = 4$ Hz, equatorial methylene H_{6e}), 1.40 (q, 1, $J_{gem} = J_{1,6e} = J_{1,6a} =$ 12 Hz, axial methylene H_{6a}).

The product was shown by ir spectrum and mixture melting point to be identical with an authentic sample of deoxyscyllo-inositol.[10]

Anal. Calcd for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 43.83; H, 7.47.

Acetylation in the usual manner gave the **pentaacetate**: colorless needles; mp 187–189° (lit.[10] mp 190°); ir (Nujol) 1235, 1265, and 1750 cm^{-1}. The pentaacetate was shown by ir spectrum and mixture melting point to be identical with an authentic sample.[10]

The **pentabenzoate** was prepared from a 16.4-mg sample of pentol **11** (mp 242–243°) by reaction with excess benzoyl chloride in pyridine (heat 20 min at 100°). The recrystallized (from 95% ethanol) product, 51.5 mg (75%), was obtained as colorless needles: mp 295–296°; ir (Nujol) 704, 1100, 1610, 1620, and 1725 cm^{-1}.

Anal. Calcd for $C_{41}H_{32}O_{10}$: C, 71.71; H, 4.99. Found: C, 70.98; H, 4.67.

The pentabenzoate was shown by ir spectrum and mixture melting point to be identical with a sample prepared from authentic *scyllo*-quercitol.

L(2,3,6/4,5) **Stereoisomer of 6-Methoxy-2,3,4,5-Tetrahydroxycyclohexanone (Inosose Monomethyl Ether), 21.**—A solution of 1,2;5,6-di-O-isopropylidene-(+)-pinitol (2.5 g, **20**) in 30 ml of dimethyl sulfoxide and 20 ml of acetic anhydride was kept at 25° for 48 hr. The solvent was removed by evaporation, giving a red-brown syrup, consisting presumably of the di-O-isopropylideneketopentol monomethyl ether: ir 1070, 1100, 1200, 1370, 1450, 1730 (ketone C=O), 2850 cm^{-1} (C–H stretch).

A solution of the syrup in 100 ml of 50% acetic acid was boiled under reflux for 2 hr, and evaporated. The residual dark-brown syrup was dissolved in 50% aqueous ethanol (treat with charcoal), and the solution evaporated. The residue was crystallized twice from 95% ethanol, giving the ketopentol monomethyl ether as colorless needles: 1.2 g (68%); mp 178–180°; ir 1080, 1110, 1140, 1280, 1450, 1730 (ketone C=O, 2900 (C–H), 3400 cm^{-1} (O–H stretch); nmr (D_2O, 60 and 100 MHz) δ 4.77 (q, 1, *J* = 1.5, 4.0), 3.5–4.4 (overlapping multiplets, total 3 H, HOCH, 3.9 (q, 1, *J* = 10.5, 2.5), 3.50 (s, 3, -OMe). At 100 MHz, using trifluoroacetic acid as solvent, no additional information was obtained.

Anal. Calcd for $C_7H_{12}O_6$: C, 43.67; H, 6.29. Found: C, 43.67; H, 6.59.

Proton Magnetic Resonance Spectrum of L(1,2,4/3,5,6) Stereoisomer of 3,4-Dimethoxy-1,2,5,6-cyclohexanetetrol [Di-O-methyl-(−)-inositol], 19.—This compound[17] was prepared as previously described: mp 189–191° (lit.[13] mp 191–192°); nmr (D_2O, 60 and 100 MHz, HA-100 frequency sweep) δ 3.3–4.1 (overlapping multiplets for two MeOCH and four HOCH protons), 3.65 (s, 6, -OMe).

Proton Magnetic Resonance Spectrum of the L(1,2,4/3,5,6) Stereoisomer of 3,4-Dimethoxy-1,2;5,6-di-(isopropylidenedioxy)-cyclohexane [Di-O-methyl-(−)-inositol Diacetone Ketal], 19.—This compound was prepared as previously described; mp 86–88° (lit.[14] mp 88–89°); nmr ($CDCl_3$, 60 and 100 MHz, HA-100 frequency-sweep) δ 4.25 [singlet, almost split, 4, $Me_2C(OCH)_2$], 3.3 (multiplets, 2, not resolved, MeOCH, H-3 and H-4), 3.60 (s, 6, -OMe), 1.54 (singlet, 6, acetal methyl, *endo*?), 1.35 (s, 6, acetal methyl, *exo*?).

Registry No.—**1**, 19647-34-8; **3**, 19647-35-9; **3** (Me = H), 551-72-4; **7**, 19647-36-0; **9**, 19647-37-1; **10**, 19647-38-2; **10** (pentaacetate), 19669-12-6; **11**, 527-42-4; **11** (pentabenzoate), 19647-40-6; **13** (X = Cl), 19647-41-7; **14** (X = Cl), 19647-42-8; **19**, 19647-43-9; **19** (diacetone ketal), 19647-44-0; **21**, 19669-13-7.

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Cyclization of D-*xylo*-Hexos-5-ulose, a Chemical Synthesis of *scyllo*- and *myo*-Inositols from D-Glucose[1,2]

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The recently described 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**1**) serves as a convenient precursor for the preparation of D-*xylo*-hexos-5-ulose (**3**). While dicarbonyl sugar **3** was obtained only in amorphous form, its structure was confirmed through reduction to D-glucitol and L-iditol. On treatment with dilute alkali, **3** readily undergoes an intramolecular aldol condensation to give 2,4,6/3,5-pentahydroxycyclohexanone (**6**, *myo*-inosose-2). The identity of **6** was confirmed through its reduction to a mixture of *scyllo*- and *myo*-inositols (**7** and **8**). Chromatographic evidence indicates that dilute alkali converts **6** in part into DL-2,3,5/4,6-pentahydroxycyclohexanone (**9** and **10**). The conversion of **3** into **6** constitutes a step in the chemical synthesis of *myo*-inositol from D-glucose—the second such synthesis to be reported. The cyclization of **3** to **6** closely resembles a step in a postulated biosynthesis of **8**.

Over 80 years have passed since Maquenne[4] made the prescient suggestion that *myo*-inositol may arise in nature through the cyclization of D-glucose. While it is now well established that D-glucose[5-7] and D-glucose 6-phosphate[7,8] are indeed converted, without fragmentation, into *myo*-inositol by several biological systems, the mechanism whereby this takes place remains uncertain. In view of the comparative stability of the D-glucopyranose ring, it is hardly to be expected that an intramolecular aldol condensation, joining carbon atoms 1 and 6, would take place. Some form of active intermediate seems called for and the fact that at least one biogenetic route to *myo*-inositol is NAD^+–NADH dependent[9] has led to the suggestion[6,10] that D-*xylo*-hexos-5-ulose 6-phosphate ("5-keto-glucose 6-phosphate") may be such an intermediate. The cyclization of this substance could lead to the formation of 2,4,6/3,5-pentahydroxycyclohexanone phosphate and the suggestion is rendered more attractive by the recent discovery[11] of *myo*-inosose-2 in nature.

In view of these considerations, it seemed appropriate to synthesize D-*xylo*-hexos-5-ulose (**3**) and to investigate some of its properties.

A number of years ago, Helferich and Bigelow[12] described the synthesis of **3** through a lengthy sequence of reactions. In the course of a synthesis of D-*xylo*-hexos-5-ulose 6-phosphate which we have recently reported,[13] 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**1**) served as an intermediate. We now report the conversion of **1** into D-*xylo*-hexos-5-ulose (**3**) and describe a study of the behavior of this dicarbonyl sugar with dilute alkali.

The benzyl group of **1** was readily removed by catalytic hydrogenolysis to give crystalline 1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranose-5-ulose (**2**) in high yield (Scheme I). An aqueous suspension of an acidic ion-exchange resin served to remove the isopropylidene group from **2** and D-*xylo*-hexos-5-ulose (**3**) was obtained as a syrup which behaved as a single substance when chromatographed on microcrystalline cellulose. Although the substance decomposed on standing at room temperature, its aqueous solutions could be stored in the frozen state at −5° for several months without detectable change.[14] On reduction with sodium boro-

(1) For a preliminary account of some of the work described here, see D. E. Kiely and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **90**, 3289 (1968).

(2) For the nomenclature of the cyclitols, use is made in this paper of the system recommended by the IUPAC Commission on the Nomenclature of Organic Chemistry and the IUPAC-IUB Commission on Biochemical Nomenclature: *Eur. J. Biochem.*, **5**, 1 (1968). To assist the reader, synonyms from older systems are sometimes given in parentheses.

(3) Staff Fellow, National Institutes of Health, 1966–1968.

(4) L. Maquenne, *Ann. Chim.* (Paris), **12**, 129 (1887); see also L. Maquenne, "Les sucres et leurs principaux dérivés," G. Carré and C. Naud, Paris, 1900, p 189.

(5) F. Eisenberg, Jr., A. H. Bolden, and F. A. Loewus, *Biochem. Biophys. Res. Commun.*, **14**, 419 (1964).

(6) H. Kindl and O. Hoffmann-Ostenhof, *Monatsh. Chem.*, **95**, 548 (1964).

(7) H. Kindl, J. Biedl-Neubacher, and O. Hoffmann-Ostenhof, *Biochem. Z.*, **341**, 157 (1965).

(8) I.-W. Chen and F. C. Charalampous, *Biochem. Biophys. Res. Commun.*, **17**, 521 (1964).

(9) I.-W. Chen and F. C. Charalampous, *J. Biol. Chem.*, **239**, 1905 (1964).

(10) F. A. Loewus and S. Kelly, *Biochem. Biophys. Res. Commun.*, **7**, 204 (1962).

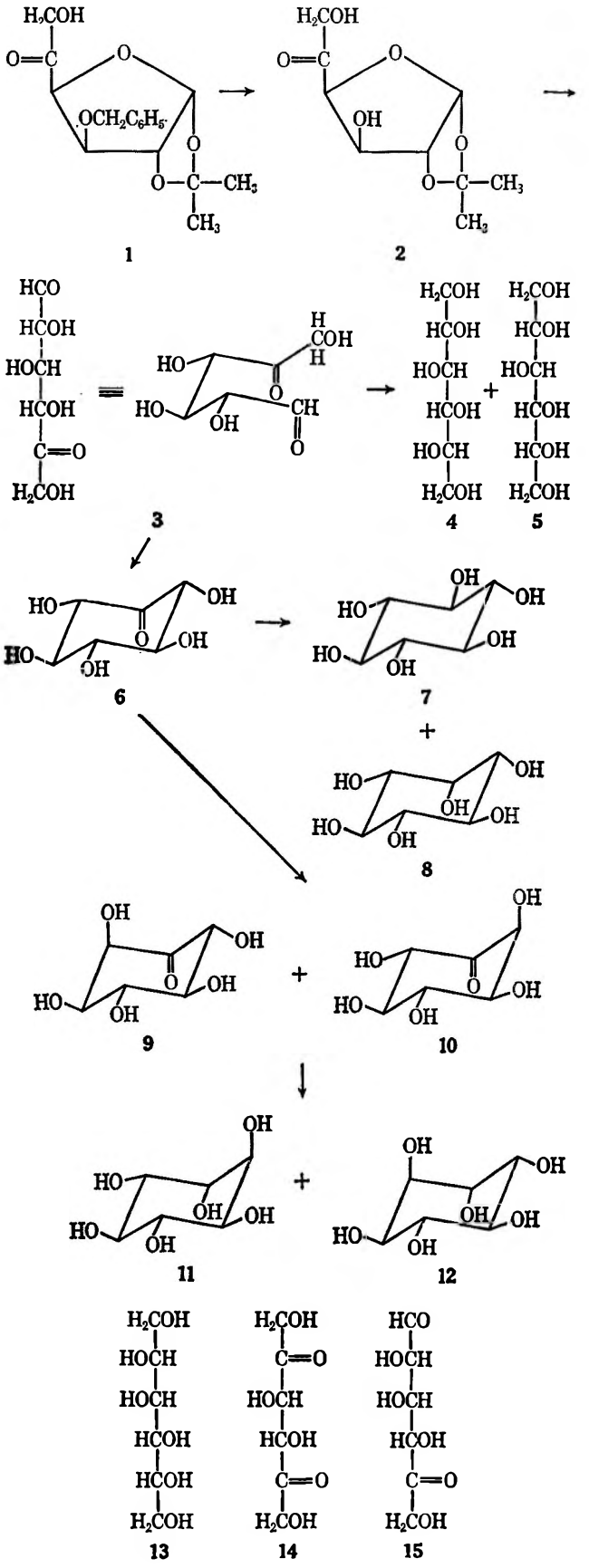
(11) W. R. Sherman, M. A. Stewart, P. C. Simpson, and S. L. Goodwin *Biochemistry*, **7**, 819 (1968).

(12) B. Helferich and N. M. Bigelow, *Z. Physiol. Chem.*, **200**, 263 (1931).

(13) D. E. Kiely and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 3723 (1968).

(14) Whether the product obtained by Helferich and Bigelow[12] was identical with that made during the course of the present research is uncertain. However, the last step in the synthesis used by the earlier researchers involved exposure of **3** to alkali; in view of the alkali lability of **3** reported in the present paper, a synthesis which releases **3** under mildly acidic conditions appears preferable to one which uses alkaline conditions.

SCHEME I



hydride and subsequent acetylation with acetic anhydride–pyridine, **3** gave only two products and these were indistinguishable from the hexaacetates of D-glucitol (**5**) and L-iditol (**4**) when examined by glpc. The formation of D-glucitol and L-iditol on reduction confirms the structure of the dicarbonyl sugar as D-*xylo*-hexos-5-ulose (**3**) but which of the various possible tautometric forms may be present in solution is not known as yet. After trimethylsilylation of **3**, glpc shows the presence of four components; whether these represent the anomeric forms of two cyclic tautomers remains a matter for speculation.

A solution of **3** in 0.1 *N* sodium hydroxide at room temperature and under nitrogen became pale brown over the course of 30–60 min. Deionization removed the color completely and, after concentration, the solution yielded a syrup which strongly reduced Fehling solution and amounted to approximately one-half the weight of the **3** which was used. Trimethylsilylation of this syrup, followed by glpc, revealed several components, one of which was chromatographically indistinguishable from the TMS derivative of 2,4,6/3,5-pentahydroxycyclohexanone (**6**, *myo*-inosose-2). The deionized product from the alkaline treatment of **3** was reduced with sodium borohydride, and a white precipitate which formed was collected and dried. The infrared spectrum (KBr disk) of this product very closely matched that of an authentic sample of disodium *scyllo*-inositol diborate.[15,16] Acetylation with acetic anhydride–sulfuric acid[15,17] gave *scyllo*-inositol hexaacetate from which the free *scyllo*-inositol (**7**) was obtained. The material remaining in the mother liquor from which the disodium *scyllo*-inositol diborate had been removed was decationized, free of boric acid, and acetylated to give the crystalline hexaacetate of *myo*-inositol (**8**), identified by its melting point and infrared spectrum and by comparison with authentic material.

The above facts clearly establish the cyclization of **3** to **6**; the fact that the reaction proceeds under such mild conditions tends to support the postulated biosynthesis of *myo*-inositol. The reaction is, however, a complex one and components which are as yet unidentified have been detected. In this regard, we have investigated the behavior of 2,4,6/3,5-pentahydroxycyclohexanone (**6**) under the conditions of the cyclization. Treatment of **6** with alkali, followed by deionization and sodium borohydride reduction, gave a product which was examined as its TMS derivative by glpc. No component with the chromatographic characteristics of the TMS derivatives of glucitol or iditol was detected. This fact may be interpreted as indicating that the conversion of **3** into **6** is not a significantly reversible reaction or that, if it is reversible, **3** is quite rapidly converted under these conditions into ionic products. No component with the chromatographic characteristics of the TMS derivatives of *neo*-, *cis*-, and *epi*-inositols[18] was detected but a peak with the retention time of the TMS derivative of DL-*chiro*-inositol (**11** and **12**) was noted. It is apparent, then, that **6** is, in part, isomerized by alkali into DL-2,3,5/4,6-pentahydroxycyclohexanone (**9** and **10**) and that this ketose must be present when **3** cyclizes to **6**. It may be noted that DL-2,3,5/4,6-pentahydroxycyclohexanone (**10**), but not its enantiomorph **9**, might have arisen

(15) A. Weissbach, *J. Org. Chem.*, **23**, 329 (1958).
(16) Th. Posternak, E. A. C. Lucken, and A. Szente, *Helv. Chim. Acta*, **50**, 326 (1967).
(17) D. Reymond, *ibid.*, **40**, 492 (1957).
(18) We wish to thank Dr. Laurens Anderson of the University of Wisconsin for authentic specimens of these three inositols.

directly in the cyclization of **6**; however, such an event would have involved the formation of a *cis* pair of vicinal hydroxyl groups and we know of no precedent for this, although it may be pointed out that the cyclization of 6-deoxy-6-nitro-D-glucose and -L-idose gives, *inter alia*, a deoxynitroinositol in which the newly formed hydroxyl group is *cis* to the nitro group.[19]

Under alkaline conditions **3** might be expected to undergo a Lobry de Bruyn rearrangement to form D-*threo*-2,5-hexodiulose (**14**, "5-ketofructose")[20] or D-*lyxo*-hexos-5-ulose (**15**, "5-ketomannose"). However, both of these substances should have yielded D-mannitol (**13**) on reduction and none of this hexitol was detected after reduction of the mixture from the cyclization of **3**.

The transformation of **3** into **8** reported here may be regarded as a sequence in the second chemical synthesis of *myo*-inositol from D-glucose. The first such synthesis was carried out *via* 6-deoxy-6-nitro-D-glucose.[21-24]

Experimental Section[25]

1,2-*O*-Isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (2).—A suspension of 10% palladium on carbon (1.60 g) in absolute ethanol (40 ml) was stirred with hydrogen until saturated, and a solution of the hemihydrate of **1**[18] (2.00 g) in absolute ethanol (100 ml) was added. The resulting mixture was stirred vigorously with hydrogen for 7 hr and the catalyst was then removed. A suspension of fresh catalyst (1.30 g) in absolute ethanol (presaturated with hydrogen) was added and the hydrogenolysis was continued for a further 5 hr. Tlc (ether and ether–benzene, 1:1) then showed the presence of but a trace of the faster moving **1**, the slower running **2** being the major component. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* at 40° (bath) to give syrupy **2** which crystallized spontaneously on storage overnight. After recrystallization from benzene, **2** (1.21 g, 88%) had mp 114.5–116°; $[\alpha]^{21}D$ −63.2° (*c* 2.0, water); infrared absorption (KBr disk) at 3400 (vs) (OH), 1725 (vs) (C=O), 1375 (s), and 1385 (s) cm^{-1} (Me_2C); nmr signals at δ 1.38 and 1.55 (singlets, Me_2C) and 6.08 (doublet, H-1, $J_{1,2}$ = 4.0 Hz).

Anal. Calcd for $C_9H_{14}O_6$ (218.21): C, 49.54; H, 6.47. Found: C, 49.55; H, 6.76.

D-*xylo*-Hexos-5-ulose (3).—Dowex 50W-X8 (H^+) (2.1 g), which had been washed with water and with acetone and dried, was added to a solution of **2** (381 mg) in water (6 ml). The mixture was stored, without stirring, at 38–40° for 48 hr; tlc (ether–methanol, 9:1) then showed the hydrolysis to be complete, only **3** being detectable. The resin was removed by filtration and the filtrate was lyophilized to give **3** in quantitative yield as a colorless glass: $[\alpha]^{20}D$ −14.6° (*c* 3.12, water). On storage at room temperature, amorphous **3** decomposed; frozen aqueous solutions of the compound stored at −5° appeared to be stable indefinitely.

Converted at room temperature into its trimethylsilyl derivative and subjected to glpc at 150° on column A, **3** characteristically gave four peaks as shown in chromatogram *i* of Figure 1. Even in the presence of an excess of the silylating reagent, the TMS derivative of **3** appeared to be unstable at room temperature, discoloration of the solution and changes in the pattern of glpc peaks being noted after 24 hr.

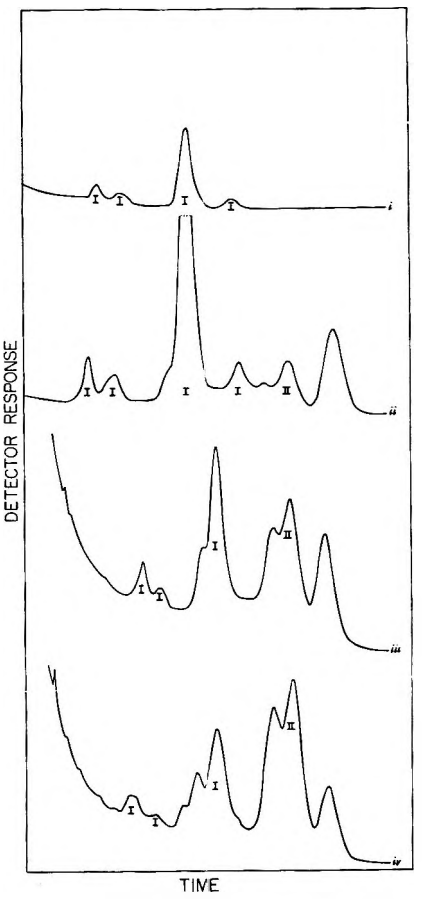


Figure 1.—Gas–liquid partition chromatography on column A of the trimethylsilyl derivatives of (*i*) D-*xylo*-hexos-5-ulose (**3**), (*ii*) **3** after 10 min in 0.1 *N* sodium hydroxide, (*iii*) after 25 min, and (*iv*) after 45 min.

Using the procedure of Frush and Isbell,[26] **3** was reduced with sodium borohydride. A sample (7 mg) of the dicarbonyl sugar was dissolved in borate buffer (3 ml, pH 4.9) and the solution was cooled. Over the course of 15 min, a solution of sodium borohydride (40 mg) in water (4 ml) was added. The reaction mixture was stored at room temperature overnight and the slightly alkaline solution (pH 9.1) was passed through a column of Amberlite IR-120 (H^+) (40 ml). The effluent (60 ml) was concentrated *in vacuo* and boric acid was removed from the residue as trimethyl borate. The syrup was finally held at room temperature and a pressure of <1 mm for 0.5 hr and then acetylated with acetic anhydride–pyridine at 110°. The acetylation mixture was concentrated under a stream of nitrogen to a volume of *ca.* 0.25 ml and samples of the resulting solution were chromatographed on column C[27] at 200°, using a flow rate of 60 ml/min. Two components, chromatographically indistinguishable from the hexaacetates of L-iditol (**4**) and D-glucitol (**5**), were detected. The ratio of the two (in the order named) was 1.3:1.

Cyclization of D-*xylo*-Hexos-5-ulose (3) in Sodium Hydroxide Solution.—A solution of **3** (102 mg) in water (3.2 ml) was deoxygenated by passing a stream of nitrogen through it for 10 min. The solution was cooled in an ice bath and a similarly deoxygenated solution of sodium hydroxide (0.8 ml, 0.52 *N*) was added dropwise, making the reaction mixture *ca.* 0.1 *N* in sodium hydroxide. Nitrogen was bubbled through the reaction mixture at room temperature for 30 min and the brownish solution was deionized (and decolorized) by passage through a column containing a mixture of Duolite A-4 (CO_3^{2-}) (30 ml) and Amber-

(19) F. W. Lichtenthaler, *Chem. Ber.*, **94**, 3071 (1961).

(20) G. Avigad and S. Englard, *J. Biol. Chem.*, **240**, 2290 (1965).

(21) M. Grosheintz and H. O. L. Fischer, *J. Amer. Chem. Soc.*, **70**, 1476 (1948).

(22) M. Grosheintz and H. O. L. Fischer, *ibid.*, **70**, 1479 (1948).

(23) B. Iselin and H. O. L. Fischer, *ibid.*, **70**, 3946 (1948).

(24) Th. Posternak, *Helv. Chim. Acta*, **33**, 1597 (1950).

(25) Melting points correspond to corrected values. Thin layer chromatography was conducted on silica gel 254 (E. Merck AG, Darmstadt) using the solvent systems specified and detecting the components by spraying with sulfuric acid and heating at 100°. Nmr spectra were obtained in $CDCl_3$ solution using a Varian A-60 spectrometer and tetramethylsilane as an internal standard. Glpc was carried out with F & M Models 500 and 5750, equipped with flame ionization detectors. Three columns were employed: (A) 3% SE-52 on Gas-Chrom A, 0.25 in. o.d. × 6 ft with nitrogen as a carrier gas; (B) 15% Apiezon N on Chromosorb P, 0.25 in. o.d. × 6.5 ft with helium as the carrier gas; (C) 3% ECNSS-M on Gas-Chrom Q, 0.25 in. o.d. × 10 ft with nitrogen as a carrier gas. These media were the products of the Applied Science Laboratories, Inc., State College, Pa. Trimethylsilyl derivatives were prepared according to the method of C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, *J. Amer. Chem. Soc.*, **85**, 2497 (1963).

(26) H. L. Frush and H. S. Isbell, *ibid.*, **78**, 2844 (1956).

(27) The utility of this system for the separation of alditol acetates was originally noted by J. S. Sawardeker, J. H. Sloneker, and A. Jeanes, *Anal. Chem.*, **37**, 1602 (1965).

lite IR-120 (H^+) (20 ml). The effluent (*ca.* 110 ml) was concentrated *in vacuo* (40° bath) to a syrup (51 mg) which strongly reduced Fehling solution at room temperature.

Investigation of the Products. A. Reduction.—The syrupy product, prepared as described above, was dissolved in water (3.5 ml) and the solution was cooled in an ice bath. While this solution was stirred, sodium borohydride (47 mg)[28] was added. On standing overnight at room temperature, the reaction mixture deposited long, colorless needles which were removed by filtration, washed with a little cold water, and dried *in vacuo*. The ir spectrum of this material (KBr disk) closely resembled that of a pure authentic specimen of disodium *scyllo*-inositol diborate.[15,16] A small sample (*ca.* 1 mg) of the salt was dissolved in water and the solution was decationized with IR-120 (H^+) (3 ml) and concentrated *in vacuo* at 44° (bath). The syrupy residue was trimethylsilylated and then subjected to glpc at 170° on column A. A major peak (90%) was obtained which was identical with one shown by authentic disodium *scyllo*-inositol diborate when treated in a similar manner. The retention time of this component was identical with that of the TMS derivative of *scyllo*-inositol (7) and thus it appears that *scyllo*-inositol diborate is broken down to the normal TMS derivative of *scyllo*-inositol on trimethylsilylation.

The remainder of the disodium *scyllo*-inositol diborate derived from **3** was dissolved in acetic anhydride (2 ml) containing 1 drop of concentrated sulfuric acid.[15,17] The solution was heated at 85° (bath) for 10 min, cooled, and poured into ice water. The mixture was stirred for 1 hr and the light brown, amorphous precipitate was removed by filtration and then dissolved in dichloromethane. The dichloromethane solution was transferred to a conical 13-ml centrifuge tube and concentrated under a stream of nitrogen to an amorphous mass which was dissolved in boiling absolute ethanol (0.5 ml). Upon cooling to room temperature, the solution deposited fine, short, colorless needles which were successively recrystallized from absolute ethanol and from acetic anhydride; thus purified, the product had mp 289–290° (sealed capillary) and showed an ir spectrum (KBr disk) identical with that of *scyllo*-inositol hexaacetate; mp 290° has been reported[29] for this substance. The *scyllo*-inositol hexaacetate, prepared as described above, was deacetylated with methanolic sodium methoxide and the cyclitol then converted into its TMS derivative which was subjected to glpc at 170° on column A. A single peak, indistinguishable from that of the TMS derivative of authentic **7**, was obtained.

The original aqueous mother liquor from which the disodium *scyllo*-inositol diborate had been removed was passed through a column of IR-120 (H^+) (20 ml) and the eluent (50 ml) was concentrated *in vacuo* at 44° (bath) to a flocculent mass. The residue was freed of boric acid as the trimethyl ester and the syrupy material was then acetylated with acetic anhydride–pyridine (2 ml, 1:1) at 78° for 1.25 hr. Worked up in conventional fashion, the product (83 mg) was treated with hot absolute ethanol and the insoluble portion removed by filtration. On cooling, the filtrate deposited colorless platelets which were recrystallized from absolute ethanol; they had mp 217–218° either alone or in admixture with authentic *myo*-inositol hexaacetate. The ir spectrum of the product (KBr disk) was indistinguishable from that of an authentic sample. A portion of the hexaacetate was deacetylated and converted into the TMS derivative which was chromatographed at 170° on column A. A single peak, indistinguishable from that afforded by the TMS derivative of **8**, was obtained.

B. Glpc Study of Cyclization Mixture.—D-*xylo*-Hexos-5-ulose (**3**, 31 mg) was treated with 0.1 *N* sodium hydroxide solution as described earlier, aliquots being removed from the reaction mixture at 5-min intervals. Each aliquot was deionized and decolorized by passage through a mixture of Duolite A-4 (CO_3^{2-}) and Amberlite IR-120 (H^+) and the solution were concentrated *in vacuo* at 40° (bath), to give syrups which were converted into their TMS derivatives and then subjected to glpc on column A at 150°. Chromatograms *ii*, *iii*, and *iv* in Figure 1 correspond, respectively, to aliquots taken after 10, 25, and 45 min. Peak II was indistinguishable from that of the TMS derivative of authentic 2,4,6/3,5-pentahydroxycyclohexanone (**6**, *myo*-inosose-2). Inspection of chromatograms *ii* to *iv* in Figure 1 clearly shows how the peaks due to D-*xylo*-hexos-5-ulose (marked "I") diminish with time while that due to **6** increases. The unmarked peaks are as yet unidentified.

C. Glpc Study of Cyclization Mixture after Reduction with Sodium Borohydride.—Reduction of the mixture from the alkaline cyclization of **3**, followed by glpc of the TMS derivative on column A, afforded a highly reproducible pattern of peaks such as that shown in Figure 2. Peak V corresponds to the TMS

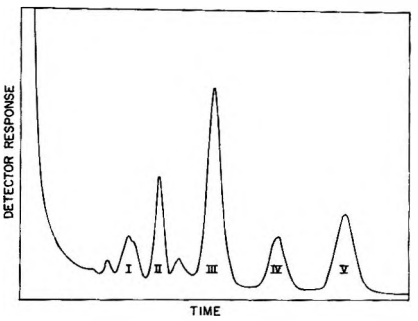


Figure 2.—Gas–liquid partition chromatography on column A of the trimethylsilyl derivatives of the sodium borohydride reduced products from the cyclization of **3**.

derivative of *myo*-inositol while peak IV denotes a retention time equal to that of the TMS derivative of *scyllo*-inositol. Peak III represents the TMS derivatives of glucitol and iditol, arising from the reduction of unreacted **3**. The TMS derivative of DL-*chiro*-inositol also falls in this peak as will be discussed later. *epi*-Inositol cochromatographs with *scyllo*-inositol in this system but its presence is rendered unlikely since DL-2,3,4,6/5-pentahydroxycyclohexanone (*epi*-inosose-2) was not detected in the direct glpc of the TMS derivative of the unreduced cyclization mixture. Peaks I and II are as yet unidentified.

The Behavior of 2,4,6/3,5-Pentahydroxycyclohexanone (6) with Alkali.—The cyclose (**6**, 29 mg) was treated with 0.1 *N* sodium hydroxide in the manner described earlier for the cyclization of **3**. Aliquots were withdrawn at 15, 30, and 45 min and, after deionization and concentration, these samples were converted into the TMS derivatives and subjected to glpc at 150° on column A. All three samples gave the pattern of peaks shown in Figure 3. The peak with the longest retention time

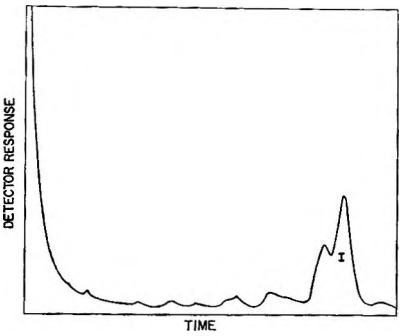


Figure 3.—Gas–liquid partition chromatography on column A of the trimethylsilyl derivative of the products obtained by treatment of **6** with 0.1 *N* sodium hydroxide.

(I) corresponds to **6**; while the adjacent peak with slightly shorter retention time has not been identified, the appearance of this partially resolved pair of peaks closely resembles that shown in chromatogram *iv* of Figure 1. The peaks of shorter retention time are very small; they will be referred to later in this paper.

In a separate experiment, 2,4,6/3,5-pentahydroxycyclohexanone (**6**, 29 mg) was treated with 0.1 *N* sodium hydroxide for 20 min and the solution was then deionized as described earlier. One-half (6 ml) of the solution was treated with sodium borohydride (45 mg) while the other half was treated with platinum oxide (70 mg) and shaken with hydrogen; after removal of solvent, the products from both reductions were trimethylsilylated. In each case, glpc on column A gave a similar pattern of peaks; that obtained with the portion which had been reduced with sodium borohydride is shown in Figure 4. Material from each reduction procedure was also chromatographed (at 210°) on column B with the results shown in Figure 5. Peak IV arises from *scyllo*-inositol while peak V represents *myo*-inositol.

(28) A parallel experiment in which a boric acid buffer was used gave identical results.

(29) J. Müller, *Ber.*, **40**, 1821 (1907).

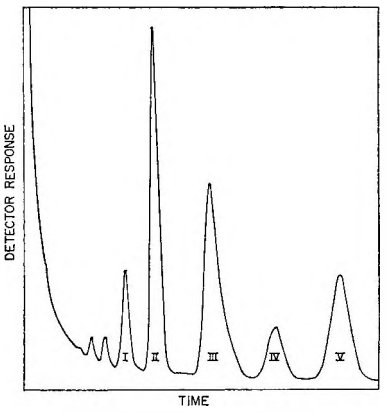


Figure 4.—Gas–liquid partition chromatography on column A of the trimethylsilyl derivative of the sodium borohydride reduced products from the alkaline treatment of 6.

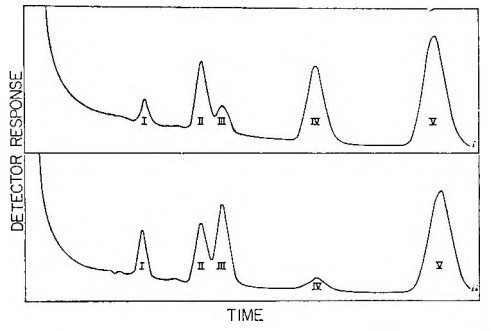


Figure 5.—Gas–liquid partition chromatography on column B of the trimethylsilyl derivative of alkali-treated 6 which had been (*i*) reduced with sodium borohydride and (*ii*) reduced with hydrogen in the presence of platinum oxide.

Cochromatography with authentic samples of *neo*-inositol, *cis*-inositol, and *epi*-inositol clearly showed that none of these three inositols was present in either mixture. The material giving rise to peaks I–III in Figure 5, chromatogram *ii*, was separated on a preparative scale using column B, equipped with a stream splitter. The homogeneity of each of the three fractions was confirmed by rechromatography on columns A and B. The material from peak III had the same retention time as the TMS derivative of DL-*chiro*-inositol; after hydrolysis and acetylation, it was chromatographed on column C at 180° and found to migrate as a single compound with the retention time of authentic DL-*chiro*-inositol hexaacetate. In column B the component from peak II had a retention time which was indistinguishable from that of the TMS derivatives of iditol, mannitol, and glucitol; in column A, however, the component from peak II shows a retention time which sharply differentiates it from these three hexitols. It is unlikely, therefore, that the minor peaks of short retention time in Figure 3 represent D-*xylo*-hexos-5-ulose. The identity of the material represented by peaks I and II remains unknown.

The identification of peaks III–V in Figure 5 is supported by further considerations. The catalytic reduction of inososes in neutral solution and in the presence of platinum oxide leads largely to the formation of axial hydroxyl groups while reduction with sodium borohydride gives a mixture of the epimeric axial and equatorial products.[30] This generalization is reflected in features of Figure 5, the ratio of *scyllo*-inositol to *myo*-inositol being much lower in the catalytic reduction (chromatogram *ii*) than when sodium borohydride was used (chromatogram *i*). Similarly, the ratio of DL-*chiro*-inositol to *myo*-inositol is larger when the mixture is reduced catalytically (chromatogram *ii*) than when sodium borohydride is used (chromatogram *i*); these are the results to be expected in the reduction of **9** and **10**.

Registry No.—**2**, 19684-32-3; **3**, 19684-22-1; **7**, 488-59-5; **8**, 87-89-8.

Acknowledgments.—We are indebted to the staff of the Section on Microanalytical Services and Instrumentation of this institute for elemental analyses and spectra and to Dr. Alexander J. Fatiadi of the National Bureau of Standards for an authentic sample of **6**.

(30) Th. Posternak, "The Cyclitols," Hermann, Paris, 1965, p 157.

Nucleosides. LVIII. Transformations of Pyrimidine Nucleosides in Alkaline Media. III.[1] The Conversion of 5-Halogenouridines into Imidazoline and Barbituric Acid Nucleosides[2,3]

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Reaction of 2′,3′-*O*-isopropylidene-5-bromouridine (**3b**) with alkoxide affords 5′,6-anhydro-2′,3′-*O*-isopropylidene-6-hydroxyuridine (**15**) which is converted by acid hydrolysis into 1-β-D-ribofuranosylbarbituric acid ("6-hydroxyuridine") (**18**) in high over-all yield. Treatment of **15** with NaOBz–DMF gives the 5′-*O*-benzoate of isopropylidene-6-hydroxyuridine (**19**). In aqueous alkali, 2′,3′-*O*-isopropylidene-5-fluorouridine (**3a**) is converted into 1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic acid (**20**) which, after acid hydrolysis, gives the unblocked imidazoline ribo nucleoside (**2**) in good over-all yield. A total synthesis of **2** *via* condensation of methyl 2-oxo-4-imidazoline-4-carboxylate with tri-*O*-benzoyl-D-ribofuranosyl chloride is given. Unlike the 5-fluoro derivative (**3a**), the 5-bromo (**3b**) and the 5-iodo (**3c**) analogs in aqueous alkali give poor yields of **20** along with other 2′,3′-*O*-isopropylidenated products, namely, 5′,6-anhydro nucleoside (**15**), uridine (**12**), 5-hydroxyuridine (**17**), and barbituric acid ribo nucleoside (**13**). It is shown that the conversion of nucleosides **3** into **12**, **17**, and **20** involves anchimeric assistance by the 5-hydroxyl group of the sugar moiety and, further, that the presence of a 2′,3′-*O*-isopropylidene group promotes this participation. Evidence obtained from a study of the 5′-deoxy analog (**9b**) of **3b** suggests that the formation of **13** from **3b** or **3c** occurs mainly by direct attack by hydroxide ion on C-6 and to a lesser extent by solvolysis of **15**.

Recent investigations in this laboratory have shown that 5-halogenated 1-β-D-arabinofuranosyluracils are converted in alkaline media into 2′,6-anhydro-6-hydroxyuracil- and 2-oxo-4-imidazoline-4-carboxylic acid

(1) For the previous paper in this series, see R. J. Cushley, S. R. Lipsky, and J. J. Fox, *Tetrahedron Lett.*, 5393 (1968).

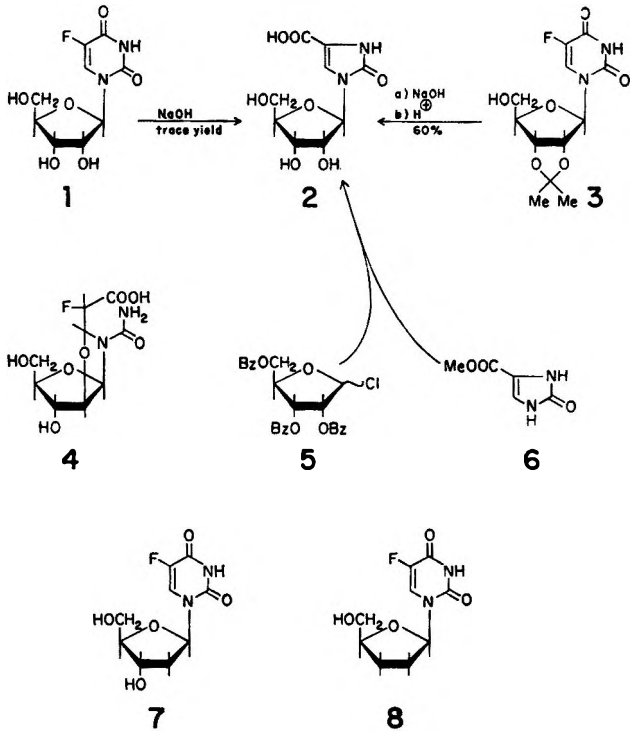
(2) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08478).

(3) A preliminary account of part of this work has been published: B. A. Otter, E. A. Falco, and J. J. Fox, *ibid.*, 2967 (1968).

nucleosides.[4] These reactions proceed *via* dihydropyrimidine intermediates formed as a result of nucleophilic attack of the 2′-hydroxyl group on C-6 of the pyrimidine ring. As an extension of this work we have examined the properties of some 5-halogenated 1-β-D-ribofuranosyluracils in alkaline media. The aim of this study was to determine whether the possible formation of 5′,6-anhydrodihydropyrimidine intermediates would lead to rearrangements similar to those observed in the arabinofuranosyl series.

Previous studies[5] had shown that 5-fluorouridine (**1**) is stable is aqueous sodium hydroxide under conditions where the arabinosyl analog of **1** is completely converted into the 2′,6-anhydro acyclic ureide **4**. We have since found that **1** is relatively stable under conditions where the ureide **4** is converted into an arabinosylimidazoline nucleoside. Thus, treatment of **1** with 1 *N* sodium hydroxide at 55° for 16 hr resulted in only ~15% decrease in the uv absorption peak at 268 mμ. Electrophoresis of the reaction mixture revealed the presence of starting material (**1**) and a trace of a uv-absorbing product which was identified as the imidazoline nucleoside **2** (Scheme I). These results indicate that the

SCHEME I



conversion of **1** into a 5′,6-anhydro acyclic ureide (analogous to **4**) proceeds only to a minor extent. However, for reasons to be discussed later, it was expected that formation of 5′,6-anhydro intermediates would proceed more easily from 2′,3′-*O*-isopropylidene-5-fluorouridine (**3**). When **3** was treated with 1 *N* sodium hydroxide at 55° the initial absorption peak at 268 mμ decreased by 50% over a 40-min period. This rapid decrease was followed by the much slower appearance (~14 hr) of a new peak at 252 mμ. After acidic hydrolysis of the isopropylidene group, a 60% yield of 1-β-D-ribofuranosyl-2-oxo-4-imidazoline-4-carboxylic acid (**2**) was obtained. The structure of **2** was established by the similarity of the uv and nmr spectral characteristics to those previously reported[4b] for the corresponding arabinofuranosyl compound, and by total synthesis. Condensation of tri-*O*-benzoyl-α,β-D-ribofuranosyl chloride (**5**) with methyl 2-oxo-4-imidazoline-4-carboxylate (**6**), according to the mercuric cyanide–nitromethane procedure of Yamaoka, *et al.*,[6] afforded crude material from which a 20% yield of **2** was obtained after base-catalyzed removal of the protecting groups.

The proposed intermediates in the ring contraction of **3** are shown in Scheme II. Formation of the ureide **16a**, *via* the 5′,6-anhydro intermediates **10a** and **11a**, occurs rapidly as shown by the initial loss of the uv absorption of **3**. Ring closure of **16a** to imidazoline **20** (λ_{max} 252 mμ) could then proceed by nucleophilic displacement of the 5-fluoro atom by the amide nitrogen (possibly with participation of the neighboring carboxyl group), followed by elimination of the sugar alcohol as previously suggested[4] for the *arabino* analog **2**.

The premise that 5′,6-anhydro bond formation would be promoted by the presence of a 2′,3′-*O*-isopropylidene group was based on our own work in another area[7] and on some previous reports on the properties of 5′-thiouridines. Thus 2′,3′-*O*-isopropylidene-5′-thiouridine[10a,b] is completely converted at pH 3–7 into a 5′,6 cyclic sulfide whereas, under similar conditions, a solution of 5′-thiouridine[10c] itself contained only 20% corresponding cyclic sulfide. To explain this difference it was suggested[10c] that the isopropylidene ring "forces the furanose ring into a conformation that favors the proximity of the thiol group to the uracil double bond." More recently, 5′,6-anhydro nucleosides have been implicated in the base-catalyzed, deuterium exchange of H-5 in uracil nucleosides. Moreover, in both aqueous[1] and nonaqueous[11] base, the exchange reaction of isopropylideneuridine proceeds at a much faster rate than that of uridine itself, again indicating the ready formation of the 5′,6-anhydro intermediate from the isopropylidenated compound. These observations were again rationalized on conformational grounds.

The striking difference observed in the reactivity of 5-fluorouridine (**1**) and its isopropylidene ketal (**3**) in aqueous base may also be due to conformational fac-

(4) (a) B. A. Otter and J. J. Fox, *J. Amer. Chem. Soc.*, **89**, 3663 (1967); (b) B. A. Otter, E. A. Falco, and J. J. Fox, *J. Org. Chem.*, **33**, 3593 (1968).

(5) J. J. Fox, N. C. Miller, and R. J. Cushley, *Tetrahedron Lett.*, 4927 (1966).

(6) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965).

(7) An indication that a 2′,3′-*O*-isopropylidene group facilitated interaction between the 5′ position and the aglycon of uridine derivatives came from some work on the reactions of 5′-iodouridines with silver salts. Treatment of 2′,3′-di-*O*-acetyl-5′-deoxy-5′-iodouridine (i) with silver fluoride in pyridine affords the corresponding 4′,5′-unsaturated nucleoside in high yield.[8] When 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine (ii) was treated with AgF in pyridine, the major product was 5′-deoxy-5′-fluoro-2′,3′-*O*-isopropylideneuridine (iii).[9] The same product (iii) was formed in high yield when 2,5′-anhydro-2′,3′-*O*-isopropylideneuridine was treated with AgF in pyridine. It therefore appears that the isopropylidenated compound (ii), unlike the diacetate (i), reacts preferentially to give the anhydro nucleoside which is then converted into the 5′-fluoro nucleoside (iii).

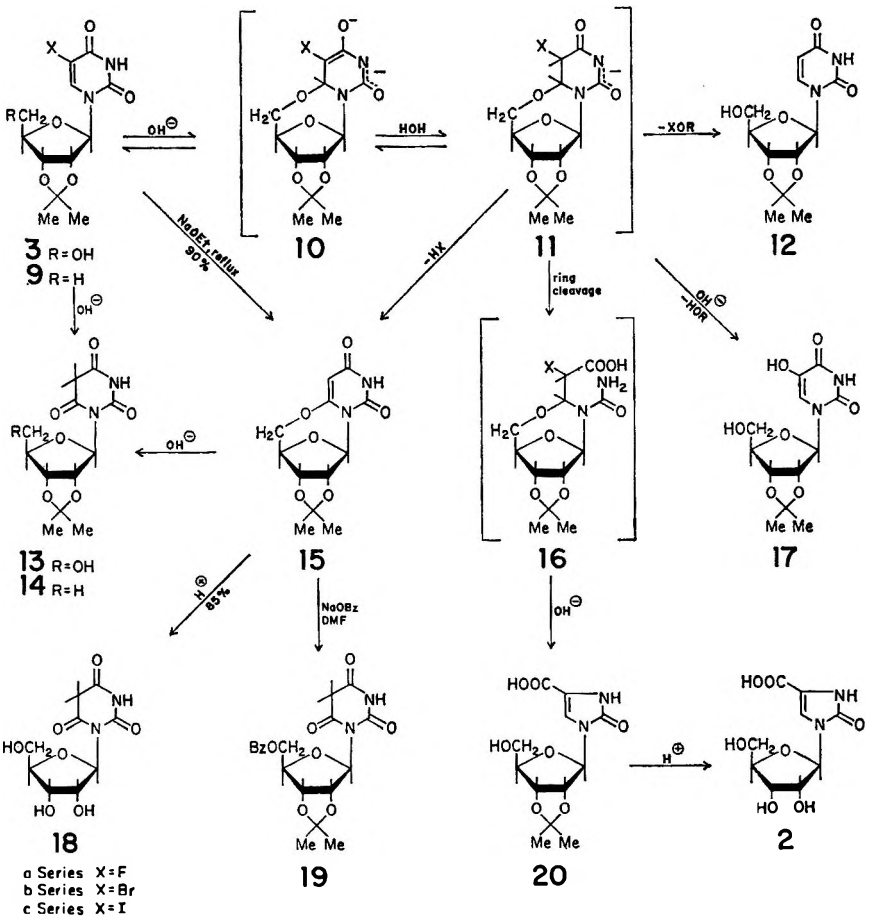
(8) J. P. H. Verheyden and J. G. Moffat, *J. Amer. Chem. Soc.*, **88**, 5684 (1966).

(9) B. A. Otter and J. J. Fox, unpublished results.

(10) (a) B. Bannister and F. Kagan, *J. Amer. Chem. Soc.*, **82**, 3363 (1960); (b) R. W. Chambers and V. Kurkov, *ibid.*, **85**, 2160 (1963); (c) E. J. Reist, A. Benitez, and L. Goodman, *J. Org. Chem.*, **29**, 554 (1964).

(11) D. V. Santi and C. F. Brewer, *J. Amer. Chem. Soc.*, **90**, 6236 (1968).

SCHEME II



tors.[12] Furanose rings can exist in a large number of conformations; for the maximally puckered envelope and twist conformations a total of 20 modes is possible. That compounds **1** and **3** occupy different parts of this conformational cycle is shown by the different H-1′,2′ coupling constants (4.0 and 2.5 Hz, respectively) observed in the nmr spectra determined in D_2O at 55°. It is therefore possible that the conformational population of **3** contains a much larger percentage of conformers in which the 5′-hydroxyl group can participate in the reversible saturation of the 5,6 double bond. It should be pointed out, however, that examples of 5′,6-anhydro bond formation in ribo nucleosides lacking an isopropylidene group are known. Lipkin[15a] has reported (in abstract) that treatment of 5-iodouridine under "alkaline conditions" affords 5′,6-anhydro-6-hydroxyuridine. Similarly, 5-azauridine was found to exist in neutral solution and the solid state as the 5′,6-anhydro derivative.[15b] In neither of these cases was the behavior of the corresponding isopropylidenated compound examined. On the basis of the present work it would be expected that the presence of an isopropylidene group in such compounds would facilitate the formation of the 5′,6-anhydro linkage.

It is probable that the 5-fluoropyrimidines (**1**, **3**, **7**, and **8**) undergo a reversible hydration of the 5,6 double bond initiated by attack of hydroxide ion on C-6. However, products arising from the 5-fluoro-6-hydroxy-5,6-dihydropyrimidine intermediates were not observed. Lozeron and coworkers[16] have shown that 5-fluoro-6-hydroxy-5,6-dihydrouracil is unstable in alkali, the initial products being urea and fluoromalonaldehydic acid. Similar decomposition may account for some of the decrease in uv absorption observed when **1**, **7**, and **8** were heated in alkali. As will be shown later, the reactions of isopropylidene-5-iodo- and -5-bromouridine (**3c** and **3b**) do involve attack of hydroxide ion on C-6. This intermolecular attack is competitive with the intra-

(12) Other factors to be considered are the relative acidities of the participating 5′-hydroxyl groups and the relative orientations of the 5,6 double bond with the 5′-hydroxyl group. Since ionization of the sugar moiety of **1** would occur first at the 2′ position,[13] there may be a small acid weakening effect on the 5′-hydroxyl group. Ionization of the 5′-hydroxyl group—and hence the attack on C-6[14]—would therefore take place less readily in **1** than in **3**. Further, repulsion between the ionized aglycon and the 5′-hydroxyl anion of **3** would restrict rotation about the glycosyl bond and favor a rotamer population in which the 5,6 double bond and the 5′-hydroxyl anion were in a favorable *endo* orientation. In **1**, however, the combined repulsion between the ionized aglycon and the 2′- and 5′-hydroxyl anions may lead to a rotamer population different from that of **3**. The attack of the 5′-hydroxyl anion on C-6 of **1** may therefore be less favorable or lead to the more unstable of the two possible C-6 diastereoisomers. To test the importance of the above factors, 2′-deoxy-5-fluorouridine (**7**) and 1-(2,3-dideoxy-β-D-glycero-pentofuranosyl)-5-fluorouracil (**8**) were treated with 1 *N* sodium hydroxide at 55°. In both cases the uv absorption at 268 mμ decreased by only ~10% over a 16-hr period. Since **7** and **8** lack a 2′-hydroxyl group, these results suggest that the ionization and orientation effects associated with the prior ionization of the 2′-hydroxyl group of **1** are not a major case of the lack of reactivity of this compound.

(13) The 2′-hydroxyl group is known to be more acidic than the 5′-hydroxyl group in ribo nucleosides. See J. J. Fox, L. F. Cavalieri, and N. Chang, *J. Amer. Chem. Soc.*, **75**, 4315 (1953); R. M. Izatt, J. H. Rytting, L. D. Hansen, and J. J. Christensen, *ibid.*, **88**, 2641 (1966).

(14) It is assumed that at pH 14 the attack on C-6 involves the 5′-hydroxyl anion. The undissociated 5′-hydroxyl group could participate under less strongly basic conditions but, since the conversion of the 5′,6-anhydro intermediates into the imidazoline nucleosides requires strong base, no overall reaction would result.

(15) (a) D. Lipkin, F. B. Howard, D. Nowotny, and M. Sano, Abstracts, *Intern. Cong. Biochem., 6th*, New York, Paper No. 1-117 (1964); (b) A. Piskala and F. Šorm, *Coll. Czech. Chem. Commun.*, **29**, 2060 (1964).

(16) H. A. Lozeron, M. P. Gordon, T. Gabriel, W. Tautz, and R. Duschinsky, *Biochemistry*, **3**, 1844 (1964).

molecular addition of the 5′-hydroxyl anion and products resulting from both these events are observed.

When 2′,3′-*O*-isopropylidene-5-iodouridine (**3c**) was treated with 1 *N* sodium hydroxide at 55°, the uv-spectral pattern of the monitored reaction differed from that observed for isopropylidene-5-fluorouridine (**3a**). The loss of the initial absorption band at 280 mμ occurred with the concomitant appearance of a new peak which reached a final λ_{max} of 260 mμ after 3 hr. Examination of the neutralized reaction mixture by tlc revealed two major and three minor uv-absorbing products. In addition, three nonchromophoric products were detected; these compounds were not investigated further. Both of the major products were isolated in crystalline form. One of these compounds was identified as 2′,3′-*O*-isopropylideneuridine (**12**) by comparison of the physical properties with those of an authentic sample. Quantitative uv analysis of **12** eluted from tlc plates indicated a yield of ~15%. The other major product, isolated in 30% yield, was 5′,6-anhydro-2′,3′-*O*-isopropylidene-6-hydroxyuridine (**15**). The structure of **15** was indicated by the elemental analysis ($C_{12}H_{14}N_2O_6$) and confirmed by the nmr spectrum in DMSO-d_6. The nmr spectrum showed clearly resolved signals including an NH proton (δ 11.4), a single vinylic proton (5.40, H-5), and a widely spaced quartet (centered at 4.4, $J_{5',5'}$ = 13 Hz). This quartet is characteristic of the H-5′ signals of anhydro nucleosides containing an oxygen bridge between C-5′ and the aglycon.[17]

The three minor products formed in the reaction of **3c** with sodium hydroxide were identified as 2′,3′-*O*-isopropylidene-5-hydroxyuridine[17] (**18**), the barbituric acid nucleoside **13**, and the imidazoline nucleoside **20**. These compounds were not isolated in crystalline form but their identities were established by comparison of chromatographic mobility with those of authentic samples, by uv spectra of eluted materials, and by characteristic color reactions.

The initial uv-spectral changes observed when 2′,3′-*O*-isopropylidene-5-bromouridine (**3b**) was treated with 1 *N* sodium hydroxide at 55° were similar to those described for the 5-iodo analog **3c**. After a reaction time of 3 hr, tlc revealed starting material and a mixture of the same products (**12**, **13**, **15**, **17**,[18] and **20**) as were formed from **3c**. After a longer reaction period (20 hr) the disappearance of starting material (**3b**) was noted along with a substantial decrease in the concentrations of the barbituric acid nucleoside **13** and the anhydro nucleoside **15**. Under these conditions the major product was the imidazoline nucleoside **20** (~20% yield).

Four of the products (**12**, **15**, **17**, and **20**) of the reactions of **3b** and **3c** with sodium hydroxide could be formed from the 5′,6-anhydro intermediates **11b** and **11c**. Like the fluoro analog **11a**, both **11b** and **11c** can undergo ring cleavage at the 3,4 position. The resulting ureides **16b** and **16c** could then be converted into the imidazoline nucleoside **20**, as suggested previously for the 5-fluoro analog **16a**. Because of the more reactive halogen substituent, however, compounds **11b** and **11c** could give rise to products not observed in the fluoro case. Thus, the major reaction of **11c**, and to a smaller extent of **11b**, is elimination of the elements of hydrogen halide to give the anhydro nucleoside **15**. Isopropylideneuridine (**12**) could be formed from **11b**–**11c** by elimination of XOR (OR = sugar moiety). Alternatively, displacement of the halogen atom of **11b**–**11c** by hydroxide ion, followed by the elimination of HOR would give isopropylidene-5-hydroxyuridine (**17**). The 5′-deoxy analogs of compounds **12**, **17**, and **20** were not formed when 5′-deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (**9b**) was heated (55°) with 1 *N* sodium hydroxide. Since **9b** cannot be converted into the 5′,6-anhydro intermediate **11b**, this observation affords evidence that compounds **11b** and **11c** are intermediates in the formation of **12**, **17**, and **20** from **3b** and **3c**.

The only uv-absorbing product observed in the reaction of **9b** with sodium hydroxide was the 5′-deoxyribosylbarbituric acid **14**. Compound **14** is itself unstable in aqueous base and decomposes to nonchromophoric products. The formation of **14** from **9b** was not unexpected because it has been shown previously that 1-methyl-5-bromouracil,[4b] and other 5-halouracils,[19] are converted into barbituric acids on treatment with strong base. These barbituric acids are probably formed by dehydrohalogenation of 5-halogeno-6-hydroxy-5,6-dihydropyrimidine intermediates formed by attack of hydroxide ion on C-6 of the pyrimidine ring. The barbituric acid nucleoside **13** observed in the reaction of **3b** and **3c** with sodium hydroxide is formed *via* two pathways. The major pathway involves competitive attack of hydroxide ion on C-6, as described above, and the minor pathway involves solvolysis of the 5′,6-anhydro nucleoside **15**. When **15** was treated with 1 *N* sodium hydroxide at 55°, the uv maximum at 260 mμ decreased by 40% over a 24-hr period. Examination of the reaction mixture by tlc revealed a small amount of **13** and three nonchromophoric products which probably result from the decomposition of **13**. This finding explains the observed decrease in concentration (between 3 and 20 hr) of **15** formed in the reaction of **3b** with sodium hydroxide.

The formation of the barbituric acid nucleoside **13** by solvolysis of **15**, although of little practical value, indicated that the 5′,6-anhydro bond of **15** could be cleaved. It was therefore of interest to investigate this ring-opening reaction under conditions where the barbituric acid products would be expected to be stable. It was first necessary, however, to devise a higher yielding synthesis of **15** than that available (30% yield) from the 5-iodopyrimidine nucleoside **3c**. This was accomplished by treating isopropylidene-5-bromouridine (**3b**) with an excess of sodium ethoxide in refluxing ethanol. Under these conditions, the 5′,6-anhydro nucleoside **15** was obtained in 90% yield. Treatment of **15** with warm, dilute hydrochloric acid cleaved the anhydro bridge as well as the isopropylidene group to give an 85% yield of 1-β-D-ribofuranosylbarbituric acid (**18**).

(17) I. L. Doerr, R. J. Cushley, and J. J. Fox, *J. Org. Chem.*, **33**, 1592 (1968).

(18) It is of interest to note that isopropylidene-5-hydroxyuridine (**17**) is converted in high yield into the imidazoline nucleoside **20** when treated with dilute alkalis.[3] However, this rearrangement (which does not involve participation of a sugar hydroxyl group) does not take place under the present reaction conditions and in fact **17** is stable in 1 *N* NaOH at 55° as is shown by the constancy of the uv spectrum over a 24-hr period.[3] It is therefore concluded that **17** is not an intermediate in the formation of **20** from **3a**–**3c**. A detailed account of the ring contraction of **17** is presented in a forthcoming paper (*ibid.*, in press).

(19) E. R. Garrett, H. J. Nestler, and A. Somodi, *ibid.*, **33**, 3460 (1968); E. R. Garrett and G. J. Yakatan, *J. Pharm. Sci.*, **57**, 1478 (1968).

Compound **18** was therefore available from **3b** in an over-all yield of 77%. That compound **18** was a barbituric acid derivative was indicated by the similarity of the pK_a (3.75) and uv-absorption data to that reported[20] for 1-methylbarbituric acid (pK_a = 4.20). The ribofuranosyl structure of **18** was established by periodate oxidation; thus **18** consumed 2 equiv of sodium metaperiodate within 5 min, whereas 1-methylbarbituric acid consumed only 1 equiv of oxidant during this period. Both compounds then exhibited a much slower uptake of another equivalent of oxidant over a 48-hr period. The *rapid* uptake of the second equivalent by **18** is consistent with the *cis*-vicinal glycol system. The nmr spectrum of **18** in DMSO-d_6, although not well resolved, confirmed the nucleoside structure and indicated that **18** exists in this solvent in the trioxo form as shown. A total synthesis of the sodium salt of **18** from tri-*O*-benzoyl-β-D-ribofuranosylurea and malonic acid has been reported.[21] However, the over-all yield in this synthesis is low (37%) and the purity of the product is in doubt.[22] Since the completion of the present work, compound **18** has been prepared by an alternative method involving condensation of tribenzoylribofuranosyl bromide with the tristrimethylsilyl derivative of barbituric acid and deesterification of the blocked intermediate.[23]

An alternative approach to the ring opening of the 5′,6-anhydro nucleoside **15** is reaction with nucleophiles to give 5′-substituted ribosylbarbituric acids. Thus, treatment of **15** with sodium benzoate in hot DMF affords a 37% yield of 1-(5-*O*-benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)barbituric acid (**19**). The structure of **19** was established from the uv spectrum and from the nmr spectrum in DMSO-d_6 which showed an exchangeable, two-proton multiplet (δ 3.70) for the geminal H-5 protons in addition to the benzoyl, ring-proton, and isopropylidene resonances. Compound **19** is conveniently substituted with both acid- and base-labile protecting groups and is suitable for further studies on transformations of the sugar moiety. Such studies, together with investigations of the chemistry and biochemistry of barbituric acid nucleosides, are currently under investigation in this laboratory.

Experimental Section

Melting points were determined on a Thomas–Hoover apparatus (capillary method) and are corrected. The uv spectra were determined on a Cary Model 15 spectrometer; the nmr spectra were determined on a Varian A-60 spectrometer using DMSO-d_6 as solvent and tetramethylsilane as internal reference. Chemical shifts are reported in parts per million (δ) and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet), or m (complex multiplet). Values given for coupling constants (hertz) are first order. Thin layer chromatography was performed on glass plates (10 × 20 cm) coated with silica-gel GF (Merck), and developed with the following solvent systems: A, ethyl acetate; B, *n*-butyl alcohol–water, 86:14 v/v. Separated materials were detected with uv light and by spraying with 10% v/v sulfuric acid in ethanol followed by heating at *ca.* 110°. Evaporations were carried out *in vacuo* with bath temperatures kept below 45°. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich.

2′,3′-*O*-Isopropylidene-5-iodouridine (3c).—The general procedure of Hampton[24] was used with modifications. 5-Iodouridine (3.7 g, 10 mmol), (prepared according to the method of Prusoff[25]) was added to a solution of dimethoxypropane (10 ml) and di(*p*-nitrophenyl)phosphoric acid (340 mg, 1 mmol) in 100 ml of acetone. The suspension was stirred at room temperature for 1 hr, during which time the solid material dissolved. An excess of aqueous NH_4OH was added and the solution was concentrated to dryness. The syrupy residue was dissolved in 100 ml of 50% ethanol and the solution was treated with 5 ml of Dowex-1 (Cl^-). Crystallization of the product commenced during concentration and was completed by cooling. Recrystallization from aqueous ethanol afforded pure material (3.0 g, 73%): mp 225–227°; nmr δ 11.5 (1, broad s, NH), 8.27 (1, s, H-6), 5.80 (1, d, H-1′), 5.07 (1, t, 5′OH), 4.8 (2, m, H-2′, H-3′), 4.06 (1, m, H-4′), 3.5 (2, m, H-5′, H-5′), 1.43, 1.24 (two singlets, six protons, isopropylidene methyls) ($J_{1',2'}$ = 2.5, $J_{5',OH}$ = 5.0 Hz).

Anal. Calcd for $C_{12}H_{15}IN_2O_6$: C, 35.14; H, 3.69; N, 6.83. Found: C, 35.13; H, 3.75; N, 6.70.

5′-Deoxy-5-bromouridine.—An excess of bromine (~0.9 ml, ~17 mmol) was dissolved (dropwise addition) in a solution of 5′-deoxyuridine[26] (3.42 g, 15 mmol) in 100 ml of water. The acidic solution was then concentrated to dryness at 50°. The residue was dissolved in ethanol and the solution again was concentrated to dryness. A solution of the residue in ethyl acetate deposited crystals when diluted with petroleum ether (bp 30–60°). Recrystallization from the same solvent pair afforded pure material (3.7 g, 80%): mp 172–173° (eff) dec, darkened above 160°; nmr δ 11.9 (1, broad s, NH), 8.00 (1, s, H-6), 5.70 (1, d, H-1′), ~5.1 (2, broad s, 2′-OH, 3′-OH), ~4.4 (3, m, H-2′, H-3′, H-4′), 1.30 (3, d, 4′-methyl) ($J_{1',2'}$ = 5.0, $J_{4',5'}$ = 6.0 Hz).

Anal. Calcd for $C_9H_{11}BrN_2O_5$: C, 35.18; H, 3.61; N, 9.13. Found: C, 35.13; H, 3.55; N, 8.96.

5′-Deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (9b).—5′-Deoxy-5-bromouridine (1.54 g) was converted into **9b** as described above for the preparation of **3c**. The yield of pure **9b** (from aqueous ethanol), mp 108–110°, was 1.41 g (80%): nmr δ 11.9 (1, broad s, NH), 8.20 (1, s, H-6), 5.77 (1, d, H-1′), 5.07 (1, q, H-2′), 4.59 (1, q, H-3′), 4.10 (1, m, H-4′), 1.30 (3, d, 4′-methyl), 1.49, 1.29 (two singlets, six protons, isopropylidene methyls) ($J_{1',2'}$ = 2.4, $J_{2',3'}$ = 6.8, $J_{3',4'}$ = 4.5, $J_{4',5'}$ = 6.5 Hz).

Anal. Calcd for $C_{12}H_{15}BrN_2O_5$: C, 41.50; H, 4.35; N, 8.07. Found: C, 41.14; H, 4.28; N, 7.96.

Reactions of 2′,3′-*O*-isopropylidene-5-halouridines in Alkali. General Procedure.—The following proportions of reactants were used, although not all experiments were conducted on this scale. The halouridine (1 mmol) was dissolved in 1 *N* sodium hydroxide (10 ml, 10 mmol) and the solution was thermostated at 55°. Aliquots (0.1 ml), taken immediately, and at suitable intervals thereafter, were diluted to 100 ml with water (pH ~11, 1 × 10^{-4} *M* in starting material), and the uv spectra were recorded.

A. 2′,3′-*O*-Isopropylidene-5-fluorouridine (3a). Preparation of 1-β-D-Ribofuranosyl-2-oxo-4-imidazoline-4-carboxylic Acid (2).—When **3a** (151 mg, 0.5 mmol) was heated in NaOH the absorption maximum at 268 mμ decreased by 50% in 40 min. This decrease was followed by the appearance of a peak at 252 mμ which reached a maximum (OD 0.77) at 14 hr. Chromatography (solvent B) of the neutralized reaction mixture revealed a single uv-absorbing compound (**20**) with R_f 0.15. The cooled reaction mixture as passed through a column containing 7 ml of Dowex-50 (H^+). The acidic effluent and washings were concentrated to a syrup which crystallized when triturated with acetone. Recrystallization from aqueous acetone afforded colorless needles, 89 mg (60%) of 1-(β-D-ribofuranosyl)-2-oxo-4-imidazoline-4-carboxylic acid dihydrate (**2**): mp 107–110° (resolidified and remelted at 195–200°); $\lambda_{max}^{pH\ 1}$ 263 mμ, $\lambda_{max}^{pH\ 7}$ 252 mμ, $\lambda_{max}^{pH\ 14}$ 268 mμ.

Anal. Calcd for $C_9H_{12}N_2O_7 \cdot 2H_2O$: C, 36.49; H, 5.44; N, 9.46. Found: C, 36.67; H, 5.33; N, 9.22.

Anhydrous **2**, obtained by drying the hydrate at 130° over P_2O_5, melted at 174–176° (eff) dec: nmr δ 10.7 (1, broad s, NH), 7.50 (1, d, H-5), 5.47 (1, d, H-1′), ~5.5 (3, very broad band, hy-

(20) J. J. Fox and D. Shugar, *Bull. Soc. Chim. Belg.*, **61**, 44 (1952).

(21) T. Ukita, M. Yoshida, A. Hamada, and Y. Kato, *Chem. Pharm. Bull.*, **12**, 459 (1964).

(22) Ukita, *et al.*,[21] reported that **18**, in 0.1 *N* HCl, was converted in part into an isomeric product with λ_{max} 252 mμ. Our product (**18**), however, is stable under these conditions. It is apparent that their product contains a substantial amount of another compound. This is reflected in the 30% *lower* extinction coefficient at pH 7 reported for their compound.

(23) R. K. Robins, private communication.

(24) A. Hampton, J. C. Fratoni, P. M. Carroll, and S. Wang, *J. Amer. Chem. Soc.*, **87**, 5481 (1965).

(25) W. H. Prusoff, W. L. Holmes, and A. D. Welch, *Cancer Research*, **13**, 221 (1953); W. H. Prusoff, *Biochem. Biophys. Acta*, **32**, 275 (1959).

(26) I. Wempen, I. L. Doerr, L. Kaplan, and J. J. Fox, *J. Amer. Chem. Soc.*, **82**, 1624 (1960).

droxyl protons), ~4.4–3.8 (3, m, H-2′, H-3′, H-4′), ~3.6 (2, m, H-5′, H-5″) ($J_{1',2'}$ = 5.5, $J_{5,NH}$ = 1.5 Hz).

When 5-fluorouridine[27] (1), 2′-deoxy-5-fluorouridine[28] (7), and "2′,3′-dideoxy-5-fluorouridine"[29] (8) were treated with 1 *N* NaOH, as described above, the uv-absorption maxima (268 mμ) decreased by only 10–15% over a 16-hr period. Paper electrophoresis (acetate buffer, pH 3.5) of the reaction mixture of 1 revealed starting material and trace amounts of a product which was identified as the imidazoline **2** by the uv spectrum of eluted material.

B. **2′,3′-*O*-Isopropylidene-5-iodouridine (3c).**—The decrease in the absorption maximum (280 mμ) of **3c** (820 mg, 2 mmol) occurred concomitantly with the appearance of a new peak which reached a final λ_{max} of 260 mμ (OD 0.71) at 3 hr. In addition, a gradual increase in absorption at ~300–320 mμ (to OD 0.03) was noted. Chromatography (solvent A) of the neutralized reaction mixture revealed a trace of starting material (R_f 0.92), small amounts of uv-absorbing materials with R_f <0.1 and 0.2, and two major components with R_f 0.75 and 0.50. The material with R_f 0.75 was isolated by extraction of the neutralized (HOAc) reaction mixture with five 10-ml portions of chloroform. Concentration of the dried ($MgSO_4$) chloroform solution to dryness, and crystallization of the syrupy residue from ethanol afforded colorless needles of **15** (170 mg, 30%), mp 251–253°. The uv and nmr spectra of this compound were identical with those of **15** described below. Extraction of the aqueous layer (remaining after the removal of **15**) with ethyl acetate afforded a solution containing the material with R_f 0.50. A crystalline sample of this compound, obtained by preparative tlc (solvent A) gave an ir spectrum identical with that of isopropylidene uridine (**12**); the mixture melting point of the present sample with authentic **12** was undepressed (162–164°). The yields of **12** and **15** were 15 and 34%, respectively, as determined by uv analysis of materials eluted from tlc plates used to fractionate known amounts of the reaction mixture. The material with R_f 0.2 (solvent A) comigrated with authentic 2′,3′-*O*-isopropylidene-5-hydroxyuridine[3] (**17**); both samples gave a blue spot when sprayed with aqueous $FeCl_3$ solution. The absorption at ~300–320 mμ observed in the uv spectrum of the total reaction mixture is due to the presence of **17** ($\lambda_{max}^{pH\ 12}$ 304 mμ).

Chromatography of the reaction mixture using solvent B revealed **12** and **15** (both R_f 0.72), starting material (**3c**, R_f 0.89), **17** (R_f 0.55), and small amounts of two other uv-absorbing products with R_f 0.15 and 0.33. The component with R_f 0.15 was identified as the imidazoline nucleoside **20** (R_f 0.15, see section A above) from the characteristic uv spectrum of eluted material. The uv spectrum of the component with R_f 0.33 was characteristic of a barbituric acid derivative ($\lambda_{max}^{H_2O}$ 260 mμ, peak disappeared on acidification) and, in agreement with this formulation, the material gave an orange spot when sprayed with Erlich reagent. Furthermore, this material comigated with 2′,3′-*O*-isopropylidene ribofuranosyl barbituric acid (**13**, R_f 0.33) which was prepared *in situ* by treating compound **19** (see below) with dilute NaOH. (Barbituric acid itself had R_f ~0.1 in solvent B.) In addition to the above uv-absorbing products of the reaction of **3c** with NaOH, three nonchromophoric products (R_f 0.07, 0.50, and 0.80, solvent B) were detected with the H_2SO_4 spray. These compounds were not investigated further.

C. **2′,3′-*O*-Isopropylidene-5-bromouridine (3b).**—The initial uv-spectral changes observed when **3b**[30] (363 mg, 1 mmol) was heated in 1 *N* NaOH were similar to those described above for **3c**. Thus, after a reaction time of 3 hr, peaks at 260 mμ (OD 0.53) and ~310 mμ (OD 0.08) were present. After a 20-hr reaction period, the 260-mμ peak had decreased in intensity (to OD 0.35) and shifted to 255 mμ. Chromatography (solvents A and B) of the 3-hr reaction mixture revealed starting material, small amounts of **12**, **13**, and **17**, and **20** and **15** as the major products. After 20 hr, the spot for **15** had decreased in intensity leaving **20** as the major product (20% yield based on the uv extinction of material eluted from quantitative tlc plates). The decrease in uv extinction observed between 3 and 20 hr is due to the decomposition of the 5′,6-anhydro nucleoside **15** and the barbituric acid nucleoside **13**. Thus, when **15** (1 mmol) was treated with 1 *N* NaOH at 55°, the absorption peak (260 mμ) decreased by 40% over a 24-hr period. Chromatography (solvent B) showed **15** (R_f 0.72), a trace of the barbiturate **13** (R_f 0.33), and three nonchromophoric products (R_f 0.07, 0.50, and 0.80).

D. **5′-Deoxy-2′,3′-*O*-isopropylidene-5-bromouridine (9).**—Spectra determined at pH 7 showed a gradual decrease in the absorption at 278 mμ and appearance of a peak which reached a final λ_{max} at 261 mμ (OD 0.84 at 4 hr). Spectra determined at pH 1 showed only the decrease at 278 mμ (50% loss in 4 hr), indicating that the product was a barbituric acid derivative. Chromatography (solvent B) showed starting material (R_f >0.95) and a *single* uv-absorbing product (**14**, R_f 0.37) which gave an orange spot when sprayed with Erlich reagent. The uv spectrum of **14** eluted from the tlc plate showed $\lambda_{max}^{H_2O}$ 261 mμ (peak disappeared on acidification) and $\lambda_{max}^{pH\ 14}$ 263 mμ. After a 20-hr reaction period, the peak at 261 mμ in the uv spectrum of the total reaction mixture had decreased to OD 0.15.

1-β-D-Ribofuranosyl-2-oxo-4-imidazoline-4-carboxylic Acid (2) by Total Synthesis.—A suspension of finely divided 6[4b] (1.42 g, 10 mmol) in 300 ml of nitromethane was dried by azeotropic distillation of 100 ml of solvent. A solution of 5[31] [prepared from 10.1 g (20 mmol) of 1-*O*-acetyl-tri-*O*-benzoylribofuranose], in nitromethane, and mercuric cyanide (2.52 g, 10 mmol) were added to the hot suspension. The mixture was refluxed for 30 min during which time most of the solid material dissolved. Unreacted **6** (200 mg) was filtered off and the dark filtrate was concentrated to dryness. The syrupy residue was partitioned between chloroform (200 ml) and 30% KI solution (two 40-ml portions). The chloroform extracts were washed with water, dried ($MgSO_4$), and concentrated to dryness. NaOH (1 *N*, 100 ml) was added to a solution of the residue in ethanol (100 ml) and the mixture was refluxed for 2 hr. The cooled solution was passed through a column containing an excess of Dowex-50 (H^+) and the effluent and washings were concentrated to a small volume. This solution was placed on a column (2 × 10 cm) of Dowex-1 (OAc^-). The column was eluted with 0.1 *N* acetic acid until the effluent was free of uv-absorbing materials and then with 0.5 *N* HCl. Fractions containing uv-absorbing material were combined and concentrated to a small volume. Some of the HCl was removed by repeated codistillation with water. Acetone was added to the concentrated solution (~2 ml); crystallization commenced on cooling. The product (120 mg, 20%) had mp and mmp 107–110° [resolidified and remelted at 195–200° (eff) dec] and gave ir and uv spectra identical with those of hydrated **2** prepared from **3a**.

5′,6-Anhydro-2′,3′-*O*-isopropylidene-6-hydroxyuridine (15).—A sample of **3b** (36.3 g, 0.1 mol) was dissolved in ethanol (1000 ml) containing sodium (5.75 g, 0.25 mol) and the solution was refluxed for 17 hr. The cooled solution was neutralized with acetic acid and evaporated to ~200 ml. Water (300 ml) was added and the solution was cooled, whereupon crystalline material (15.5 g) separated. Concentration of the filtrates afforded an additional 10 g (total yield 25.5 g, 90%) of material. Recrystallization of the product from ethanol, and then from ethyl acetate, afforded pure **15**: mp 251–253°; uv absorption at $\lambda_{max}^{pH\ 7}$ 261 mμ (ε 13,050) and λ_{min} 230 (2400), $\lambda_{max}^{pH\ 1}$ 261 mμ (ε 13,050) and λ_{min} 230 (1300), $\lambda_{max}^{pH\ 12}$ 262 mμ (ε 9300) and λ_{min} 241 (5000). The nmr spectrum of **15** showed an AB subspectrum for the 5′ protons [δ 4.08, 4.73 ($J_{5',5''}$ = 13 Hz, $J_{4',5'}$ ~ 1.0 Hz)] and another AB system for H-2′ and H-3′ [δ 5.00, 5.11 ($J_{2',3'}$ = 6.0, $J_{1'',2'}$, $J_{3',4'}$ ~ 0 Hz)]. Other nmr signals were at 11.4 (1, broad s, NH), 6.43 (1, s, H-1″), 5.40 (1, s, H-5), 4.71 (1, narrow multiplet with poorly resolved splitting, H-4′), and 1.43 and 1.33 (two singlets, six protons, isopropylidene methyls).

Anal. Calcd for $C_{12}H_{14}N_2O_6$: C, 51.06; H, 4.96; N, 9.93. Found: C, 51.03; H, 4.94; N, 9.97.

1-β-D-Ribofuranosylbarbituric Acid (18).—The 5′,6-anhydro nucleoside **15** (5.64 g, 20 mmol) was dissolved in a mixture of 200 ml of 1 *N* HCl and 200 ml of ethanol and the solution was heated at 50° for 8 hr. Triethylamine (19.4 g) was added to neutralize the HCl and the solution was evaporated to dryness. The residue was suspended in ethanol (75 ml) and the insoluble **18** (4.5 g, 86%) was removed by filtration. Recrystallization from ~300 ml of hot ethanol afforded colorless needles of the monoethanolate of **18**: mp 116–118° (eff); uv absorption at $\lambda_{max}^{pH\ 7}$ 260 mμ (ε 22,160), $\lambda_{max}^{pH\ 14}$ 265 (ε 15,225), $\lambda_{max}^{pH\ 0}$ 214 mμ (shoulder) and 260 (ε 7400 and <300); pK_{a1} = 3.75 ± 0.05 (determined

(27) N. C. Yung, J. H. Burchenal, R. Fecher, R. Duschinsky, and J. J. Fox, *J. Amer. Chem. Soc.*, **83**, 4060 (1961).

(28) M. Hoffer, R. Duschinsky, J. J. Fox, and N. Yung, *ibid.*, **81**, 4112 (1959).

(29) T. A. Khwaja and C. Heidelberger, *J. Med. Chem.*, **10**, 1066 (1967). The authors are indebted to Dr. Heidelberger for the gift of compound **8** used in this study.

(30) Purchased from Zellstoff-fabrik Waldhof, Mannheim, West Germany.

(31) J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, *J. Amer. Chem. Soc.*, **78**, 2117 (1956).

spectrophotometrically). Integration of the nmr spectrum of **18** indicated 18 protons including peaks at δ 10.6 (1, broad s, NH), 5.97 (1, d, H-1'), and 1.06 (3, t, CH_3 of ethanol). A broad peak at δ 4.6 (hydroxyl protons) disappeared on addition of D_2O to reveal peaks at 4.4 (1, q, H-2') and 4.1 (1, t, H-3'). The remaining protons (H-4, H-5', H-5, H-5, and CH_2CH_3) gave rise to a seven-proton multiplet at δ 3.3–3.9 which decreased in area to a five-proton multiplet after deuterium exchange of the geminal H-5 protons ($J_{1',2'} = 3.2$, $J_{2',3'} = J_{3',4'} \simeq 6.0$ Hz).

Anal. Calcd for $C_9H_{12}N_2O_7 \cdot C_2H_5OH$: C, 43.14; H, 5.88; N, 9.15. Found: C, 43.00; H, 5.64; N, 9.34.

1-(5-*O*-Benzoyl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)barbituric acid (19).—Sodium benzoate (3.02 g, 21 mmol) was added to a solution of **15** (5.64 g, 20 mmol) in 600 ml of DMF and the mixture was heated at 120° for 3 hr. The cooled solution was concentrated to dryness and the residue was dissolved in water (150 ml). The solution was acidified (~pH 2) with 1 *N* HCl and the resulting precipitate was filtered off and washed with water. Recrystallization from 50% ethanol, and then from ethanol, afforded pure material (3.0 g, 37%): mp 163–166°; nmr δ 11.8 (1, broad s, NH), ~8.2–7.3 (5, m, aromatic protons), 6.30 (1, d, H-1'), ~5.0 (2, m, H-2', H-3'), ~4.50 (3, m, H-4', H-5', H-5'), 3.70 (2, broad s which exchanges in D_2O, H-5, H-5), 1.51, 1.31 (two singlets, six protons, isopropylidene methyls) ($J_{1',2'} = 1$ Hz); uv absorption at $\lambda_{max}^{H_2O}$ 232 and 260 mμ, $\lambda_{max}^{pH\ 1}$ 230 mμ.

Anal. Calcd for $C_{19}H_{20}N_2O_8$: C, 56.48; H, 4.95; N, 6.93. Found: C, 56.31; H, 4.91; N, 6.91.

Registry No.—**2**, 19556-57-1; **3c**, 19556-58-2; **9b**, 19556-59-3; **12**, 362-43-6; **14**, 19556-61-7; **15**, 19556-62-8; **18**, 19556-63-9; **19**, 19556-64-0; 5'-deoxy-5-bromouridine, 19556-65-1.

The Preparation of 6-Fluoropurines by the Modified Schiemann Reaction[1]

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The use of forcing conditions in the modified Schiemann reaction has now permitted the preparation of a number of 6-fluoro- and 2,6-difluoropurines. In the latter cases, the 2-aminoadenines are converted first into the 2-fluoroadenines which nitrosate more favorably than the corresponding adenines and are then converted into the 2,6-difluoropurines.

In a systematic study of the action of nitrous acid on a number of condensed 2,4-diaminopyrimidine ring systems, Trattner, *et al.*,[2] found that in all cases including 2-aminoadenine, nitrosation of the 2- but not the 4-amino group took place giving the corresponding 2-hydroxy-4-amino heterocycles.[3] They explained their results by assuming that protonation takes place at N-1 rather than at N-3.[4,5] These results and those of other investigators[6-10] have led to the conclusion[11] that the modified Schiemann reaction[12] is limited to the synthesis of 2-fluoropurines and this conclusion has been generally accepted. Despite the foregoing precedents, we now wish to report cases in which we have found that derivatives of adenine and 2-aminoadenine do undergo a modified Schiemann reaction to give 6-fluoropurines.[13]

9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)-2,6-dichloropurine[14] (**1a**), prepared by the fusion procedure,[15] was converted through diazide **2a** into 2-amino-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**3a**) (Scheme I). Treatment of **3a** with sodium nitrite in 48% fluoroboric acid gave a mixture from which 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)isoguanine (**4a**, 24%), 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2-fluoroadenine (**5a**, 13%), and 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2,6-difluoropurine (**6a**, 16%) were isolated by means of column chromatography on silica gel. **4a** was identified by its chromatographic behavior and by its infrared and ultraviolet spectra. **6a** was identified by its elemental analysis; by its ultraviolet, infrared, and pmr spectra; and by its conversion into 2-fluoro-9-β-D-xylofuranosyladenine (**5b**) by treatment with alcoholic ammonia. **5a** was also converted into **5b** by treatment with alcoholic ammonia. **5b** was initially prepared by the diazotization of **3b** in 48% fluoroboric acid.

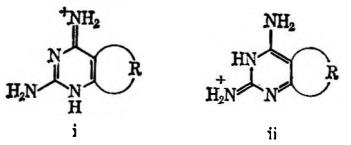
It is logical to assume that **3a** is initially converted into **5a**, which reacts further to give **6a**, and evidence in support of this pathway is found in our inability to identify any 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2-amino-6-fluoropurine[16] in the diazotization of 2',3',5'-tri-O-acetyl-2-aminoadenosine in fluoroboric acid,[17] and also in the conversion of 2',3',5'-tri-O-acetyl-2-fluoroadenosine (**9**) into 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2,6-difluoropurine (**12**) in 25% yield (*vide*

(1) This work was supported by funds from the Southern Research Institute, the C. F. Kettering Foundation, and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51.

(2) R. B. Trattner, G. B. Elion, G. H. Hitchings, and D. M. Sharefkin, *J. Org. Chem.*, **29**, 2674 (1964).

(3) In purine the numbering is not systematic so that 2-aminoadenine gives 2-hydroxy-6-aminopurine (isoguanine).

(4) Here again purine numbering causes confusion. Protonation in this case is at the ring nitrogen designated N-3 (i) not at N-1 (ii). In the other ring systems the designations are reversed.



i ii

(5) This line of reasoning might also explain why adenine is more resistant to nitrosation than 2-aminopurine, except for the fact that adenine is thought to protonate at N-1, at least in the crystal, even though it undergoes nucleophilic attack primarily at N-3.

(6) A. Bendich, P. J. Russell, Jr., and J. J. Fox, *J. Amer. Chem. Soc.*, **76**, 6073 (1954).

(7) A. G. Beaman, *ibid.*, **76**, 5634 (1954).

(8) A. Bendich, A. Giner-Sorolla, and J. J. Fox, *Ciba Found. Symp. Chem. Biol. Purines*, 3 (1957).

(9) A. Giner-Sorolla and A. Bendich, *J. Amer. Chem. Soc.*, **80**, 5744 (1958).

(10) A. G. Beaman and R. K. Robins, *J. Med. Pharm. Chem.*, **5**, 1067 (1962).

(11) A. G. Beaman and R. K. Robins, *J. Org. Chem.*, **28**, 2310 (1963).

(12) J. A. Montgomery and K. Hewson, *J. Amer. Chem. Soc.*, **79**, 4559 (1957); **82**, 463 (1960).

(13) A preliminary account of this work has appeared: J. A. Montgomery and K. Hewson, *J. Heterocycl. Chem.*, **4**, 463 (1967).

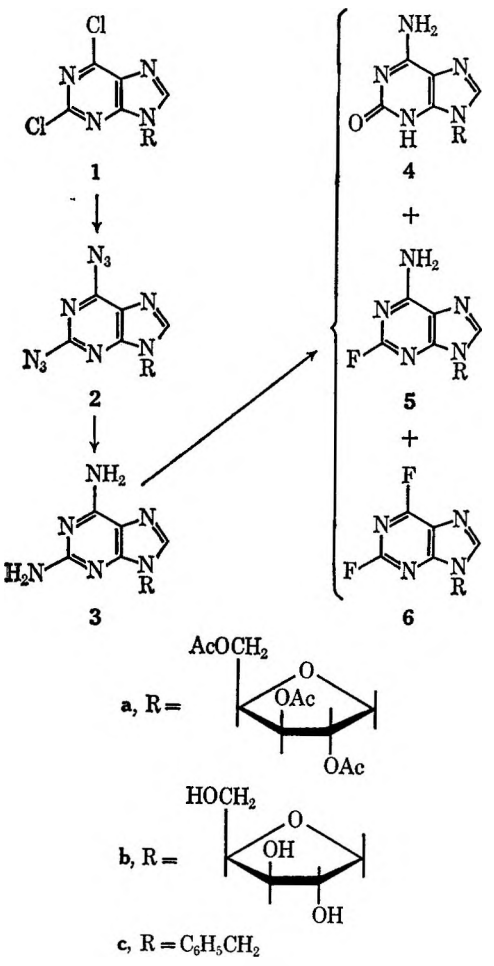
(14) E. J. Reist and L. Goodman, *Biochemistry*, **3**, 15 (1964).

(15) This fusion reaction gave predominantly the β anomer (<10% α).

(16) J. F. Gerster, A. G. Beaman, and R. K. Robins, *J. Med. Chem.*, **6**, 340 (1963).

(17) J. A. Montgomery and K. Hewson, *J. Org. Chem.*, **33**, 432 (1968).

SCHEME I



infra). Furthermore, the yield of **12** from 2′,3′,5′-tri-O-acetyl-2-aminoadenosine can be greatly increased at the expense of the yield of **9** by using excess sodium nitrite.

In contrast to our results with **9**, the reaction of 2′,3′,5′-tri-O-acetyladenosine[18] was extremely sluggish, but, even though a high recovery of **10** was obtained, 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-6-fluoropurine (**13**) was formed and isolated in 3.3% yield (traces of other unidentified nucleosides were detected by thin layer chromatography).[18a] A much weaker base than **10**, 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2-trifluoromethyladenine (**11**)—prepared from 6-chloro-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2-trifluoromethylpurine (**7**)[19] *via* the azidopurine **8**—was nitrosated more readily giving a 30% yield of the 6-fluoropurine **14** (Scheme II). This result and the conversion of **9**, which is also a much weaker base than **10**, into **12** in 25% yield lend support to the idea that protonation in the strongly acid 48% fluoroboric acid may interfere with the nitrosation of 2′,3′,5′-tri-O-acetyladenosine (**10**) (adenosine is converted in high yield into inosine in aqueous acetic acid[20,21] in which it is not fully protonated).

Not only does the amino group at C-2 of purines differ from the amino group at C-6 in the readiness with which it undergoes nitrosation in strongly acid media, but the

(18) H. Bredereck and A. Martini, *Chem. Ber.*, **80**, 401 (1947).

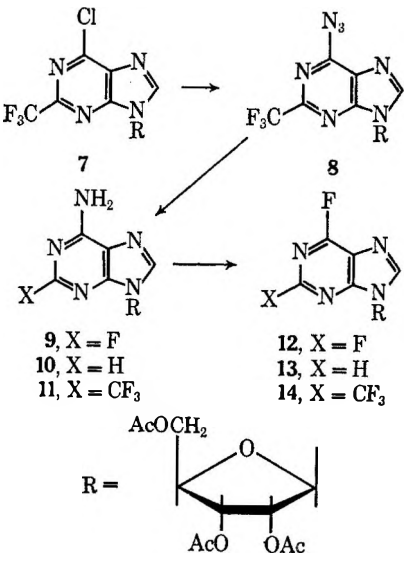
(18a) NOTE ADDED IN PROOF.—A 30% yield of **13** was obtained by the action of Ag_2F_2 on 9-(2,3,5-tri-O-acetyl-D-β-ribofuranosyl)-6-chloropurine (unpublished observation of the authors).

(19) G. Gough and M. H. Maguire, *J. Med. Chem.*, **8**, 866 (1965).

(20) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **111**, 313 (1935).

(21) J. M. Gulland and E. R. Holiday, *J. Chem. Soc.*, 765 (1936).

SCHEME II



diazonium salts, once formed, also react differently as evidenced by the fact that the 2-aminopurines give a higher yield of 2-oxopurines than 2-fluoropurines,[22] whereas the 6-aminopurines give only 6-fluoropurines. Aromatic diazonium salts are thought to react with nucleophiles *via* the aromatic carbonium ion, and presumably the 2-diazopurinium salts react in the same fashion. It would appear that the 6-diazopurinium salts react by a different mechanism, perhaps an SNi type mechanism.

The reaction of 2-amino-9-benzyladenine (**3c**) with sodium nitrite in fluoroboric acid[12] was reinvestigated and found to give a 9.6% yield of 9-benzyl-2,6-difluoropurine (**6c**) in addition to 9-benzyl-2-fluoroadenine (**5c**, 34%) and 9-benzylisoguanine (**4c**, 37%). In contrast, 2-aminoadenosine gave 2-fluoroadenosine and crotonoside,[12] but no evidence for the formation of 9-β-D-ribofuranosyl-2,6-difluoropurine (**15**).

Experimental Section

SilicAR-TLC-7 (Mallinckrodt) was used for column and thin layer (1 mm) chromatographic separations. Silica gel H (Brinkmann) was used for thin layer (0.25 mm) analyses. Spots were detected with either ultraviolet light after spraying the plates with Ultraphor WT highly concentrated (BASF Colors & Chemicals, Inc., Charlotte, N. C.) or heat charring after spraying with ammonium sulfate.[23] The ultraviolet absorption spectra were determined in 0.1 *N* HCl, 0.1 *N* NaOH, and pH 7 buffer with a Cary Model 14 spectrophotometer, the infrared absorption spectra were determined in pressed KBr disks with a Perkin-Elmer Model 521 spectrophotometer, and the pmr spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as an internal reference. The mass spectra were determined with an Hitachi-Perkin-Elmer RMU-7 mass spectrometer.

9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)-2,6-dichloropurine (1a).—A mixture of 1,2,3,5-tetra-O-acetyl-β-D-xylofuranose[14] (7 g, 22 mmol) and 2,6-dichloropurine (4.2 g, 22 mmol) was heated with continuous stirring *in vacuo* (10 mm) at 130° until an opaque melt was obtained and vigorous gas evoluton had ceased (5–10 min). After the reaction flask had cooled but before the melt solidified, the vacuum was broken and *p*-toluenesulfonic acid (200 mg) was added. Vacuum and heat were reapplied and the reaction mixture was heated with continuous stirring at 130–135° for 20 min. A C_6H_6 (40 ml) solution of the resulting clear glass was washed with saturated aqueous $NaHCO_3$ (40 ml) and then

(22) An insignificant amount of 2′,3′,5′-tri-O-acetyl crotonoside is formed in the conversion of **9** into **12**, indicating that under the conditions of these reactions little hydrolysis of the 2-fluoro group occurs.

(23) T. Ziminski and E. Borowski, *J. Chromatogr.*, **23**, 480 (1966).

H_2O (20 ml). The washed C_6H_6 solution was dried ($MgSO_4$) before it was concentrated *in vacuo*. The resulting concentrate (10 ml) was absorbed on a silica gel column (2.6 × 35 cm), which had been packed and equilibrated (18 hr) with C_6H_6. The column was eluted with C_6H_6 (*ca.* 200 ml) to remove unreacted sugar before the solvent was changed to $CHCl_3$. Elution was continued until all the xyloside had been eluted (the column fractions were monitored by thin layer chromatography using 1:1 C_6H_6–EtOAc as the eluent). The combined column fractions containing the homogeneous product were evaporated to dryness *in vacuo* to give **1** as an oil: yield 6.86 g (78%); λ_{max} mμ (ε × 10^{-3}) (pH 1, 7) 273 (9.2), (pH 13) 265 (broad) (8.5); $\bar{\nu}_{max}$ cm^{-1} 3150, 3120, 3000–2930 (CH), 1745 (C=O), 1590, 1555 (C=C, C=N), 1240–1210 (C–O–C ester), 1050 (C–O–C sugar); δ ppm ($CDCl_3$) 2.07, 2.11, and 2.15 ($C-CH_3$), 4.36 m (C_4'-H and C_5'-H), 5.43 and 5.48 (C_2'-H and C_3'-H), 6.13 d ($J_1'J_2'$ = 1Hz) (C_1'-H), 8.3 (C_8-H). The presence of the α anomer (<10%) was detected by a small doublet at 5.56 ($J_1'J_2'$ = 2.5 Hz) and a small singlet at 8.1 ppm.

9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)2,6-diazidopurine (2a).—A sodium azide solution (2.0 g, 30 mmol in 8 ml of H_2O) was added to a warm solution of 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2,6-dichloropurine (**1a**, 6.8 g, 15 mmol) in EtOH (60 ml), and the resulting reaction mixture was refluxed for 1 hr. The inorganic salts that precipitated were removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in C_6H_6 (100 ml), and the resulting mixture concentrated *in vacuo* to remove residual EtOH and H_2O. The resulting dry C_6H_6 solution was filtered through dry Celite, and the filtrate was evaporated to dryness *in vacuo* to give **2a** as a glass, yield 6.6 g (93%). Thin layer chromatography using anhydrous Et_2O as the eluent indicated that the amorphous product contained only trace impurities and was suitable for use as an intermediate: $\bar{\nu}_{max}$ cm^{-1} 2160, 2130 (N≡N).

9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)-2-aminoadenine (3a).—5% Pd–C (1.3 g) was added to a solution of 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2,6-diazidopurine (**2a**, 6.6 g, 14 mmol) in absolute EtOH (500 ml), and the mixture was hydrogenated at atmospheric pressure for 6–18 hr. The hydrogen atmosphere was removed and replaced with fresh hydrogen after 30 min, 1 hr, and 2 hr. After hydrogenation was complete, the catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in EtOAc (10 ml), and the solution was filtered through dry Celite. The filtrate was evaporated to dryness *in vacuo* to give essentially pure **3a** as a glass, yield 4.6 g (78%). Thin layer chromatography using 95:5 $CHCl_3$–MeOH as the eluent indicated the product was sufficiently pure for use as an intermediate: λ_{max} mμ (ε × 10^{-3}) (pH 1) 253 (11.3), 291 (9.5), (pH 7) 255 (9.1), 278 (9.5), (pH) 13) 255 (8.7, 278 (9.7); δ ppm (DMSO-d_6) 4.04, 4.17, and 4.22 ($C-CH_3$), 4.30 m and 4.48 m (C_4'-H and C_5'-H), 5.48 m (C_3'-H), 5.67 (C_2'-H), 5.93 d ($J_1'J_2'$ = 1.8 Hz) (C_1'-H), 6.84 broad (NH), 7.90 (C_8H); δ ppm (DMSO-d_6) 4.04, 4.17, and 4.22 ($C-CH_3$), 4.30 m and 4.48 m (C_4'-H and C_5'-H), 5.48 m (C_3'-H), 5.67 (C_2'-H), 5.93 d ($J_1'J_2'$ = 1.8 Hz) (C_1'-H), 6.84 broad (NH), 7.90 (C_8-H).

2-Amino-9-β-D-xylofuranosyladenine (3b).—A solution of 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2-aminoadenine (**3a**, 4.6 g, 11 mmol) in absolute MeOH (250 ml) was saturated at 5° with dry ammonia. After refrigeration for 3 days, the reaction solution was evaporated to dryness, and the residue was triturated with two 65-ml portions of Et_2O. The Et_2O insoluble residue solidified on trituration with hot EtOH (65 ml), and the solid that formed was collected by filtration and recrystallized from EtOH to give essentially pure **3b**, yield 1.9 g (56%). A second recrystallization from EtOH gave the analytically pure material as a crystalline solid containing 0.5 mol of EtOH: yield 1.2 g (35%); indefinite, mp,140–150°; $[\alpha]^{22}D$ −32.0 ± 0.4° (*c* 1.0, H_2O); λ_{max} mμ (ε × 10^{-3}) (pH 1) 252 (11.2), 290 (10.1), (pH 7) 255 (9.6), 278 (10.4), (pH) 13–255 (9.0), 278 (10.3); $\bar{\nu}_{max}$ cm^{-1} 3460, 3320, 3200, 3110 (OH, NH), 2920, 2900–2860 (CH), 1615, 1590, 1500 (C=C, C=N, NH), 1090, 1045 (COC).

Anal. Calcd for $C_{10}H_{14}N_6O_4 \cdot 0.5$ EtOH: C, 43.31; H, 5.62; N, 27.56. Found: C, 43.31; H, 5.70; N, 27.62.

9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)-2-fluoroadenine (5a) and **9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)-2,6-difluoropurine (6a).**—A solution of 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2-aminoadenine (**3a**, 816 mg, 2 mmol) in 48% fluoroboric acid (10 ml) was cooled to −20° and stirred continuously during the dropwise addition of a $NaNO_2$ solution (280 mg, 4 mmol, in 0.6 ml of H_2O). After completion of the nitrite addition (5 min), the reaction mixture was stirred for an additional 20 min at −10°. $CHCl_3$ (10 ml) was added to the reaction mixture, and the resulting emulsion was stirred vigorously while it was cooled to −20°. The emulsion was neutralized (pH 5–6) with 50% NaOH not allowing the temperature to exceed −10°. After the neutralization was complete, the $CHCl_3$ layer was separated from the aqueous salt solution, and the aqueous layer was extracted with three 10-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined and the resulting solution was washed with cold H_2O several times before it was dried ($MgSO_4$) and then evaporated to dryness *in vacuo*. The residue was triturated with C_6H_6 (60 ml), and the insoluble solid was collected by filtration and identified as 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)isoguanine (**4a**) by its spectral data: yield 197 mg (24%); λ_{max} mμ (pH 1) 235 (7.9), 280 (10.1), (pH 7) 248 (9.5), 292 (8.3), (pH 13) 253 (7.8), 283 (7.8); $\bar{\nu}_{max}$ cm^{-1} 3400 (broad, OH), 3120, 3140–2940, 2760 (NH, CH), 1750 (C=O), 1670, 1610–1590 (NH, C=C, C=N), 1220, 1050 (COC). The C_6H_6 filtrate was diluted with an equal volume of ligroin and the mixture was triturated until a filterable solid was obtained. The solid was collected by filtration and dried *in vacuo* to give crude **5a**. The filtrate was evaporated to dryness to give crude **6a**.

Each of the crude reaction products (**5a** and **6a**) was purified by thin layer chromatography. A $CHCl_3$ solution of the crude product was streaked on a 1 × 200 mm silica gel coated plate which had been activated for 1 hr at 120°. The plate was developed for a total ascending distance of 18 cm. The bands were eluted from the silica gel to give chromatographically homogeneous material.

Crude **5a** (175 mg) was chromatographed using 19:1 $CHCl_3$–MeOH as the eluent. The chromatographically homogeneous product was eluted from the silica gel with EtOH: yield 39 mg (4%); λ_{max} mμ (pH 1) 261 (11.5), 2.68 (sh), (pH 7, 13) 261 (12.2), 268 (sh); $\bar{\nu}_{max}$ cm^{-1} 3360–3330 (NH), 3180, 3020–2930 (CH), 1745 (C=O), 1640, 1610, 1585 (NH, C=C, C=N), 1220, 1050 (COC).

Crude **6a** (135 mg) was chromatographed using EtOAc as the eluent. Elution of the major product from the silica gel with EtOAc gave the chromatographically homogeneous material as an oil which was redissolved in $CHCl_3$. Evaporation of this $CHCl_3$ solution to dryness *in vacuo* gave the pure product as a hard glass containing 0.25 mol of $CHCl_3$: yield 76 mg (8.5%); λ_{max} mμ (pH 1) 254, (pH 13) 256; $\bar{\nu}_{max}$ cm^{-1} 3120, 3000, 2940 (CH), 1745 (C=O), 1630, 1590 (C=C, C=N), 1220, 1100, 1050, 1040, 1015 (COC); δ ppm ($CDCl_3$) 2.10, 2.13 and 2.18 (CCH_3), 4.34 m and 4.44 m (C_5'-H and C_4'-H), 5.49 and 5.54 (C_3'-H and C_2'-H), 6.17 d ($J_1'J_2'$ = 2.3 Hz) (C_1'-H), 7.28 ($CHCl_3$) 8.35 (C_8-H).

Anal. Calcd for $C_{16}H_{16}F_2N_4O_7 \cdot 0.25CHCl_3$: C, 43.95; H, 3.64; N, 12.62. Found: C, 44.29; H, 3.96; N, 12.24.

2-Fluoro-9-β-xylofuranosyladenine (5b). A.—A solution of $NaNO_2$ (660 mg, 9.5 mmol) in H_2O (1.3 ml) was added dropwise with stirring to a solution of 2-amino-9-β-D-xylofuranosyladenine (**3b**, 1.7 g, 5.5 mmol) in 48% fluoroboric acid (17 ml) maintained at −20 to −10°. After the nitrite addition was complete, the reaction mixture was stirred at −10° for 15 min before H_2O-saturated *n*-BuOH (35 ml) was added. The resulting slurry was neutralized (pH 5–6) with 25% NaOH keeping the temperature below −5°. The neutral mixture was extracted with five 90-ml portions of H_2O-saturated *n*-BuOH, and the combined extracts were washed with four 45-ml portions of *n*-BuOH-saturated H_2O. The *n*-BuOH solution was evaporated to dryness *in vacuo*, and the residue (850 mg) was mixed with silica gel (850 mg). The resulting mixture was packed on a previously prepared column (1.9 × 35 cm containing 40 g of silica gel wet packed $CHCl_3$). The column was eluted with 225 ml of 9:1 $CHCl_3$–MeOH to remove pigmented impurities before the eluent was changed to 4:1 $CHCl_3$–MeOH which eluted the chromatographically homogeneous product, yield 150 mg (9%). EtOH recrystallization gave an analytically pure sample of **5b**: mp 245–247° (Mel-Temp); $[\alpha]^{25}D$ −58.5 ± 0.4 (*c* 0.51, MeOH); λ_{max} mμ (ε × 10^{-3}) (pH 1) 262 (13.3), 267 (sh), (pH 7, 13) 262 (14.8), 267 (sh); $\bar{\nu}_{max}$ cm^{-1} 3350–3300, 3180–3110 (NH, OH, CH), 2920 (CH), 1670, 1615, 1570 (NH, C=C, C=N), 1090, 1085, 1060, 1050 (COC).

Anal. Calcd for $C_{10}H_{12}FN_5O_4$: C, 42.11; H, 4.24; N, 24.56. Found: C, 42.18; H, 4.20; N, 24.26.

B.—A solution of 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-2,6-difluoropurine (**6a**, 47 mg, 0.1 mmol) in anhydrous ethanolic

ammonia (25 ml saturated at 5°) was sealed in a glass flask and allowed to stand at 5° for 3 days. The reaction solution was evaporated to dryness, and the residue was solidified by trituration with EtOH–Et_2O. The solid was collected by filtration, triturated with $CHCl_3$, and dried *in vacuo* to give 27 mg of impure **5b** as identified by its melting point (232°) and ultraviolet spectrum [λ_{max} ($\epsilon \times 10^{-3}$) (pH 1) 262 (11.5), 267 (sh), (pH 7, 13) 262 (12.8), 267 (sh)]. Thin layer chromatography on silica gel using 3:1 $CHCl_3$–MeOH as the eluent showed minor impurities.

C.—Treatment of 2-fluoro-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**5a**, 1.3 g, 3.16 mmol) as described in B gave 750 mg of crude **5b**. Recrystallization from EtOH with charcoal treatment gave 330 mg (37%) of pure **5b**: λ_{max} mμ ($\epsilon \times 10^{-3}$) (pH 1) 262 (13.7), 267 (sh), (pH 7, 13) 262 (15.0), 267 (sh).

9-Benzyl-2,6-difluoropurine (6c).—A suspension of 2-amino-9-benzyladenine (**3c**, 1.5 g, 6.2 mmol) in $CHCl_3$ (30 ml) was diluted with 48% fluoroboric acid (50 ml). The resulting mixture was cooled to −15° and stirred continuously during the dropwise addition of $NaNO_2$ (1.3 g, 18.8 mmol in 1.5 ml of H_2O). After completion of the nitrite addition (5 min), the reaction was stirred for an additional 30 min at −5° before $CHCl_3$ (25 ml) was added and the mixture was cooled to −20°. The resulting emulsion was neutralized (pH 5–6) with 50% NaOH not allowing the temperature to exceed −10°. After the neutralization was complete, the insoluble solid that formed was collected by filtration and washed with fresh $CHCl_3$. The resulting partially dried solid was triturated with excess Me_2CO, and the insoluble solid was dried *in vacuo* to give the crude 9-benzylisoguanine, (**5c**): yield 550 mg (37%); λ_{max} mμ (pH 1) 234 (sh), 242 (sh), 280; (pH 7) 250, 294; (pH 13) 255, 286.

Evaporation of the Me_2CO filtrate to dryness followed by trituration of the resulting residue with H_2O gave the crude 9-benzyl-2-fluoroadenine (**4c**): yield 460 mg (30%); λ_{max} mμ (pH 1) 264, (pH 7) 13–262.

The $CHCl_3$ layer was separated from the aqueous salt solution, combined with the $CHCl_3$ wash of the reaction mixture insoluble solid, and washed with H_2O. After drying ($MgSO_4$), the $CHCl_3$ filtrate was concentrated *in vacuo*, and the concentrate was streaked on a 1 × 200 mm silica gel coated plate. The chromatogram was developed with EtOAc and the major band was eluted with hot EtOAc. Evaporation of the EtOAc to dryness *in vacuo* gave the 9-benzyl-2,6-difluoropurine (**6c**) as an oil: yield 146 mg (9.6%); λ_{max} mμ ($\epsilon \times 10^{-3}$ (pH 1, 7) 256 (7.5), (pH 13) 256 (9.6); δ ppm 5.40 (CH_2 of benzyl), 7.35 (phenyl H), 8.06 d (C_8-H coupled to one or both fluorines). The mass spectrum of **6c** showed a strong peak at a mass to charge ratio of 246 (calcd mol wt, 246).

9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-6-azido-2-trifluoromethylpurine (8).—A sodium azide solution (350 mg, 5.4 mmol in 1 ml of H_2O) was added to a hot solution of 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-6-chloro-2-trifluoromethylpurine[19] **7**, (2.5 g, 5.2 mmol) in EtOH (50 ml), and the resulting reaction mixture was refluxed for 1 hr. The inorganic salts that precipitated were removed by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in C_6H_6 (50 ml) and the resulting mixture concentrated *in vacuo* to remove residual EtOH and H_2O. The dry C_6H_6 solution was filtered through Celite and the filtrate was evaporated to dryness *in vacuo* to give **8** as a glass. Thin layer chromatography using 3:1 $CHCl_3$–EtOAc as the eluent indicated that the amorphous product contained only trace impurities and was suitable for use as an intermediate: $\bar{\nu}_{max}$ cm^{-1} 2150, 2120 (N≡N), 1745 (C=O), 1620, 1595, 1575 (C=C, C=N), 1240–1220, 1140 (COC).

9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-2-trifluoromethyladenine (11).—5% Pd–C (400 mg) was added to a solution of 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl-6-azido-2-trifluoromethylpurine (**8**, 2.4 g, 4.9 mmol) in absolute EtOH (250 ml), and the mixture was hydrogenated at atmospheric pressure for 6 hr. The hydrogen atmosphere was removed and replaced with fresh hydrogen after 30 min, 1 hr, and 2 hr. After hydrogenation was complete, the catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in $CHCl_3$, and the resulting solution was absorbed on a previously packed silica gel column (2.6 × 35 cm). The column was eluted with 2:1 $CHCl_3$–EtOAc, and the fractions containing **11** were combined and evaporated to dryness *in vacuo* to give essentially pure material as an oil: yield 1.2 g (53%); λ_{max} mμ (pH 1, 7) 258, 275 (sh), (pH 13) 260, 274 (sh); $\bar{\nu}_{max}$ cm^{-1} 3440–3420, 3340 (NH), 3220–3200, 3000–2980, 2940 (CH), 1740 (C=O), 1650, 1640, 1590 (NH, C=C, C=N), 1220, 1130, 1090, 1040 (COC); δ ppm ($CDCl_3$) 2.02, 2.13, 2.17 (CCH_3), 4.43 m (C_4'-H and C_5'-H), 5.68 m (C_3'-H), 5.85 m (C_2'-H), 6.15 d ($J_{1'2'}$ = 1.5 Hz), 6.38 (NH), 8.04 (C_8-H).

9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-2,6-difluoropurine[17] (12).—$NaNO_2$ (69 mg, 1 mmol) suspended in H_2O (0.1 ml) was added (20 min) to a continuously stirred solution (−15°) of 9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-2-fluoroadenine[17] (**9**, 205 mg, 0.5 mmol) in 48% fluoroboric acid (3 ml). The reaction mixture was stirred an additional 20 min at −10 to 0° before $CHCl_3$ (10 ml) was added. The resulting emulsion was stirred vigorously at −15° and neutralized (pH 5–6) with 50% NaOH. The $CHCl_3$ layer was separated from the aqueous salt solution and washed with two 10-ml portions of H_2O before it was dried ($MgSO_4$) and evaporated to dryness *in vacuo*. The residue (150 mg) was dissolved in $CHCl_3$, and the resulting solution of the crude product was purified by thin layer chromatography using EtOAc as the eluent. The two major products were eluted from the silica gel with warm EtOH. Evaporation of the EtOH solutions to dryness gave 37 mg (25%) of **12** and 95 mg (65%) of recovered starting compound (**9**). The identity of the isolated products was confirmed by tlc using EtOAc as the eluent.

9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-6-fluoropurine (13).—To a solution of 2′,3′,5′-tri-O-acetyladenosine[18] (**10**, 2.9 g 7.35 mmol) in 48% fluoroboric acid (35 ml) at −20° was added dropwise with stirring a solution of $NaNO_2$ (0.86 g, 12.5 mmol) in H_2O (1.8 ml). An additional 1.2 g (17.4 mmol) of $NaNO_2$ in 25 ml of H_2O was added at 0° and 30 min later the solution was neutralized as described above (preparation of **12**). The semisolid residue resulting from evaporation of the $CHCl_3$ extracts of the reaction mixture was streaked on a 1 × 200 mm silica gel coated glass plate. After the plate was developed in 19:1 $CHCl_3$–MeOH, the fastest traveling band was eluted, and the eluate was evaporated to dryness *in vacuo* to give the pure product as a glass: yield 0.1 g (3.3%); $[\alpha]^{23}D$ −10.8 ± 0.9[6] (*c* 0.98, $CHCl_3$); λ_{max} mμ ($\epsilon \times 10^{-3}$) EtOH 243 (6.5), (pH 13) unstable; $\bar{\nu}_{max}$ cm^{-1} 3100, 2940 (CH), 1745 (C=O), 1610, 1570 (C=C, C=N), 1220, 1090, 1045, 1010 (COC); δ ppm ($CDCl_3$) 2.11, 2.14, 2.17 (CCH_3), 4.44 m (C_5'-H and C_4'-H), 5.63 t (C_3'-H), 5.95 t (C_2'-H), 6.25 d (C_1'-H), 7.27 ($CHCl_3$), 8.28 (C_8-H), 8.65 (C_2-H). The integral of the spectrum shows nine CCH_3 protons, six sugar protons, and two purine protons. The mass spectrum of **13** showed a peak at a mass to charge ratio of 396 (calcd mol wt 396) and the expected fragmentation pattern. $CHCl_3$ was detected in the mass spectrometer before the spectrum of **13** appeared.

Anal. Calcd for $C_{16}H_{17}FN_4O_7 \cdot 0.2CHCl_3$: C, 46.31; H, 4.13; N, 13.33. Found: C, 46.38; H, 4.25; N, 13.27.

9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-6-fluoro-2-trifluoromethylpurine (14).—9-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-2-trifluoromethyladenine (**11**, 1.1 g, 2.4 mmol) was diazotized as described above for the preparation of **12** from **9**. The glass (700 mg) resulting from evaporation of the $CHCl_3$ extracts of the neutalized reaction mixture was dissolved in C_6H_6, and the solution was absorbed on a previously packed silica gel column (2.6 × 35 cm). The column was eluted with 2:1 $CHCl_3$–EtOAc. The fractions containing **14** were combined and evaporated to dryness *in vacuo*. The resulting oil was dried *in vacuo* over P_2O_5 until it crystallized: yield 250 mg (25%); mp 131–133° (Heizbank); $[\alpha]^{25}D$ 0 (*c* 1.11, $CHCl_3$); λ_{max} mμ ($\epsilon \times 10^{-3}$) (pH 1) 248 (7.2), (pH 7, EtOH) 248 (7.5), (pH 13) 252.5 (11.3); $\bar{\nu}_{max}$ cm^{-1} 3480–3400 (OH), 3110, 2955 (CH), 1740 (C=O), 1620, 1610, 1575 (C=C, C=N), 1240, 1220, 1145 (COC).

Anal. Calcd for $C_{17}H_{16}F_4N_4O_7$: C, 43.97; H, 3.47; N, 12.07. Found: C, 43.77; H, 3.36; N, 11.93.

Registry No.—**1a**, 19806-62-3; **2a**, 18354-12-6; **3a**, 18354-13-7; **3b**, 19768-89-9; **4a**, 18469-59-5; **5a**, 18354-14-8; **5b**, 19768-92-4; **6a**, 18354-15-9; **6c**, 19768-94-6; **8**, 19768-95-7; **11**, 19768-96-8; **13**, 18354-17-1; **14**, 19768-98-0.

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The Synthesis and Chemistry of 2-(1-Aziridinyl)-2-oxazolines

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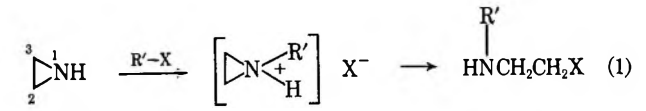
Several examples of the new 2-(1-aziridinyl)-2-oxazoline system have been synthesized by the isomerization of appropriate 1,1′-carbonylbisaziridines with catalytic amounts of tetra-*n*-butylammonium iodide. Reactions of 2-(1-aziridinyl)-2-oxazolines with Lewis and Brønsted acids indicate that complexing occurs entirely at the oxazoline nitrogen. Similar reactions with acid chlorides show that the oxazoline moiety is more nucleophilic than the aziridine function. Several novel heterocyclic systems have been synthesized from 2-(1-aziridinyl)-2-oxazolines and diacid chlorides.

Substantial and exciting developments have been reported in the area of aziridine[1] and 2-oxazoline[2] chemistry since examples in each series were first synthesized in the late 1800's. Both systems are known to undergo ring-opening reactions with a variety of reagents such as phenols, thiophenols, mineral acids, organic acids, or acid chlorides. It is generally believed that these reactions proceed by first quaternization of the nitrogen followed by nucleophilic attack by the counter ion at the 2 position of the aziridinium salt[3] (1) or at the 5 position of the oxazolinium salt[4,5] (2) to give ring-opened products as shown in eq 1 and 2. To date intermediates such as 1, where R′ is aroyl or acyl, have not been isolated; however, stable aziridinium salts have been isolated recently by several groups.[11,12] Oxazolinium salts (2), where R′ is aroyl[5] or hydrogen[9b] have been isolated and well characterized. The above reactions usually proceed in high yield to the indicated products. With this in mind it was considered of interest to incorporate these two moieties in a common molecule in an attempt to compare the relative nucleophilicities of the respective ring nitrogens when submitted to electrophiles such as mono- and diacid chlorides and to determine the preferred site of attack by Lewis and protonic acids.



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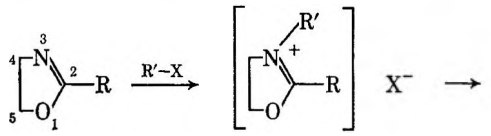


2

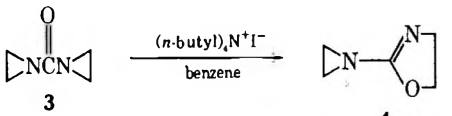
(2)

R′ = ArC(=O),[3,4] H,[4,6] H,[7] H,[8] H,[9] (alkyl—O—)$_2$P(=O)—[10]

X = Cl, ArCO(=O), ArS, ArO, Cl, Cl

Results and Discussion

Of the three possible mono (1-aziridinyl)-2-oxazolines (*i.e.*, 2, 4, or 5 substituted), the 2-(1-aziridinyl)-2-oxazoline system appeared to be useful for this study and in fact proved to be the most convenient system to synthesize. The synthesis of 2-aziridinyl-2-oxazoline was accomplished by isomerizing one of the aziridine rings in 1,1′-carbonylbisaziridine using a catalytic amount of tetra-*n*-butylammonium iodide in benzene (eq 3).



3 4 (3)

This catalyst system offered several advantages over the usual sodium iodide–acetone or acetonitrile systems[1b] in that the solvent was much easier to dry and the amount of polymeric side products was minimized. 2-(1-Aziridinyl)-2-oxazoline was obtained in 79% yield as a low melting white solid which sublimed readily. The conversion of **3** into **4** was followed by nmr spectroscopy, wherein a singlet (−2.10 ppm) for **3** gradually disappeared as a new singlet at −2.05 ppm and a set of finely split triplets at −3.66 and −4.27 ppm ($CDCl_3$) for **4** developed. Infrared (ir) analysis also confirmed this conversion in that a strong band at 1695 cm^{-1} [>NC(=O)N<] diminished as a new band at 1661 cm^{-1}, characteristic of 2-oxazolines,[13] appeared during the course of the isomerization. This isomerization appeared to be somewhat slower than that observed for the sulfur analog [*i.e.*, 1,1′-(thiocarbonyl)bisaziridine → 2-(1-aziridinyl)-2-thiazoline].[14]

Using the method of Bestian,[3] 1,1′-carbonylbis(2-

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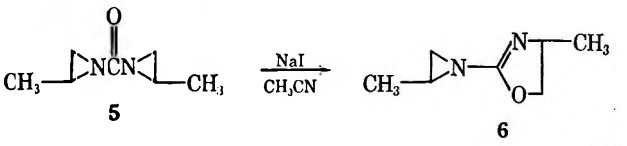
(14) D. A. Tomalia, *J. Heterocycl. Chem.*, **4**, 419 (1967).

methyl)aziridine (**5**) was obtained in 36% yield as a light yellow, distillable liquid. Nmr and ir spectra were consistent with the proposed structure (See Experimental Section). Attempts to isomerize **5** in the same manner as to isomerize **3** with *n*-tetrabutylammonium iodide in benzene were unsuccessful. Isomerization of **5** to the presumed isomer **6**[15] was observed when sodium iodide in anhydrous acetonitrile was used (eq 4). Even when this catalyst system was used the

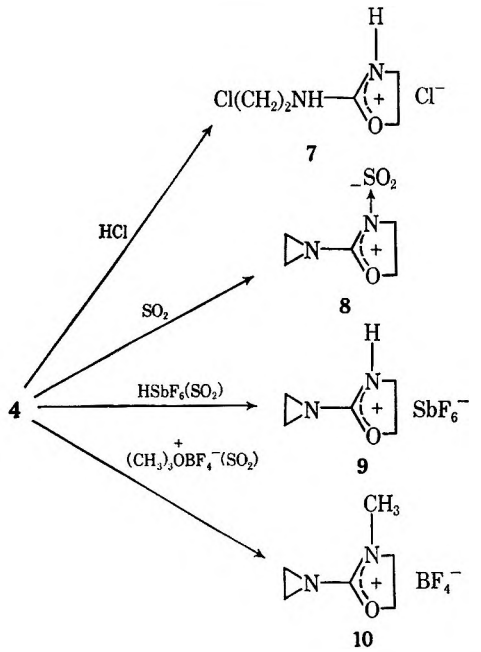


(4)

isomerization was relatively slow. The characteristic 2-oxazoline absorption was noted for the product at 1660 cm^{-1}. Although the methyl region of the nmr spectrum was too complicated by overlapping bands to determine whether both isomers were present, thin layer chromatography (tlc) indicated that a small amount of the other isomer may have been formed.

2-(1-Aziridinyl)-2-oxazoline (**4**) underwent ring opening with hydrochloric acid to yield 2-(2-chloroethylamino)-2-oxazoline hydrochloride (**7**). When the reaction was carried out with an acid possessing a nonnucleophilic counterion (*i.e.*, $HSbF_6$), with sulfur dioxide, or with trimethyloxonium tetrafluoroborate nmr analysis indicated that both rings were preserved giving in each case **8**, **9**, and **10** (Scheme I).

SCHEME I

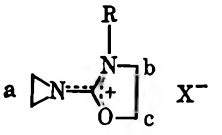


Attempts to prepare the 3-acetyl-2-(1-aziridinyl)-2-oxazolinium salt (**11**) by the reaction of methyl oxocarbonium hexafluoroantimonate with **4** were unsuccessful. Ill-defined polymeric products were obtained in all cases. Nmr data supporting these structures are recorded in Table I. Further evidence for preferential electrophilic attack at the oxazoline nitrogen was obtained by allowing a model compound, 2-dimethyl-

(15) Assignment of the structure for **6** is based on the usual selectivity observed for these iodide-catalyzed isomerizations (*cf.* ref 1b).

TABLE I

NMR CHEMICAL SHIFTS (δ) FOR 2-(1-AZIRIDINYL)-2-OXAZOLINE COMPLEXES

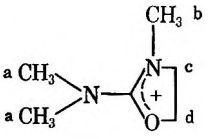


12

Compound	Solvent	Protons (a)	$\Delta\delta'$[a]	Protons (b)	$\Delta\delta''$[a]	Protons (c)	$\Delta\delta'''$[a]
4	$CDCl_3$	−2.10 (s)		−3.66 (t)		−4.27 (t)	
8	SO_2	−2.68 (s)	0.58	−4.05 (t)	0.39	−4.93 (t)	0.66
9	SO_2	−2.76 (s)	0.66	−4.14 (t)	0.48	−5.06 (t)	0.79
10	SO_2	−2.80 (s)	0.70	−4.13 (t)	0.49	−4.94 (t)	0.67

[a] The difference in chemical shift (δ) relative to uncomplexed **4** in $CDCl_3$.

amino-2-oxazoline, to react with trimethyloxonium tetrafluoroborate. A crystalline material was isolated in high yield and was assigned the following structure,



a, −3.14 (s); b, −3.25 (s); c, −3.93 (t); d, −4.63 (t)
a:b:c:d, 5.87:2.94:2.16:2.03

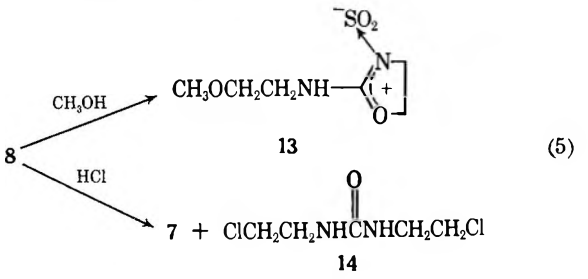
based on nmr spectral data. If quaternization had occurred at the 2-amino group one would have expected equivalent methyl groups.

The spectral data in Table I not only indicate that attachment at the oxazoline nitrogen is preferred but also suggest that the resulting complexes are best represented as resonance hybrids, as shown (Table I, **12**), whereby charge can be effectively delocalized to the aziridine ring as well as the 5 position of the oxazoline ring. The latter is apparent by comparing the amount of deshielding of these positions in the complexes relative to the uncomplexed material (*i.e.*, $\Delta\delta'$, $\Delta\delta''$, and $\Delta\delta'''$). Resonance structure **12** is not too unlike those reported for 1,3-dioxolenium cations,[16] in particular the 2-diethylamino-1,3-dioxolenium cation. Assuming that no unexpected anisotropy effects are operative, these values indicate that charge delocalization is higher at the aziridine ring and oxazoline 5 position than at the oxazoline 4 position. Just as Weinberger and Greenhalgh[17] have shown that the 2-methyl group on 2-methyl-2-oxazoline is a sensitive probe for determining the electron density on the oxazoline nitrogen, our data shows qualitatively that the aziridine ring also reflects depletion of electron density on the oxazoline nitrogen (*cf.* $\Delta\delta'$, Table I). The preferred complexing at the oxazoline nitrogen, despite the fact that aziridines[18] are usually more basic than 2-oxazolines,[10b,19] indicates that the opportunity to delocalize charge as in **12** is more important than complexation at the more basic aziridine site where charge would be localized.

Upon treatment of **8** with methanol or with anhydrous HCl, aziridine ring opening was observed, giving 2-(2-methoxyethylamino)2-oxazoline (**13**) in the first

(16) H. Hart and D. A. Tomalia, *Tetrahedron Lett.*, **18**, 1347 (1967), and previous papers.
(17) M. A. Weinberger and R. Greenhalgh, *Can. J. Chem.*, **41**, 1038 (1963).
(18) G. J. Buist and H. J. Lucas, *J. Amer. Chem. Soc.*, **79**, 6157 (1957).
(19) G. R. Porter, H. N. Rydon, and J. A. Schofield, *J. Chem. Soc.*, 2686 (1960).

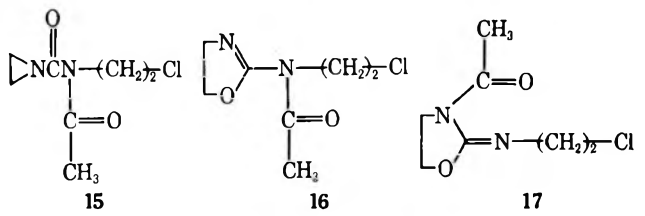
case, whereas 2-(2-chloroethylamino)2-oxazoline hydrochloride (7) and 1,3-bis(2-chloroethyl)urea (14) were formed in the later instance (eq 5). These products were identified by comparison with authentic samples obtained by an independent method.



2-(1-Aziridinyl)-2-oxazoline (4) reacted exothermally with an equivalent amount of acetyl chloride to give a thermolabile, light yellow oil which analyzed for $C_7H_{11}ClN_2O_2$. Attempts to distil this material, using routine vacuum techniques, led to the formation of an orange-red polymer. Analytical samples could be obtained only by flash distillation under vacuum. This product displayed intense bands at 1722 and 1683 cm^{-1} in the ir region, whereas the nmr spectrum consisted of a singlet at -2.55, a slightly split singlet at -3.62, and an A_2B_2 pattern centered at -4.15 ppm ($CDCl_3$). These protons were present in a ratio of 3:4:4, respectively.

When the acetylation product was allowed to react with gaseous HCl, N-acetyl-1,3-bis(2-chloroethyl)urea was obtained. This material was identified by comparison with an authentic sample which was obtained from the acetylation of 1,3-bis(2-chloroethyl)-urea.

A prior consideration of opening either or both rings in 4 forces one to postulate at least three tenable structures for this product, *i.e.*, 15, 16, or 17. Although the

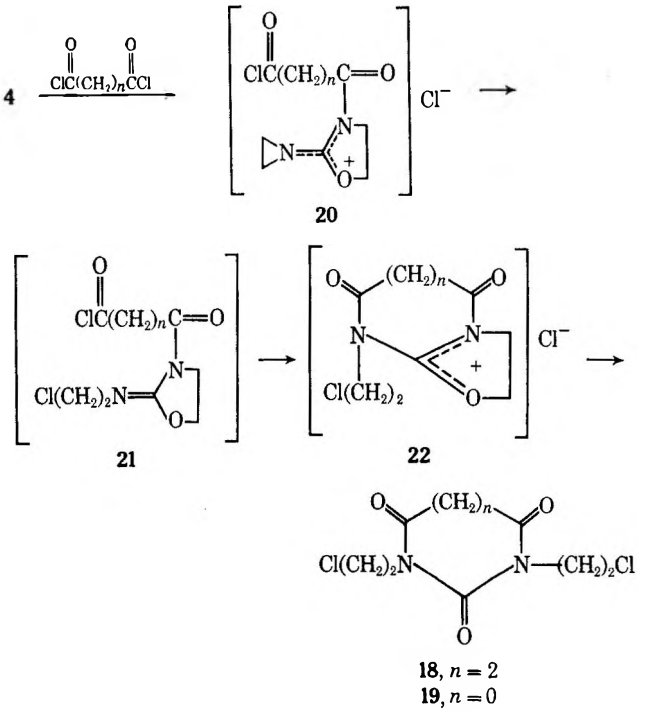


thermolability of this material is reminiscent of aziridine[1a] or oxazolidine[20] functionality, structure 15 was discounted in that no aziridine-type protons were observed in the nmr spectrum. Based on the spectroscopic data and conversion of the acetylated product into N-acetyl-1,3-bis(2-chloroethyl)urea, a choice between structures 16 and 17 cannot be decisive. In view of the spectroscopic and chemical evidence presented earlier for preferred aziridine ring opening, assignment of structure 17 to the acetylation product is favored at this time.

A survey of the literature indicated that compound 17 is a member of a relatively small class of exocyclic 2-iminooxazolidines[21] which are substituted in the 3 position with nonlabile groups such that tautomerization to a 2-amino-2-oxazoline is rendered impossible. Although related ring systems containing a labile 3 substituent[22-24] have on occasion been reported as exocyclic iminooxazolidines, more recent work has shown that the endocyclic imino tautomers usually predominate.[25]

The reaction of 4 with 2 equiv of acetyl chloride gave ill-defined products, whereas the same reaction with acetyl bromide gave a thermolabile material which was identified by nmr as 1,3-bis(2-bromoethyl)-1,3-diacetylurea. It appears that in the presence of the more nucleophilic bromide ion both the aziridine and the oxazoline moieties undergo ring opening. Despite the unsuccessful attempt to cleave both rings with 2 equiv of acetyl chloride, 4 underwent such a cleavage with diacid chlorides thus providing an interesting route to a number of heterocyclic systems. Succinyl chloride and phthaloyl chloride reacted with 4 to give the seven-membered heterocycles, 1,3-bis(2-chloroethyl)-dihydro-1H-1,3-diazepine-2,4,7(3H)-trione (18, 78%) and 2,4-bis-2-chloroethylbenzo-2,4-diazepine-1,3,5-trione (95%). These structures were confirmed by nmr, ir, and mass spectroscopy. Oxalyl chloride reacted in a similar manner with 4 to give 1,3-bis(2-chloroethyl)-imidazolidine-2,4,5-trione (19) in 92% yield. This structure was established by comparison with an authentic sample which was obtained by treating 1,3-bis-(2-chloroethyl)urea with oxalyl chloride according to the method of Blitz and Topp.[26] In each case it is believed that the cyclization occurs in four steps as outlined in Scheme II. Based on previous observations,

SCHEME II

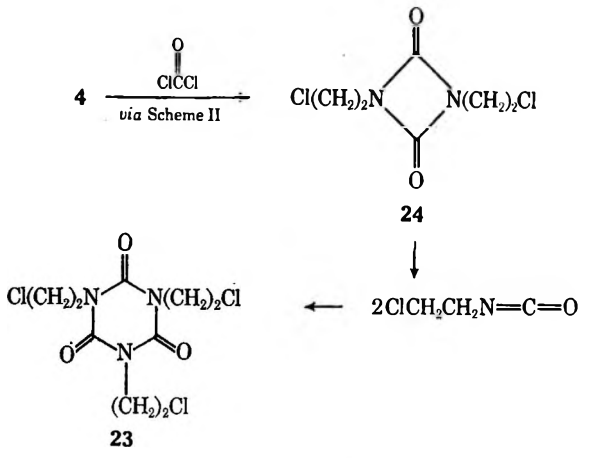


the first step probably involves formation of a 2-(1-aziridinyl)-2-oxazolinium salt (20) which then collapses to the 2-(2-chloroethyl)imino-3-acyloxazolidine derivative (21) followed by intramolecular acylation of the imino group to give the oxazolinium salt, 22. Collapse of 22 yields the heterocyclic products.

(20) E. D. Bergman, *Chem. Rev.*, **53**, 309 (1953).
(21) R. W. Leekenbaugh, U. S. Patent 2,902,356 (1959); *Chem. Abstr.*, **54**, 811*g* (1960).
(22) A. Crawshaw and A. N. Mason, *Chem. Ind.* (London), 365 (1964).
(23) E. Schmidt, F. Hitzler, and E. Lahde, *Ber.*, **71**, 1933 (1938).
(24) E. Schmidt and W. Striewsky, *ibid.*, **74**, 1285 (1941).
(25) A. R. Katritzky, *Advan. Heterocycl. Chem.*, **2**, 67 (1963).
(26) H. Blitz and E. Topp, *Ber.*, **46**, 1387 (1913).

When **4** was treated with phosgene, 1,3,5-tris(2-chloroethyl)-s-triazine-2,4,6-trione (**23**) was obtained in 28% yield rather than the expected 1,3-bis(2-chloroethyl)-2,4-uretidinedione (**24**) (Scheme III). It is quite likely that **24** is formed as a transient intermediate *via* Scheme II; however, owing to the instability of these derivatives[27] reversion to 2-chloroethyl isocyanate followed by trimerization to **23** apparently occurs.

SCHEME III



Reaction of **4** with malonyl chloride did not give the expected six-membered heterocycle *via* Scheme II. Instead, **4** functioned as a dehydrohalogenating agent, under mild conditions, to yield 2-(2-chloroethylamino)-2-oxazoline hydrochloride (**7**) and presumably carbon suboxide. Under reflux conditions 1,3-bis(2-chloroethyl)urea (**14**) was obtained. This reaction dramatizes the basicity of **4** in that it appears to parallel the well-known reaction between tertiary amines and malonyl chloride to yield carbon suboxide and tertiary amine salts.[28]

Experimental Section

Nmr spectra were obtained with a Varian A-60 spectrometer. Chemical shifts are reported as δ (parts per million) relative to tetramethylsilane (TMS). Ir spectra were scanned on a Perkin-Elmer 337 spectrometer. Melting points were determined in a capillary and are uncorrected unless otherwise noted.

1,1'-(Carbonyl)bisaziridine (3).—This compound was prepared according to the method of Bestian.[3] The white crystalline material, mp 38–40°, displayed a carbonyl band at 1700 (s) and aziridine (C–H stretching) at 3025 (w) and 3090 cm^{-1} (w). The nmr spectrum consisted of a singlet at −2.18 ppm (CCl_4).

2-(1-Aziridinyl)-2-oxazoline (4).—A solution of **3** (36.4 g, 0.33 mol) and tetra-*n*-butylammonium iodide (2.0 g) in 200 ml of anhydrous benzene was refluxed for 4 hr under anhydrous conditions. The solvent was removed *in vacuo* at room temperature. The light yellow residue was distilled, giving a major cut boiling at 62° (4.3 mm) which weighed 28.8 g (79%). The distillate solidified to a white crystalline material melting at 27–29°. At pressures below 1 mm this material sublimed readily. The nmr spectrum consisted of two triplets centered at −4.27 and −3.66, as well as a singlet at −2.05 ppm ($CDCl_3$) in a ratio of 1:1:2. The ir spectrum contained an intense band at 1661 cm^{-1} which is generally characteristic of 2-oxazoline.[13]

Anal. Calcd for $C_5H_8N_2O$: C, 65.18; H, 8.75; N, 30.41. Found: C, 65.21; H, 8.68; N, 30.23.

1,1'-(Carbonyl)bis(2-methylaziridine) (5).—A solution of 2-methylaziridine (28.5 g, 0.5 mol) and triethylamine (50.5 g, 0.5 mol) in 250 ml of ether was added dropwise to a stirred solution of phosgene (24.5 g, 0.25 mol) in 500 ml of ether while the reaction temperature was maintained at −5 to 0°. The addition took 4 hr and then the reaction was allowed to stir at 0 to 10° for 2 hr. Triethylamine hydrochloride was filtered off and the solvent was removed *in vacuo* at room temperature. The light yellow oily residue weighed 23.2 g and distilled to give a major fraction, bp 56° (5 mm), weighing 12.5 g (36%), $n^{25}D$ 1.4605. The nmr spectrum consisted of a multiplet at −2.73 to −2.13 and two doublets centered at −1.84 and −1.30 ppm (CCl_4) in a ratio of 2:1:3, respectively. The ir spectrum contained bands at 3075 (w), 3005 (w), and 1695 (s) cm^{-1} (neat).

2-(2-Methylaziridinyl)-4-methyl-2-oxazoline (6).—A solution of the aziridine **5** (1.24 g, 0.03 mol) and sodium iodide (0.6 g, 0.004 mol) in 25 ml of dry acetonitrile was refluxed under anhydrous conditions for 27 hr. After the solvent was removed *in vacuo* at room temperature, the residue was distilled to give 0.55 g (44%) of product boiling at 85–90° (2 mm), $n^{25}D$ 1.4650. The nmr spectrum consisted of multiplets at −4.84 to −3.66, −2.66 to −2.20, −2.05 to −1.90, and −1.48 to −1.14 ppm ($CDCl_3$) in a ratio of 3:2:1:6, respectively. A characteristic band for OC=N[13] was observed at 1656 cm^{-1} (neat).

Reaction of 4 with Hydrochloric Acid → 7.—2-(1-Aziridinyl)-2-oxazoline (1.0 g) was added to 25 ml of 12 *N* HCl, while stirring at room temperature, to give a homogeneous solution. Removal of the solvent gave 1.6 g of a white crystalline solid, mp 108–110°. This material was spectroscopically identical with an authentic sample of 2-(2-chloroethylamino)-2-oxazoline hydrochloride.[29]

2-(1-Aziridinyl)-2-oxazoline–Sulfur Dioxide Complex (8).—Under anhydrous conditions, **4** (1.0 g) was added dropwise into 20 ml of liquid sulfur dioxide. An nmr spectrum of the pale yellow solution was scanned at a probe temperature of −30°, giving the chemical shifts indicated in Table I.

Reaction of 8 with Methanol → 13.—The above solution was added to 35 ml of anhydrous methanol and allowed to stand overnight at room temperature. The excess methanol was removed *in vacuo* to give a somewhat viscous liquid residue. Nmr analysis of the residue revealed complete loss of the aziridine proton signal and the appearance of a new singlet at −3.17 ppm (d_6-DMSO) characteristic of CH_3O groups. The nmr spectrum was essentially identical with a sample of 2-(2-methoxyethylamino)-2-oxazoline prepared by the reaction of 1,3-bis(2-chloroethyl)urea with an equivalent amount of sodium methoxide in methanol.

Reaction of 8 with Hydrogen Chloride → 7 + 14.—Dry hydrogen chloride was bubbled into a solution of **8** in liquid sulfur dioxide. An equal volume of chloroform was added and the sample was allowed to stand overnight at room temperature. The solvent was removed *in vacuo* to give a solid residue. This residue was identified as a mixture of **7** and **14** by nmr and ir analysis, using authentic samples for the comparison. Authentic **14** was prepared according to the method of Bestian.[3]

2-(1-Aziridinyl)-2-oxazolinium Hexafluoroantimonate (9).—A solution of $HSbF_6$ was prepared by bubbling a stoichiometric amount of HCl gas into a solution of $AgSbF_6$ (1.72 g) in approximately 40 ml of liquid sulfur dioxide.[30] After silver chloride was removed 2-(1-aziridinyl)-2-oxazoline (0.56 g) was added while stirring (*ca.* −30°). A sample of this solution was scanned at −30° giving the chemical shifts listed in Table I.[31]

2-(1-Aziridinyl)-3-methyl-2-oxazolinium Tetrafluoroborate (10).—All operations were conducted in a N_2-filled drybox. To a stirred solution of trimethyloxonium tetrafluoroborate[32] (1.48 g, 0.01 mol) in 10 ml of SO_2 was added dropwise a homogeneous solution of 1.12 g (0.01 mol) of 2-(1-aziridinyl)-2-oxazoline in 5 ml of liquid SO_2. The resultant yellow solution was allowed to stand at −78° for 2 hr and at −20° for an additional 8 hr. An nmr spectrum of this solution with 1 drop of TMS added, was obtained and is described in the discussion section. One-half the remaining solution was evaporated to a small volume, 10 ml of dry CH_2Cl_2 was added, and a small amount (~20 mg) of trimethyloxonium tetrafluoroborate was obtained. The CH_2Cl_2 solution was diluted with dry Et_2O causing an oil to separate. Upon storage at −20° overnight the oil crystallized. The faintly yellow crystals were collected by suction filtration (0.73 g, 68%) and an nmr spectrum (SO_2) of it was essentially identical with that of the original SO_2 solution. The extremely hygroscopic nature of the solid, mp 34.1–37°, made reliable elemental analysis impractical.

(27) J. H. Saunders and R. J. Slocombe, *Chem. Rev.*, **43**, 211 (1948).
(28) R. Adams, *Org. Reactions*, **3**, 108 (1946).
(29) M. E. Kreling and A. F. McKay, *Can. J. Chem.*, **37**, 504 (1959).
(30) G. A. Olah, S. J. Kuhn, W. S. Tolgyesi, and E. B. Baker, *J. Amer. Chem. Soc.*, **84**, 2733 (1962).
(31) Tetramethylammonium tetrafluoroborate was used as the internal standard and related to TMS. It was found to give a singlet at −3.24 ppm relative to TMS.
(32) H. Meerwein, *Org. Syn.*, **46**, 120 (1966).

3-Acetyl-2-[(2-chloroethyl)imino]oxazolidine (17).—A solution of acetyl chloride (0.8 g, 0.01 mol) in 15 ml of chloroform was added dropwise over a period of 15 min to a solution of 2-(1-aziridinyl)-2-oxazoline (1.12 g, 0.01 mol) in 20 ml of chloroform. The reaction mixture was refluxed for 0.5 hr, followed by removal of the solvent *in vacuo* at room temperature to give 1.84 g of a pale yellow product. Attempts to use normal vacuum distillation techniques caused this material to polymerize to an orange-red polymer which was soluble in both chloroform and water. Flash distillation gave a colorless liquid, bp 120–125° (1.5 mm), $n^{25}D$ 1.5085. The nmr spectrum consisted of a singlet at −2.55, a slightly split singlet at −3.62, and an A_2B_2 pattern centered at −4.15 ppm ($CDCl_3$) in a ratio of 3:4:4. The ir spectrum displayed intense bands at 1722 and 1683 cm^{-1} (neat).

Anal. Calcd for $C_7H_{11}ClN_2O_2$: C, 44.10; H, 5.80; N, 14.7. Found: C, 44.30; H, 5.65; N, 14.7.

Reaction of 17 with Hydrogen Chloride.—Gaseous hydrogen chloride was bubbled into a solution containing 1 g of 17 in 40 ml of benzene. A white precipitate was formed and then subsequently dissolved to give a homogeneous reaction mixture. Evaporation of the solvent gave a white crystalline material, mp 53–55°. An admixture melting point of this material with authentic N-acetyl-1,3-bis(2-chloroethyl)urea was not depressed and the ir spectra for each of these materials were identical (see below).

N-Acetyl-1,3-bis(2-chloroethyl)urea.—1,3-Bis(2-chloroethyl)-urea (5 g, 0.03 mol) and pyridine (2.6 g, 0.032 mol) in 40 ml of anhydrous benzene was stirred while a solution of acetyl chloride (2.4 g, 0.03 mol) in 30 ml of benzene was added dropwise over a period of 15 min. The reaction mixture was refluxed for 3 hr and then filtered free of pyridinium hydrochloride. Concentration of the filtrate gave a white crystalline product weighing 5.9 g (90%), mp 53–55°. The nmr spectrum consisted of a multiplet at −4.24 to −3.59 and a singlet at −2.43 ppm ($CDCl_3$) in a ratio of 8:3. The ir spectrum contained a carbonyl absorption band at 1683 cm^{-1} (Fluorolube).

Reaction of 2-(1-Aziridinyl)-2-oxazoline with 2 Mol of Acetyl Bromide.—A 50-ml, three-necked, round-bottomed flask, equipped with a magnetic stirrer, an addition funnel, and a reflux condenser capped with a drying tube was charged with 1.12 g (0.01 mol) of 2-(1-aziridinyl)-2-oxazoline in 15 ml of dry CH_2Cl_2. To this was added, dropwise, with stirring 2.46 g (0.02 mol) of acetyl bromide in 15 ml of dry CH_2Cl_2 at a rate to maintain gentle reflux. Upon completion of the addition (~20 min) the clear colorless solution was heated under reflux for additional 1 hr and allowed to stand at room temperature overnight. The solvent was removed at reduced pressure to give a quantitative recovery of light yellow slightly viscous oil. The nmr spectrum ($CDCl_3$) was in agreement with the formulation of the compound as 1,3-bis(2-bromoethyl)-1,3-diacetylurea: −2.38 (s, 6), −3.54 (m, 4), −3.98 ppm (m, 4); ir (film) 1705 broad (C=O), no band near 950 cm^{-1} (oxazoline). Attempted distillation of the material at reduced pressure led to tar formation with no distillate obtained.

1,3-Bis(2-chloroethyl)dihydro-1H-1,3-diazepine-2,4,7(3H)-trione (18).—To a stirred solution of succinyl chloride (3.12 g, 0.02 mol) in 100 ml of benzene was added a solution of 2-(1-aziridinyl)-2-oxazoline (2.24 g, 0.02 mol) in 25 ml of benzene in a dropwise manner over a period of 2 hr. A slight exotherm was noted with a maximum temperature of 35°. This was accompanied by some solid precipitate. After the addition was complete, the reaction was refluxed for 3.5 hr. The homogeneous solution was concentrated to a volume of 10 ml. This residue crystallized to a white mass upon standing at room temperature. After recrystallization from absolute ethanol the white crystalline product weighed 4.2 g (78%) and melted at 82–83°. The nmr spectrum consisted of two triplets centered at −4.24 and a singlet at −2.97 ppm ($CDCl_3$) in a ratio of 1:1:1. The ir spectrum contained intense carbonyl bands at 1705 and 1667 cm^{-1} (Nujol mull). Mass spectrometry gave a parent ion peak of 266.02 (mol wt 267.11).

Anal. Calcd for $C_9H_{12}Cl_2N_2O_3$: C, 40.8; H, 4.33; N, 10.05. Found: C, 40.8; H, 4.61; N, 10.32.

Reaction of 4 with Oxalyl Chloride → 19.—A solution of 2-(1-aziridinyl)-2-oxazoline (1.12 g, 0.01 mol) in 25 ml of dry chloroform was added dropwise to a stirred solution of oxalyl chloride (1.27 g, 0.01 mol) in 25 ml of chloroform. The reaction mixture was refluxed for 1 hr and the solvent was removed *in vacuo* to yield 2.2 g (92%) of a cream-colored solid, mp 109–111°. Recrystallization from ethanol gave white needles melting at 112–113°. This material showed no depression in melting point when mixed with authentic 1,3-bis(2-chloroethyl)imidazolidine-2,4,5-trione. Similarly, reaction of 2-(1-aziridinyl)-2-oxazoline with oxalyl bromide under the same conditions gave a 97.2% recrystallized yield of the corresponding dibromo compound, mp 92.5–94.5° (from benzene–isopropyl alcohol). The nmr spectrum (acetone-d_6) consisted of a pair of multiplets at −3.69 and −4.10 ppm. The ir spectrum (Nujol mull) showed a broad carbonyl absorption at 1728 cm^{-1}.

1,3-Bis(2-chloroethyl)imidazolidine-2,4,5-trione (19).—1,3-Bis(2-chloroethyl)urea (5.55 g, 0.03 mol) in 50 ml of diethyl ether was stirred as oxalyl chloride (3.75 g, 0.03 mol) in 15 ml of ether was added dropwise. A vigorous reaction ensued and the reaction mixture was then refluxed for 30 min. During this time a white solid mass fell out of solution. The solid was filtered, washed with 2 × 10 ml of cold ether, and dried. The white, clingy product weighed 6.3 g (89%) and melted at 105–109°. Recrystallization from absolute ethanol gave white needles, mp 112–113°. The nmr consisted of an A_2M_2 pattern which was centered at −3.91 ppm ($CDCl_3$). The ir spectrum contained an intense carbonyl absorption at 1739 cm^{-1}.

Anal. Calcd for $C_7H_8Cl_2N_2O_3$: C, 35.15; H, 3.35; N, 11.71. Found: C, 35.10; H, 3.37; N, 11.60.

Preparation of 2,4-Bis-2-chloroethylbenzo-2,4-diazepine-1,3,5-trione.—Into a 250-ml, three-necked, round-bottomed flask, equipped with a reflux condenser, protected from atmospheric moisture by a calcium chloride tube, a 125-ml addition funnel, and thermometer, was placed 10.15 g (0.05 mol) of phthaloyl chloride in 50 ml of dry $CHCl_3$. To this magnetically stirred solution was added dropwise, at a rate to maintain the temperature between 40 and 50°, 5.61 g (0.05 mol) of 2-aziridinyl-2-oxazoline in an additional 50 ml of dry $CHCl_3$. Upon completion of the addition the solution was heated under reflux (~78°) for 1 hr. The $CHCl_3$ was removed at reduced pressure to give a viscous yellow liquid which was, with some difficulty, induced to crystallize (crude mp 75–79°), yield 14.98 g (95%). One recrystallization from hot isopropyl alcohol gave 9.01 g (57%) of fine, white needles, mp 87.5–89°. The nmr spectrum ($CDCl_3$) showed the typical A_2B_2 pattern for the group NCH_2CH_2Cl at −3.84 (4.12 H) and −4.46 (3.92 H) and a complex multiplet at −7.94 ppm (3.94 H) for the aromatic protons. The ir spectrum (CCl_4, CS_2) showed carbonyl bands at 1730 and 1680 (doublet), and aromatic absorptions at 1603 and 1596 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}N_2O_3Cl$: C, 49.54; H, 3.84; N, 8,89. Found: C, 49.4; H, 4.03; N, 8.89.

1,3,5-Tris(2-chloroethyl)-s-triazine-2,4,6-trione (23.)—A solution of 4 (2.24 g, 0.02 mol) in 40 ml of benzene was added dropwise to a stirred solution of phosgene (2.07 g, 0.02 mol) in 75 ml of benzene over a period of 0.5 hr. The reaction temperature was maintained at 0–10° during the addition; the mixture was then stirred at room temperature for 0.5 hr, followed by refluxing for 3 hr. After removal of the solvent by using vacuum at room temperature a somewhat viscous liquid residue was obtained which crystallized out of absolute ethanol giving 1.2 g (28%) of product. Several recrystallizations from diethyl ether gave a white crystalline material melting at 96–97°. The nmr spectrum contained two triplets centered at −4.27 and −3.73 ppm ($CDCl_3$) in a ratio of 1:1, whereas the ir spectrum displayed an intense carbonyl band at 1683 cm^{-1}. Mass spectroscopy confirmed this structure in that three chloride ion peaks were observed and a parent ion peak of 314.99 was obtained (mol wt 316.58).

Anal. Calcd for $C_9H_{12}Cl_3N_3O_3$: C, 34.2; H, 3.90; N, 13.3. Found: C, 34.4; H, 3.80; N, 13.1.

Reaction of 4 with Malonyl Chloride → 7.—A solution of the aziridine 4 (2.8 g, 0.025 mol) in 20 ml of anhydrous ether was added dropwise to a stirred solution of freshly distilled malonyl chloride (3.5 g, 0.025 mol) in 100 ml of ether. After reflux for 0.5 hr and filtration, a brilliant yellow powder (4.63 g) was obtained which melted over a range of 82–96°. Recrystallization of this material from a mixture of acetonitrile and ether gave a white crystalline product which exhibited a double melting point at 109–111° and 126–127°. This material was spectroscopically identical with 2(2-chloroethylamino)-2-oxazoline hydrochloride which had been prepared by an alternate method.[29]

1,1-Dimethyl-3-(2-chloroethyl)urea.—To a stirred solution of 26.89 g (0.25 mol) of dimethylcarbamoyl chloride in 100 ml of dry CH_2Cl_2 was added dropwise 10.77 g (0.25 mol) of aziridine in an additional 100 ml of dry CH_2Cl_2 with protection against moisture. The cloudy solution was heated under reflux for 1 hr and decanted from a small amount of resinous material. The solvent was evaporated at reduced pressure to give a quantitative recovery of yellow oil which slowly solidified to a yellow semisolid.

The nmr spectrum indicated it to be a 1:2 mixture of 2-dimethylamino-2-oxazolinium hydrochloride and the desired product: nmr ($CDCl_3$) −2.95 (s, 6), −3.62 (m, 4), −3.29 (s, 3), −4.08 (m, 1), −4.91 (m, 1). Since the materials are isomeric and both require 1 mol of base to generate 2-dimethylamino-2-oxazoline, the mixture was used without further purification in the next step.

2-Dimethylamino-2-oxazoline.—To 24.15 g (0.16 mol) of N,N-dimethyl-N′-(2-chloroethyl)urea dissolved in 50 ml of methanol was added, all at once, 160 ml of 1.000 *N* potassium methoxide in methanol. An immediate precipitate of potassium chloride was noted and the mixture was heated under reflux with magnetic stirring for 1.5 hr. The precipitated potassium chloride was removed by suction filtration. The methanol was removed from the filtrate at reduced pressure and 50 ml of CH_2Cl_2 was added to precipitate the remaining KCl, which was filtered off (total weight of KCl, 11.90 g; 99.8%). The CH_2Cl_2 solution was dried over $CaSO_4$ for 3 hr and filtered and the CH_2Cl_2 was removed at reduced pressure to give 18.13 g (99.4%) of crude product. Distillation at reduced pressure gave 10.42 g of colorless, mobile liquid, bp 96–98.5° (80 mm). The nmr spectrum contained a sharp singlet at −2.965 (6 H) and an A_2B_2 multiplet at −3.79 (2 H) and −4.315 ppm (2 H), in accord with the proposed structure. The ir spectrum (CCl_4, CS_2) showed 1670 (N=CO) and 936 cm^{-1}, characteristic of the oxazoline ring.

2-Dimethylamino-2-oxazolinium Tetrafluoroborate.—In a nitrogen-filled drybox 1.48 g (0.01 mol) of trimethyloxonium tetrafluoroborate was slurried in 20 ml of dry CH_2Cl_2. To this stirred slurry was added dropwise 1.14 g (0.01 mol) of 2-dimethylamino-2-oxazoline in 10 ml of dry CH_2Cl_2. The reaction mixture was stirred at room temperature for 1 hr. The CH_2Cl_2 solution was concentrated at reduced pressure to a small volume causing the formation of a white precipitate, which was collected by suction filtration to give 1.66 g (77%) of small white crystals: mp 168.5–169.5° dec; nmr (CD_3CN) −3.14 (s, 6), −3.25 (s, 3), −3.93 (m, 2), −4.63 (m, 2); ir (Nujol mull) 1700 (broad, NC^+O) and 1170 cm^{-1} (very broad, BF_4^-).

Registry No.—**4**, 19587-77-0; **5**, 7259-82-7; **6**, 19587-79-2; **8**, 19587-80-5; **9**, 19598-91-5; **10**, 12344-31-9; **17**, 19587-81-6; **18**, 19587-82-7; **19**, 19587-83-8; **23**, 6299-37-2; 1,3-bis(2-bromoethyl)imidazolidine-2,4,5-dione, 19587-84-9; N-acetyl-1,3-bis(2-chloroethyl)urea, 19587-85-0; 2,4-bis(2-chloroethyl)benzo-2,4-diazepine-1,3,5-trione, 19587-86-1; 2-dimethylamino-2-oxazoline, 19587-87-2; 2-dimethylamino-2-oxazolinium tetrafluoroborate, 19598-92-6.

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Base-Catalyzed Hydrogen–Deuterium Exchange in Some Pyridine N-Oxides. Chloro and N-Oxide Rate Factors and Mechanism[1,2]

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Rates of deuterium–hydrogen exchange for deuterated pyridine N-oxide (I) and 3-chloro- (II) and 3,5-dichloropyridine N-oxide (III) in CH_3ONa–CH_3OH were obtained by nmr methods. At 138° relative rates for I-4, I-3,5, and I-2,6 are 1.0, 10, and 1500, respectively. At 50° relative rates for II-4, I-2,6, II-6, III-4, II-2, and III-2,6 are 0.37, 1.0, 12.2, 1370, 1840, and 11800. Log rate factors (relative to benzene) at 50° for Cl and N-oxide groups are *o*-Cl = 3.27 ± 0.24; *p*-Cl = 0.95 ± 0.14; *o*-NO = 9.58, and *p*-NO = 5.88. The N-oxide group is one of the most strongly activating groups for carbanion formation yet reported; its effect appears to be largely inductive. Exchange proceeds by direct deprotonation to give carbanions.

Base-catalyzed hydrogen exchange reactions in aromatic carbocyclic systems have been studied in considerable detail[4] and continue to draw interest as the fine points of the reaction mechanism become clearer.[5,6] Considerable attention has recently been directed to exchange in heteroaromatic ring systems, particularly five-membered-ring systems forming ylidic intermediates.[7] Information relating to exchange at annular positions in the six-membered heterocycles is more sparse.[2,8,9]

An intriguing problem is posed by the mechanism of base-catalyzed hydrogen–deuterium exchange on six-membered heteroaromatic substrates since they readily add nucleophiles.[10] For such compounds hydrogen exchange could take place on the adduct which results from the addition of base to the ring (addition–deprotonation pathway) or it could result from attack of base directly on a ring hydrogen.

This paper is one of several reporting a systematic study of hydrogen–deuterium exchange in heteroaromatic systems. This study is an attempt to elucidate the effects of heteroatoms on the position and rate of exchange and on the mechanism. We report a kinetic study of sodium methoxide catalyzed H–D exchange of deuterated forms of pyridine N-oxide (I) and of 3-chloro-(II) and 3,5-dichloropyridine N-oxide (III) in methanol. Chlorine substituents were chosen since they activate aromatic rings for hydrogen exchange. Moreover, methoxide ion catalyzed hydrogen exchange

(1) This work was presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

(2) A preliminary account of this work has appeared: J. A. Zoltewicz and G. M. Kauffman, *Tetrahedron Lett.*, 337 (1967).

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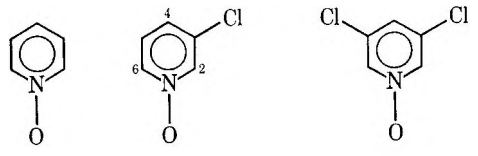

I II III

data are available for 1,3-dichlorobenzene-2-*d* (IV) in methanol;[11] this compound provides a convenient reference substrate for comparisons between the benzene and pyridine N-oxide ring systems.

Experimental Section

Pyridine-d_5 N-Oxide.—Pyridine N-oxide (15.4 g, 0.19 mol) was dissolved in 27 g (1.35 mol) of deuterium oxide and 3 g of sodium deuteroxide. The solution was heated in a Monel bomb at 180–210° for 3 hr. After extraction the product was dried by azeotropic distillation in benzene and crystallized from that solvent. The product is very hygroscopic and material used in the kinetic study was doubly sublimed and dried under vacuum over phosphorus pentoxide. The white crystals melted at 65–67° (lit.[12] mp 66–68°). Mass spectral analysis indicated an over-all deuterium content of 76%. The nmr spectrum of the product showed an area ratio of the 3,5 and 4 protons to the 2,6 protons of 1.59 (1.50 for equilibrium distribution).

3,5-Dichloropyridine N-Oxide.—A mixture of 13.2 g of 3,5-dichloropyridine and 13 ml of 40% peroxyacetic acid was allowed to stand at room temperature for 3 days. The solution then was heated at 70–80° for 3 hr with 10 ml of 30% hydrogen peroxide. Volatile materials were removed under reduced pressure and the solid residue was dissolved in 50 ml of chloroform. After drying overnight (K_2CO_3) and treatment with charcoal, the chloroform was removed to give 12.5 g (84.5% yield) of the white crystalline N-oxide, mp 109–111.5°. The analytical sample, mp 110–111.5°, was prepared by recrystallization from ether.

Anal. Calcd for $C_5H_3Cl_2NO$: C, 36.59; H, 1.83; N, 8.54. Found: C, 36.80; H, 1.91; N, 8.75.

3,5-Dichloropyridine-d_3 N-Oxide.—Deuteration of 3,5-dichloropyridine N-oxide was accomplished according to reported conditions.[2] The product contained 97% D at each position as indicated by mass spectrometry and by nmr analysis employing *t*-butyl alcohol standard. By combustion analysis the value is 95 ± 2% deuterium. Exchange rates at positions 2,6 and 4 were obtained using this substrate.

3-Chloropyridine-4-*d* N-Oxide.—3-Chloropyridine-4-d[9a] was oxidized with peroxyacetic acid according to the method in the literature.[13] Analysis of the N-oxide by nmr employing *t*-butyl alcohol as an internal reference standard indicated >95% deuteration. This substrate was employed to determine exchange rates at the 4 position of II.

3-Chloropyridine-2,6-d_2 N-oxide was prepared by deuteration of 3-chloropyridine N-oxide.[2] Analysis by nmr indicated 94% 2-D and 81% 6-D. Mass spectrometry indicated an average of 88% D for the two positions. This substrate was used in the determination of exchange rates at the 2 and 6 positions of II.

Rate Expression.—The exchange reaction may be symbolized

$$ArD_n + n\text{ROH} \underset{k_{-2}(\text{RO}^-)}{\overset{k_2(\text{RO}^-)}{\rightleftharpoons}} ArH_n + n\text{ROD}$$

where n is the number (1 or 2) of chemically equivalent exchanging positions. Experimentally, because the concentration of RO^- catalyst remains constant, the rate is pseudo first order within a given run. Since there is no important equilibrium isotope effect, it may be assumed that $k_2 = k_{-2}$, a = (substrate)$_0$, b = (ROH)$_0$, x = mole fraction of D in substrate, (ROD) = $(x_0 - x)an$, (ROH) = $b - (x_0 - x)an$. The rate of disappearance of deuterated substrate is

$$-\frac{dx}{dt} = \frac{k_2(\text{RO}^-)}{b}\{x[b - (x_0 - x)an] - (1 - x)(x_0 - x)an\} \quad (1)$$

At equilibrium, $x_e = anx_0/(an + b)$. Substituting and integrating gives

$$k_{exp}t = k_2(\text{RO}^-)t\left(\frac{an + b}{b}\right) = 2.303 \log \left(\frac{x_0 - x_e}{x - x_e}\right) \quad (2)$$

where

$$k_2 = \frac{k_{exp}}{(\text{RO}^-)}\left(\frac{b}{an + b}\right) \quad (3)$$

In our studies the fraction $b/(an + b)$ generally exceeded 0.9, even in cases where several centers in substrate were involved in exchange. Consequently this fraction was assumed to equal one.

In using nmr spectra to follow exchange, the ratio of the area of the nmr signal of the proton of interest, A, to the area of reference standard proton, A_{std}, was determined. The actual

$$k_{exp}t = 2.303 \log \frac{(A/A_{std})_e - (A/A_{std})_0}{(A/A_{std})_e - (A/A_{std})} \quad (4)$$

equation employed to obtain rate constants was eq 4. Note that the nmr ratios are directly proportional to the mole fraction of hydrogen at each reactive position. Hence, rate constants for substrates having two chemically equivalent positions, the 2,6 positions of I, for example, represent values for exchange at just a single position.

Reagents.—*t*-Butyl alcohol was distilled from potassium *t*-butoxide and stored under dry nitrogen. Methanol was dried by distillation from magnesium methoxide. Sodium methoxide stock solutions were prepared by dissolving freshly cut sodium in dry methanol in a dry nitrogen atmosphere. The solutions were standardized by adding an aliquot to excess standard hydrochloric acid and titrating potentiometrically with standard sodium hydroxide. Stock solutions of deuterated pyridine N-oxides were prepared by weighing a sample of the N-oxide and an equivalent amount of a proton reference compound, *t*-butyl alcohol or *p*-xylene, into a volumetric flask and filling to the mark with dry methanol. All transfers of the N-oxide were done in a dry nitrogen atmosphere. The solutions were protected from the air by serum stoppers and all transfers were made by syringe.

Kinetic Procedure. Pyridine-d_5 N-Oxide.—The reaction solution for a typical run was prepared by syringing aliquots of sodium methoxide and the N-oxide stock solution containing the reference compound into a 1-ml volumetric flask and filling with dry methanol. N-Oxide concentration was generally 0.5–0.8 *M* after mixing. One aliquot of this solution was placed in a nitrogen-filled nmr tube which was then sealed. Another aliquot of the reaction solution was titrated. The reaction was initiated by immersing the nmr tube in a constant-temperature bath and the nmr spectrum of the quenched mixture was obtained on a Varian A-60A spectrometer and integrated. At the conclusion of exchange at the 2,6 positions the nmr tube was placed in a higher temperature bath and exchange at the 3,5 and 4 positions followed.

The ratio of the areas of the nmr peaks of the reacting site and of the reference compound provides a measure of the extent of reaction. The ratios used were based on the average of five or more integration sweeps, caution being taken to avoid saturation effects. The butyl protons of *t*-butyl alcohol or the ring protons of *p*-xylene were used as references for exchange at the 2,6 position. The 2,6-H signal was used as the reference signal for exchange at the 3,5 and 4 positions.

Kinetic plots were constructed by plotting the log term in eq 4 against time. Pseudo-first-order rate constants, k_{exp}, were obtained from the slope of the best visual line through the points. This procedure is preferred to use of a least-squares treatment since scatter in the data is not completely random. The more or less constant integration error in the areas of the peaks becomes a large relative error late in the reaction. Good straight lines were generally obtained through two to three half-lives with some scatter toward the end of the reaction. The base concentrations shown are corrected for solution expansion by multiplying concentrations at room temperature by the ratio of the density of methanol[14] at the reaction temperature to that at room temperature. Results are given in Table I. The base concentration in runs 1–3, Table I, is varied by a factor of 10 and the rate constants show some variation as the concentration increases. It is not clear whether this is due to experimental error or whether this may be due to a salt effect.

We find no evidence for an equilibrium isotope effect. The

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TABLE I

RATES OF DEDEUTERATION OF PYRIDINE-d_5 N-OXIDE IN METHANOLIC SODIUM METHOXIDE

Run no.	Position of exchange	Temp,[a] °C	$(CH_3ONa)^b$	10^4k_{exp}, sec^{-1}	10^4k_2, M^{-1} sec^{-1}
1	2,6	75	0.46	4.33 ± 0.05	(9.50 ± 0.21)
2	2,6	75	0.046	0.195 ± 0.010	4.23 ± 0.25
3	2,6	75	0.094	0.500 ± 0.023	5.32 ± 0.27
4	2,6	100	0.045	3.77 ± 0.13	38.9 ± 5.0
5	2,6	100	0.045	3.57 ± 0.08	79.5 ± 5.3
6	2,6	117.2	0.021	6.48 ± 0.37	306 ± 24
7	2,6	117.2	0.021	6.48 ± 0.27	306 ± 21
8[c]	2,6	117.2	0.021	5.93 ± 0.25	280 ± 20
9[d]	2,6	117.2	0.021	5.57 ± 0.22	263 ± 18
10	3,5	110.5	0.43	0.432 ± 0.012	1.00 ± 0.05
11[e]	3,5	110.7	0.41	0.452 ± 0.007	1.11 ± 0.06
12	3,5	138	0.085	1.20 ± 0.02	14.2 ± 0.7
13	3,5	138	0.041	0.473 ± 0.013	11.5 ± 0.6
14	4	110.5	0.43	0.0400 ± 0.0017	0.095 ± 0.006
15[e]	4	110.7	0.41	0.0540 ± 0.0012	0.133 ± 0.008
16	4	138	0.085	0.120 ± 0.003	1.42 ± 0.07
17	4	138	0.041	0.0470 ± 0.0037	1.14 ± 0.11

[a] ±0.2°. [b] Corrected for solution expansion. [c] Contains added water: $(H_2O)/(\text{N-oxide}) = 0.6$. [d] Contains added water: $(H_2O)/\text{N-oxide} = 1.2$. [e] Acid quench method.

equlibrium distribution of deuterium in these reactions is, within experimental error, about ±5%, equal to the mole fraction of deuterium in the system. That this is also true in D_2O is indicated by the preparative deuteration of pyridine N-oxide.

In basic methanol solution the nmr signals of the 3,5 and 4 protons overlap but the exchange rates of the 3,5 and 4 protons differ by about a factor of 10 and it is possible to separate the rates of the two positions by a consideration of the exchange in the combined peak area. Kinetically the situation can be treated as parallel reactions producing a common product.[15]

A typical plot of one of the runs (run 12–16, Table I) is shown in Figure 1. The curved pseudo-first-order plot of the combined

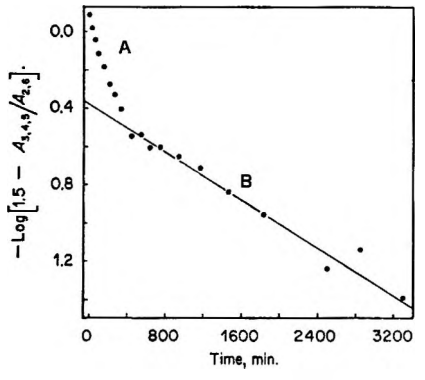


Figure 1—Typical kinetic run (run 12–16 in Table I) for hydrogen exchange at the 3,5 and 4 positions of pyridine-3,4,5-d_3 N-oxide with CH_3ONa in CH_3OH. Region A refers to dedeuteration at positions 3,5 and 4 while region B corresponds to dedeuteratation at position 4.

signal, log $[(A_{3,5+4}/A_{std})_e - (A_{3,5+4}/A_{std})]$, becomes linear after the more acidic 3,5 position has essentially completely reacted. The line for the slower 4 position can be drawn from the linear portion of the curve. This line is a plot of log $[(A_4/A_{std})_e - (A_4/A_{std})]$. Values of $(A_4/A_{std})_e - (A_4/A_{std})$ were then calculated for the first part of the reaction and were subtracted from the measured values of the composite function to give values of $(A_{3,5}/A_{std})_e - (A_{3,5}/A_{std})$. Logarithms of these values were then plotted to give the curve for 3,5 exchange shown in Figure 2.

The reference area used for these positions was the signal area of the 2,6 protons. This position is in isotopic equilibrium with the solvent under the conditions for exchange of the 3,5 and 4 positions. As a result, the area of the 2,6 protons is not precisely constant but decreases slightly due to back deuteration. The small change in the area of the 2,6-H signal, however, has only

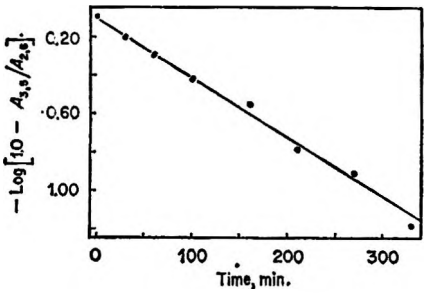


Figure 2.—A plot of dedeuteration at positions 3,5 of pyridine-3,4,5-d_3 N-oxide after correcting for exchange at position 4. Data are taken from region A in the kinetic plot in Figure 1.

a small effect on the slope of the line, at most, 2 or 3% and no attempt was made to correct for this small error.

As a check on this analysis of the kinetics of 3,5 and 4 exchange, a run (run 11–15, Table I) was made in which the two positions could be analyzed separately. Aliquots of the reaction solution were sealed in glass tubes and heated at the reaction temperature. Periodically, a tube was removed and quenched by cooling and the contents were acidified with perchloric acid. In acid solution the 3,5-H and 4-H signals in the nmr are resolved, so the areas of the peaks may be determined separately. (In acid solution the 4-H signal is at lower field than the 3,5-H signal.[16]) Acidification thus allowed separate determination of the rates at the two positions. Rate constants determined in this manner were in good agreement for the 3,5-H reaction and somewhat poorer agreement for the 4-H position.

Kinetic Procedure. Chloropyridine N-Oxides.—Kinetic runs were conducted using an nmr spectrometer equipped with a Varian V-6057 variable-temperature accessory. In most of the runs the probe itself was used as a constant-temperature device. The temperature scale of the probe was calibrated in the usual manner using the chemical shift of ethylene glycol as a function of temperature.[17]

In a typical run a dry nmr tube was filled with nitrogen and immersed in a Dry Ice–acetone bath. An aliquot of the N-oxide solution was syringed into the tube followed by an aliquot of sodium methoxide solution. N-Oxide concentration was 0.3–0.8 *M* after mixing. Just prior to insertion of the sealed tube into the probe the tube was warmed and the reactants were mixed. The tube was allowed to equilibrate 7–10 min in the probe after which the spectrum was obtained and integrated. Areas of the nmr signals employed in construction of the rate plots represent the average of several integration sweeps through the peaks. The time at the midpoint of the scanning interval was recorded

(15) A. A. Frost and R. G. Person, "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1961, p 162.

(16) R. A. Abramovitch and J. B. Davis, *J. Chem. Soc., B*, 1137 (1966).

(17) Varian Associates, Palo Alto, Calif., Publication No. 87-202-006, pp 1–7.

TABLE II

RATES OF DEDEUTERATION OF 3-CHLOROPYRIDINE-d_x N-OXIDE IN METHANOLIC SODIUM METHOXIDE

Run no.	Position of exchange	Temp, °C	$(CH_3ONa)^a$	10^4k_{exp}, sec^{-1}	10^4k_2, M^{-1} sec^{-1}
1	2	22	0.0427	1.33 ± 0.01	3.11 ± 0.15
2	2	22	0.111	3.48 ± 0.03	3.13 ± 0.16
3	2	22	0.111	4.22 ± 0.05	3.80 ± 0.20
4	2	35	0.0619	8.67 ± 0.11	14.0 ± 0.7
5	2	35	0.0810	12.7 ± 0.2	14.1 ± 0.7
6[b]	2	52.8	0.00959	4.38 ± 0.13	45.7 ± 2.7
7[b]	2	52.8	0.00959	5.45 ± 0.16	56.8 ± 3.3
8[c]	4	60	0.595	0.202 ± 0.018	0.0338 ± 0.0035
9[c]	4	60	0.441	0.135 ± 0.006	0.0307 ± 0.0021
10	4	70	0.839	0.697 ± 0.020	0.0830 ± 0.0048
11	4	70	0.839	0.705 ± 0.037	0.0840 ± 0.0060
12	4	80	0.620	1.92 ± 0.08	0.310 ± 0.020
13	4	80	0.620	1.83 ± 0.12	0.295 ± 0.024
14[c]	6	50	0.0747	0.183 ± 0.005	0.245 ± 0.014
15[c]	6	50	0.194	0.587 ± 0.042	0.302 ± 0.026
16	6	60	0.106	0.982 ± 0.029	0.927 ± 0.054
17	6	60	0.106	1.13 ± 0.04	1.06 ± 0.07
18	6	75	0.0598	2.35 ± 0.03	3.92 ± 0.20
19	6	75	0.0782	2.93 ± 0.10	3.75 ± 0.23

[a] Corrected for solution expansion. [b] Acid quench method. [c] External bath, thermal quench method.

as the time of reaction. Equilibrium values for the area ratios are experimental values except for those involving the 4 position of II. In these runs, since it was not practical to determine them experimentally, they were calculated assuming the absence of an equilibrium isotope effect. Runs in which equilibrium was attained showed, within experimental error (±5%), a statistical distribution of isotope between solvent and substrate.

After completing the reaction of the 2 position of II or the 2,6 position of III the same reaction solutions were used to study the 6 position of II and the 4 position of III, respectively. The 4,5-H signal of II was used as the reference standard for runs involving exchange at the 2 and 6 positions of this same molecule. For runs involving the 4 position of II, the combined areas of the 2 and 6 positions served as the standard. In the case of III added *t*-butyl alcohol served as the standard for exchange at all positions.

Pseudo-first-order rate constants were determined from the best visual line drawn through the data plotted according to eq 4. The data gave good straight lines for two to three half-lives in most cases. A typical plot is given in Figure 3. An exception

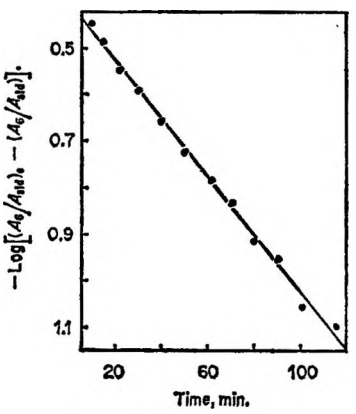


Figure 3.—A typical kinetic run (run 18 in Table II) for the dedeuteration of 3-chloropyridine-6-*d* N-oxide with CH_3ONa in CH_3OH. The variable-temperature nmr probe was employed to maintain a controlled temperature.

was exchange of the 4 position in II where methoxydechlorination was a competing reaction. Rate constants for exchange at this position are based on only the first half-life of the reaction. The reactions are first order in base as can be seen from runs 1–5 of Table II and runs 3, 5, and 6 of Table III. Rate constants were generally repeatable within about 10%. Temperatures in the nmr probe are resettable to ±2° and are constant only to ±1° under typical conditions.[17] This, no doubt, is responsible for much of the scatter in the rate constants and the uncertainties in the activation parameters.

Several runs were made in an external bath using either the thermal or acid quench techniques described for I. These are so indicated in the tables.

Errors.—The estimated errors in the rate constants were determined by standard methods.[18] Errors in k_{exp} estimated from the standard deviations of the nmr measurements were 2–3%. These are shown in Table I for exchange at the 2,6 position of I. Uncertainties estimated from the point scatter in the kinetic plots were in the range 2–5%. Since these are of the same order of magnitude the latter estimate is shown in the tables for all other runs.

Titration of the reaction mixtures after reaction sometimes showed base concentrations to be low by several per cent. The titrations are in themselves uncertain, however, owing to the small volumes of solution available and the low concentration of base. Only a single titration for each run was possible. There seemed to be no systematic loss of base. Some uncertainty in this quantity must also result from the approximate correction applied to the concentration for the expansion of the solution at the reaction temperatures. We estimate the over-all uncertainty in the base concentrations reported may be as much as 5%. Thus the second-order rate constants are probably uncertain in the range of 5–10%. Repeatability of the rate constants was generally within 10%.

Results

The N-oxide group strongly activates the aromatic ring hydrogen atoms for hydrogen–deuterium exchange. The reactivity order for dedeuteration in pyridine N-oxide is 2,6 ≫ 3,5 > 4; kinetic data are given in Table I. The 2,6 positions exchange readily at temperatures as low as 75°, while convenient dedeuteration rates for the 3,5 and 4 positions require temperatures well above 100°.

Evidence for the order in which the hydrogen or deuterium atoms at the several positions of II and III undergo exchange has been presented.[2] The order of decreasing ease of exchange is 2 > 6 > 4 > 5. Exchange at position 5 was not observed owing to the incursion of methoxydechlorination at higher reaction temperatures. The same reactivity order has been reported for exchange in 3-bromopyridine N-oxide in

(18) W. N. Bond, "Probability and Random Errors," E. Arnold and Co., London, 1935, p 91.

TABLE III
RATES OF DEDEUTERATION OF 3,5-DICHLOROPYRIDINE-d_3 N-OXIDE IN METHANOLIC SODIUM METHOXIDE

Run no.	Position of exchange	Temp, °C	$(CH_3ONa)^a$	10^4k_{exp}, sec^{-1}	10^4k_2, M^{-1} sec^{-1}
1	2,6	0	0.114	2.80 ± 0.13	2.45 ± 0.17
2	2,6	0	0.114	3.13 ± 0.03	2.75 ± 0.14
3	2,6	10	0.0221	1.52 ± 0.04	6.87 ± 0.39
4	2,6	10	0.113	5.12 ± 0.13	(4.52 ± 0.25)
5	2,6	10	0.0433	2.82 ± 0.07	6.50 ± 0.36
6	2,6	10	0.0637	4.30 ± 0.38	6.74 ± 0.68
7	2,6	22	0.0110	2.87 ± 0.08	26.0 ± 1.5
8[b]	2,6	30	0.0099	4.95 ± 0.22	50.0 ± 3.4
9[b]	2,6	30	0.0099	5.27 ± 0.17	53.1 ± 3.2
10	4	22	0.111	1.98 ± 0.07	1.79 ± 0.11
11	4	22	0.111	2.45 ± 0.12	2.21 ± 0.15
12	4	35	0.0421	3.60 ± 0.10	8.56 ± 0.50
13	4	35	0.0619	4.37 ± 0.15	7.05 ± 0.48
14	4	50	0.0106	3.48 ± 0.15	32.9 ± 0.22

[a] Corrected for solution expansion. [b] Acid quench method.

TABLE IV
RELATIVE RATES AND ACTIVATION PARAMETERS FOR DEUTERIUM–HYDROGEN EXCHANGE OF SOME PYRIDINE N-OXIDES IN METHANOLIC SODIUM METHOXIDE AT 50° [a]

Compd	Position of exchange	Relative rate	ΔH^*, kcal/mol	ΔS^*, eu
I	2,6	1.0	26.4 ± 1.1	+1.7 ± 2.6
I	3,5	(0.0067)[b]	(27.1 ± 1.3)[b]	(−6.7 ± 3.2)[b,c]
I	4	(0.00067)[b]	(26.1 ± 1.7)[b]	(−13.9 ± 4.5)[b,c]
II	2	1840	16.4 ± 1.4	−14.4 ± 2.8
II	4	0.37	25.5 ± 2.6	−2.9 ± 3.5
II	6	12.2	22.9 ± 2.0	−4.1 ± 3.1
III	2,6	11800	16.0 ± 0.7	−11.7 ± 1.3
III	4	1370	18.4 ± 1.8	−8.8 ± 2.4

[a] Parameters were determined by a least-squares treatment in which individual second-order rate constant were given equal weight. Rate constants in parentheses in Tables I and III were not included. H. D. Young, "Statistical Treatment of Experimental Data," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 115–123. [b] Approximate value, based upon only two temperatures. [c] At 110°.

NaOD–D_2O.[19] The order of exchange for III is 2,6 > 4.[20] The rate data for these compounds are presented in Tables II and III.

Rate constants for exchange at position 4 of II are approximate values because methoxydechlorination of II occurs under conditions required for exchange. Nucleophilic substitution of chloride by methoxide ion in II has been studied.[13] At 50° it is estimated that exchange occurs *ca.* seven to eight times faster than substitution (both rates extrapolated). The presence of chloride ion was easily detected in the reaction mixture by precipitation with silver ion. Titration of reaction mixtures indicated that about 9–12% loss of base and substrate had occurred at the end of one half-life of the exchange reaction. Exchange rate plots were linear over one half-life but showed curvature over longer periods. The reported pseudo-first-order rate constants are based on the initial, linear portion of the curve. The second-order rate constants were calculated using the initial base concentrations.

Substitution was not a serious side reaction for exchange at the 2 or 6 positions of II because of the generally lower temperatures and/or base concentrations. Only traces of chloride ion were detectable after exchange of III.

The effect of water on the exchange rates for pyridine-d_5 N-oxide was determined. Addition of 0.6 and 1.2 mol of water/mol of N-oxide (runs 8 and 9, Table I) reduced the reaction rate only slightly. The presence of trace amounts of water in other runs probably has no significant effect on the rate constants.

Rate constants were extrapolated to 50° using the Arrhenius equation. Relative rates using the exchange rate for the 2,6 positions of I as a standard as well as activation parameters are given in Table IV. It is evident that both ΔH^* and ΔS^* influence relative positional reactivities.

Rate Factors.—A quantitative measure of the ability of a Cl atom or an N–O group to activate the aromatic nucleus for base-catalyzed hydrogen exchange is obtained from a comparison of second-order rate constants according to the partial rate factor method. The following treatment assumes that the effect of Cl and N–O substituents on the energy of activation for hydrogen exchange are additive.[21] Using logarithmic symbolism the values in Table V may be written. *ortho* and *para* rate factors are symbolized by o_f and p_f, respectively; k_0 is the second-order rate constant for dedeuteration of benzene, the reference substrate. Included in this set is the rate constant (extrapolated) for methoxide ion catalyzed exchange of 1,3-dichlorobenzene-2-d[11] (IV). Inclusion of this value allows an estimate of the rate factor for the N–O group

(19) R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967).

(20) Although the order of decreasing ease of exchange in both II and III corresponds to decreasing chemical shift in the nmr spectra, relative chemical shifts are not good criteria for the relative rates of deprotonation. Thus for 3-chloropyridine the order of the chemical shift (increasing field) is 2-H, 6-H, 4-H, and 5-H, but it is 4-H which undergoes the most rapid base-catalyzed exchange.[9a]

(21) Pyridine N-oxide is considered to be a derivative of benzene in which an annular C–H is replaced by an annular N–O. The position of an N-oxide group relative to a C–D reaction center is indicated by *ortho*, *meta*, or *para* nomenclature.

TABLE V

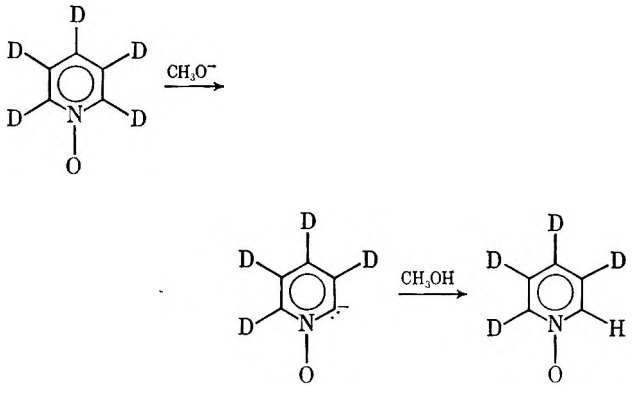
	Log k_2 (50° extrapolated)
Log $k_{2(\text{I-2,6})} = \log k_0 + o_f^{NO}$	−4.625
Log $k_{2(\text{II-2})} = \log k_0 + o_f^{NO} + o_f^{Cl}$	−1.355
Log $k_{2(\text{II-6})} = \log k_0 + o_f^{NO} + p_f^{Cl}$	−3.534
Log $k_{2(\text{II-4})} = \log k_0 + p_f^{NO} + o_f^{Cl}$	−5.052
Log $k_{2(\text{III-2,6})} = \log k_0 + o_f^{NO} + o_f^{Cl} + p^{Cl}$	−0.550
Log $k_{2(\text{III-4})} = \log k_0 + p_f^{NO} + 2o_f^{Cl}$	−1.483
Log $k_{2(\text{IV-2})} = \log k_0 + 2o_f^{Cl}$	−7.360

to be made. From these equations three independent values of the o_f^{Cl} [22] and two values of the p_f^{Cl} [23] may be obtained. The average log chloro factors with their standard deviations are $o_f^{Cl} = 3.27 \pm 0.24$; $p_f^{Cl} = 0.95 \pm 0.14$. The logarithmic value of the *para* N–O factor,[24] p_f^{NO}, is 5.88 and the *ortho* factor,[25] o_f^{NO}, is 9.58. The uncertainty in the N–O factors is almost certainly larger than that of the Cl factors, owing to the extensive extrapolations. The log k_0 value of −14.2 is in approximate agreement with an earlier derived value of −16.8 (40°).[6]

Discussion

Mechanism.—Several types of deprotonation mechanisms need to be considered to account for hydrogen exchange in pyridine N-oxides. The first type has been found to be the effective mechanism in the vast majority of base-catalyzed exchange reactions in carbocyclic aromatic systems.[4] This pathway involves proton abstraction by base to give an intermediate carbanion. Scheme I illustrates this mechanism for pyridine-d_5 N-oxide.

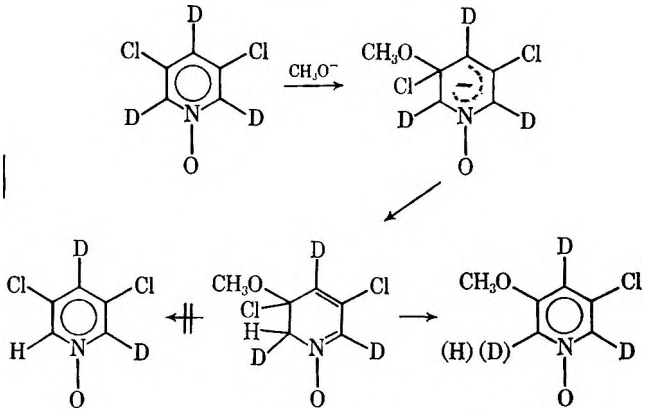
SCHEME I



The positional order of exchange and the relative rates give strong indication that the exchange observed for N-oxides does involve proton abstraction by methoxide ion to give an intermediate carbanion. The N-oxide reactivity pattern resembles closely those found in many carbocyclic systems for base-catalyzed hydrogen exchange.[4] More importantly, the relative rates of dedeuteration of I parallel those for the decarboxylation of the isomeric N-methylpyridinium carboxylate betaines.[26,27] Relative rates of decarboxylation of these betaines at 196° at positions 2, 3, and 4 are 1600, 2.8, and 1, respectively. These decarboxylation reactions presumably involve the intermediate formation of carbanions. Relative rates for the dedeuteration of I at 138° are 2:3:4 = 1500:10:1. While the close numerical correspondence of the positional reactivities of this reaction with our data is probably coincidental, the formation of similar intermediates would be expected to take place with similar reactivity patterns.

It is necessary to consider a second type of mechanism for exchange. Since pyridine N-oxides readily add nucleophiles, hydrogen exchange could take place on the anionic adduct formed by the addition of methoxide ion to carbon. This mechanism is indicated for 3,5-dichloropyridine-d_3 N-oxide in Scheme II. This

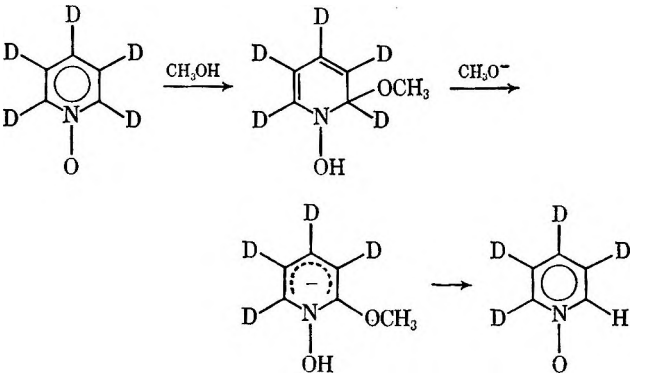
SCHEME II



pathway is easily ruled out by the fact that of the two groups in the adduct, chlorine and methoxyl, chlorine is by far the better leaving group. The adduct would give substitution products rather than dichloro compound with reduced deuterium content. Since exchange occurs with negligible substitution, this kind of mechanism is clearly ruled out.

Still another addition mechanism for exchange involves reversible addition of solvent to N-oxide to give a dihydro type of intermediate prior to the formation of a delocalized carbanion (Scheme III). Precedent for

SCHEME III



this type of pathway is found in the reaction of the 4-cyano adduct of the nicotinamide group of nicotinamide–adenine dinucleotide. Base-catalyzed exchange of this dihydropyridine derivative takes place only at

(22) III-4 *vs.* II-4, III-2,6 *vs.* II-6, and II-2 *vs.* I-2,6.
(23) III-2,6 *vs.* II-2 and II-6 *vs.* I-2,6.
(24) III-4 *vs.* IV-2.
(25) Obtained from the *para* N–O factor and the log *ortho/para* ratio of 3.70 (II-2 *vs.* II-4). This value of the log *ortho/para* ratio may be compared with that (3.19) obtained at 138° by direct comparison of the I-2,6 and I-4 rates. The later value at the higher temperature is smaller as expected.
(26) P. Haake and J. Mantecon, *J. Amer. Chem. Soc.*, **86**, 5230 (1964).
(27) J. A. Zoltewicz, G. M. Kauffman, and C. L. Smith, *ibid.*, **90**, 5939 (1968).

the 4 position.[28] Little is known about the characteristics of such a mechanism. It would be highly coincidental that such a pathway would give rise to a positional reactivity pattern which is an imitation of that for direct deprotonation.

In light of the proposed mechanism involving carbanion formation by direct deprotonation the positional reactivity pattern indicates that the primary mode of activation by the N-oxide group is inductive. Typically, inductive effects fall off rapidly as the distance between the activating group and the reaction site is increased.

Dipole moment,[29] infrared,[30] and nmr[16] studies indicate the presence of a resonance effect in the ground states of N-oxides. However, the donation of electrons into the ring by the oxygen of the N-oxide group must have only a minor influence on exchange reactivities. The relative rates of exchange of I and of decarboxylation of N-methylpyridinium carboxylates are proportional on a logarithmic scale. These carboxylates do not contain oxygen capable of donating electrons into the ring. The minor importance of electron donation by oxygen in the exchange reactions is understandable. The orbitals of the generated carbanions are orthogonal to the orbitals of the π system and interaction between them is at a minimum.

Rate Factors.—Our determination of partial rate factors for substituents assumes that the same reaction mechanism is followed by all the reactions considered here and that the effects of the several substituents on the reaction site are additive. The general agreement of the rate factors determined from different compounds having a rate spread of about 10^4 (50°) supports these assumptions.

The magnitudes of the *ortho* and *para* N-oxide log rate factors, 9.58 and 5.88, respectively, are to be compared with those for fluorine, 5.25 and 1.13,[6] respectively. Fluorine is known to exert one of the most powerful acidifying effects on aryl hydrogens.[4] Clearly the effect of the highly polar N-oxide group is considerably greater.

The mechanism for the hydrogen exchange reactions may be written so the rate of collapse to starting ma-

$$\text{C–D} + \text{CH}_3\text{O}^- \rightleftharpoons \underset{\text{A}}{\text{C}^-\cdots\text{DOCH}_3} \xrightarrow{\text{HOCH}_3}$$

$$\underset{\text{B}}{\text{C}^-\cdots\text{HOCH}_3} \longrightarrow \text{exchange}$$

terials of the hydrogen-bonded anion, A, may successfully compete with the rate of replacement of one hydrogen bond for another to give B. When this occurs the observed rates include contributions from these steps in addition to the initial step giving A. We expect this mechanism, internal return, to be important in the exchange reactions reported here. Delocalized anions are not formed and the acidity of the annular positions is considerably less than that of the solvent.[31] The observed ΔS^* values are in keeping with this suggestion. According to the internal return mechanism ΔS^* is a composite of the entropy changes of the several steps and the observed values may be less negative than those for normal second-order reactions.[6] Our ΔS^* values, Table IV, include positive and negative values and range over 16 eu.

In summary, pyridine N-oxides undergo hydrogen exchange by simple deprotonation reactions. Positional reactivity is determined primarily by the activating effect of the N-oxide group and secondarily by chlorine substituents. Entropies of activation suggest that a more detailed description of the exchange mechanism must include internal return.

Registry No.—I-d_5, 19639-76-0; II-4-d, 19639-77-1; II-2,6-d_2, 19639-78-2; III, 15177-57-8; III-d_3, 19639-80-6.

Acknowledgment.—We are pleased to acknowledge helpful discussions with Professor Gardiner Myers.

(28) A. San Pietro, *J. Biol. Chem.*, **217**, 579 (1955).
(29) A. R. Katritzky, E. W. Randall, and L. E. Sutton, *J. Chem. Soc.*, 1769 (1957).
(30) A. R. Katritzky, A. M. Monro, J. A. T. Beard, D. P. Dearnaley, and N. J. Earl, *ibid.*, 2182 (1958).
(31) M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964).

Cyanation and Hydrocyanation of Unsaturated Hydrocarbons. II. Oxidation and Reduction of the Intermediate[1,2]

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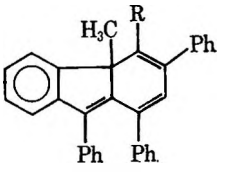
The cyanation of the heavily arylated hydrocarbon 4a-methyl-1,3,9-triphenyl-4aH-fluorene (Ia) proceeds almost quantitatively when solutions prepared from the hydrocarbon and sodium cyanide in aprotic solvents are treated with certain oxidizing agents. Of a number of oxidants studied, chromium trioxide, lead dioxide, and sodium 9,10-anthraquinone-1-sulfonate are most effective, and the last is the most conveniently used. Certain dibenzofulvenes, namely 9-benzylidenefluorene (IIa), 9-(*p*-bromobenzylidene)fluorene (IIc), and 9-ethylidenefluorene (IIe), are cyanated when treated with the same combinations of reagents, and the yields, especially from the arylidene compounds, are high. The roles in the cyanation process of the carbanions formed by addition of cyanide ion to the unsaturated systems, of radicals formed from such carbanions by electron exchange, and of hydrocyanation products formed by protonation of the carbanions are discussed.

The facile reaction of cyanide ion with 4a-methyl-1,3,9-triphenyl-4aH-fluorene (Ia) is attributed to the presence in this hydrocarbon of an extended, conjugated π-bond system, which stabilizes the incipient carbanion through resonance.[2a] This structural feature, as well

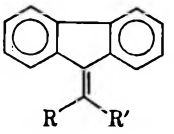
(1) Grateful acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the U. S. Army Research Office [Grants PRF-2042-A1 and DA-ARO(D)-G679 and G857] for the partial support of this work.

(2) For previous related papers, see (a) B. E. Galbraith and H. R. Snyder, *J. Org. Chem.*, **32**, 380 (1967), and (b) R. G. Landolt and H. R. Snyder, *ibid.*, **33**, 403 (1968).

as a polarized double bond, is also inherent in the nitro[2b,3] and cyano[4] derivatives of some aromatic systems, which readily undergo attack by cyanide ion, and in the dibenzofulvene compounds which we now discuss.

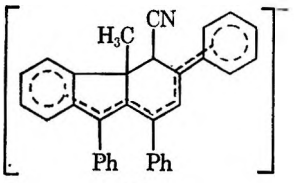


Ia, R = H
b, R = CN

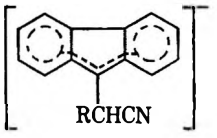


IIa, R = Ph; R′ = H
b, R = Ph; R′ = CN
c, R = *p*-C_6H_4Br; R′ = H
d, R = *p*-C_6H_4Br; R′ = CN
e, R = CH_3; R′ = H
f, R = CH_3; R′ = CN

Intensely dark, almost black solutions are produced upon mixing 9-benzylidenefluorene (IIa), 9-(*p*-bromobenzylidene)fluorene (IIc), and 9-ethylidenefluorene (IIe) with sodium cyanide in dipolar aprotic solvents under nitrogen at room temperature. As in the reaction of cyanide ion with hydrocarbon Ia, in which the carbanion III is formed, the generation of color in these reactions is considered due, at least in part, to the initial formation of carbanion species (IVa–c), for dibenzofulvenes have long been known to be susceptible to nucleophilic attack at the 10 position.[5] However, the

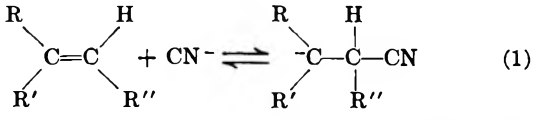


III



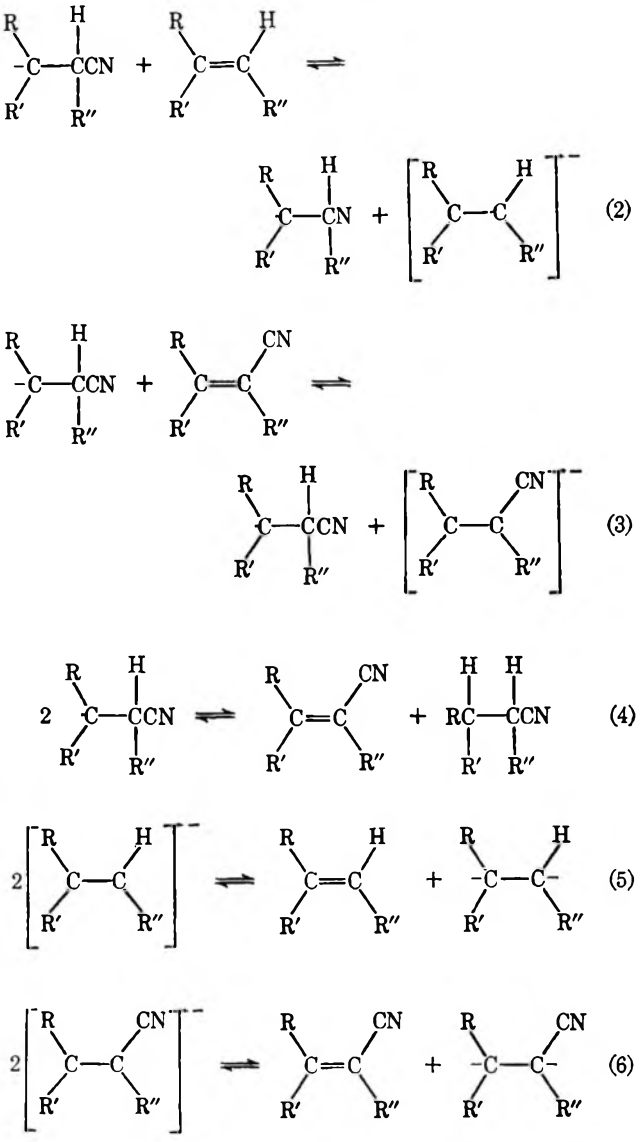
IVa, R = Ph
b, R = *p*-C_6H_4Br
c, R = CH_3

departure from the usual red color associated with the fluorenyl anion[6,7] and the detection of epr signals[8] in the solutions suggest the coexistence of radical species. Russell and coworkers[9] have recently cited numerous examples of electron-transfer reactions in which a carbanion spontaneously loses an electron to a molecule of the parent compound, and the electron-accepting ability of phenyl-substituted dibenzofulvenes is known to be very good.[10] Carbanion formation (reaction 1) in



(1)

these cyanide–hydrocarbon mixtures will therefore likely be accompanied by electron-transfer reactions 2 and 3 between the carbanion and the hydrocarbon, or its cyanation derivative, as well as disproportionation

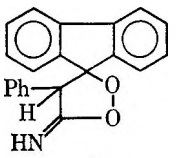


(2) (3) (4) (5) (6)

reactions 4, 5, and 6 of the resulting radical and anion radicals.

Cyanation of the hydrocarbons is achieved if the colored cyanide–hydrocarbon mixtures are treated with oxygen or air, but, although in the case of hydrocarbon Ia a 63% yield of cyanation product Ib is obtained,[2a] molecular oxygen is considerably less effective in the cyanation of dibenzofulvene IIa. When hydrocarbon IIa was treated with sodium cyanide, in dimethylformamide (DMF) or dimethyl sulfoxide (DMSO), in the presence of air, the cyanation product, 9-(α-cyanobenzylidene)fluorene (IIb), was isolated in only 28% yield. Similar reactions run under nitrogen and later exposed to air or oxygen yielded fluorenone and a colorless, high-melting compound of possible structure V.[11a] Apparently with this compound oxygenation of the intermediate occurs at the expense of hydrogen removal. The decomposition of unstable hydroperoxide anions, formed by reaction of carbanions with molecular oxygen, is well established,[11b] and the formation of fluorenone is yet another example in which such decomposition is accompanied by carbon–carbon bond scission.

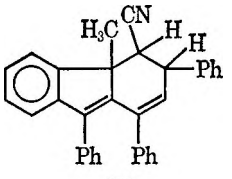
(3) R. F. Aycock, unpublished work; B. Vickery, *Chem. Ind.* (London), 1523 (1967).
(4) K. E. Whitaker, unpublished work.
(5) E. D. Bergmann in "Progress in Organic Chemistry," Vol. 3, J. W. Cook, Ed., Academic Press, New York, N. Y., 1955, p 81.
(6) D. Lavie and E. D. Bergmann, *Bull. Soc. Chim. Fr.*, **18**, 250 (1951).
(7) D. J. Cram and D. R. Wilson, *J. Amer. Chem. Soc.*, **85**, 1249 (1963).
(8) R. G. Landolt, private communication.
(9) G. A. Russell and W. C. Danen, *J. Amer. Chem. Soc.*, **90**, 347 (1968), and previous papers here mentioned.
(10) S. Wawzonek and J. W. Fan, *ibid.*, **68**, 2541 (1946).
(11) (a) Structure V for compound $C_{21}H_{13}NO_2$ was suggested by a referee; it is in agreement with the analytical and spectral data. (b) G. A. Russell, E. G. Janzen, A. G. Bemis, E. J. Geels, A. J. Moye, S. Mak, and E. T. Strom, Advances in Chemistry Series, No. 51, American Chemical Society, Washington, D. C., 1965, p 112.



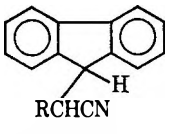
V

The facile cyanation of hydrocarbons in high yield has potential synthetic importance; so alternative oxidizing agents were investigated. Certain properties were considered necessary prerequisites for an efficient oxidizing agent. (1) It should have high solubility in the aprotic solvents. (2) Either it should be inert to attack by cyanide ion, or it should oxidize the reaction intermediate at a much faster rate than it reacts with cyanide ion. (3) It should not degrade the hydrocarbon. (4) The unreacted oxidizing agent, together with its reduced form, should be easily separated, preferably by physical means, from the anticipated cyanation product. (5) It should be readily available. Table I contains the product distributions from reactions of hydrocarbons Ia and IIa with sodium cyanide in the presence of various oxidizing agents.

The observed nonspecificity of the kind of oxidizing agent employed is understandable, for, in forming the unsaturated nitrile (cyanation product), the oxidizing agent may directly remove a hydride ion from the carbanion generated in reaction A, or it may accept an electron to give a radical, which then disproportionates (reaction 4) or undergoes further oxidation with loss of a hydrogen atom. Except in those cyanation reactions where very prolonged reaction times were employed, or the action of the oxidizing agent was very fast, hydrocyanation products were isolated. The presence of



VI



VIIa, R = Ph
b, R = *p*-C_6H_4Br
c, R = CH_3

these compounds can be attributed to reactions 4 and 6, as well as to possible protonation of the carbanion during the oxidation, by traces of moisture present. With a fast oxidizing agent, oxidation of the carbanion is completed before any protonation or electron-exchange can occur; and, in the case of a prolonged reaction time, the hydrocyanation product, when formed, is apparently sufficiently acidic to be eventually completely oxidized, in the presence of cyanide ion, to the cyanation product. It has already been shown[2a] that compound VI is oxidized by oxygen to compound Ib, in the presence of sodium cyanide; and, in the present work, this oxidation was accomplished in 87% yield when compound VI was treated, under nitrogen, with sodium anthraquinone-1-sulfonate. In a similar experiment in which nitrile VIIa was the substrate, only a 24% conversion into the unsaturated nitrile (IIb) was achieved. Removal of a proton from this compound by cyanide ion is evidently more difficult, and this would explain why in many cases the over-all yield of cyanation product from 9-benzylidenefluorene (IIa) was inferior to that from the arylated triene (Ia).

Oxidations with chromium trioxide were exceedingly efficient, and the absence of any hydrocyanation product indicates a very rapid oxidation of the carbanion, for under similar conditions chromium trioxide failed to oxidize the hydrocyanation derivative VI, even in the presence of sodium cyanide. The rate of reaction of the hydrocarbon with cyanide ion evidently is slower than the rate of oxidation of cyanide ion by chromium trioxide, since, in an experiment in which sodium cyanide was added to a solution of hydrocarbon IIa and chromium trioxide, no cyanation took place and a complete recovery of the hydrocarbon was realized. Hexamethylphosphoramide (HMP) was chosen as the solvent for this oxidizing agent, as DMF and DMSO violently inflamed when they were dropped onto chromium trioxide. The high solubility of chromium trioxide in the reaction mixture is no doubt partially responsible for its swift oxidizing action. Potassium ferricyanide, potassium iodate, manganese dioxide, and lead dioxide are barely soluble in DMF and DMSO and they necessitate a long reaction time before the characteristic intense color of the mixtures fades. However, the yields from some of these oxidations were very good. The addition of water, to enhance the solubility of potassium ferricyanide in DMF, resulted in very little cyanation (<2%) of hydrocarbon Ia, probably because of the hydrolysis of the sodium cyanide, for hydrocarbon Ia has been shown to be unreactive to hydrogen cyanide.[2a] The failure of the ceric salts, N-bromosuccinimide, crystal violet, and Fremy's salt to oxidize effectively the cyanide–hydrocarbon mixtures is attributed to the competing reaction of these reagents with sodium cyanide, whereby the process of carbanion formation is reversed (condition 2). Triphenylformazan contaminated the products when triphenyltetrazolium chloride was used to oxidize the cyanide–hydrocarbon mixtures.

Quinones constitute the most powerful and versatile organic oxidizing agents, being both electron acceptors and hydride ion abstractors. Although their ability to dehydrogenate organic compounds *via* a hydride ion removal mechanism has been well established,[12] no work has dealt with the use of quinones for removing a hydride ion from a preformed carbanion.[13] The cyanation reactions with the high-potential quinones, chloranil and DDQ, were only moderately successful, because of their side reactions with sodium cyanide. In order to have the quinone nucleus blocked against cyanide attack, anthraquinone was used, and the commencement of the oxidations was readily apparent by the rapid development of the magenta color, characteristic of the anthraquinone dianion.[14] Anthraquinone, however, is not very soluble in either DMF or DMSO; and its use also gave rise to the problem of separating it from the products of the reaction, since the sodium salt of the anthraquinone dianion is oxidized back to anthraquinone[14] immediately as the reaction mixture is exposed to air on work-up. As an example of a quinone-type oxidizing agent soluble in the aprotic solvents used and relatively free from cyanide ion attack, sodium anthraquinone-1-sulfonate was chosen. It gave very clean

(12) L. M. Jackmann, *Advan. Org. Chem.*, **2**, 329 (1960).

(13) Jackmann[12] has commented on the possibility of using quinones for this purpose.

(14) L. F. Fieser and M. Fieser, "Organic Chemistry," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1956, p 766.

TABLE I

CYANATION REACTIONS OF 4a-METHYL-1,3,9-TRIPHENYL-4aH-FLUORENE (Ia) AND 9-BENZYLIDENEFLUORENE (IIa)

				Hydrocarbon Ia			Hydrocarbon IIa		
Oxidizing agent	Solvent	Temp, °C	Reaction time,[a] hr	Unchanged hydrocarbon, %	Cyanation product Ib, %	Hydrocyanation product V, %	Unchanged hydrocarbon, %	Cyanation product IIb, %	Hydrocyanation product VIa, %
Potassium ferricyanide	DMSO	R.t.[b]	24	0	67	0[c]	0	39	9[d]
Potassium iodate	DMF	R.t.	70	0	80	0[c]	0	36	0[d]
Potassium metaperiodate	DMSO	R.t.	2	21	48	0[c,e]			
Manganese dioxide	DMF	R.t.	46	0	53	0[f]			
Lead dioxide	DMF	R.t.	20	0	87	0[c]	0	79	0[c,g]
Chromium trioxide	HMP	R.t.	0.5	0	87	0[c]	0	88	0[c]
Ceric sulfate	DMSO	R.t.	12	0	16	44[h]			
Ceric ammonium nitrate	DMF	R.t.	12	98	0	0[d,e]			
N-Bromosuccinimide	DMF	R.t.	1.5	61	9	5[i]			
2,3,5-Triphenyltetrazolium chloride	DMF	R.t.	1	*j*	48	0[d]			
2,3,5-Triphenyltetrazolium chloride	DMF	R.t.	5	*j*	74	0[d]			
Tetrachloro-1,4-benzoquinone (chloranil)	DMF	R.t.	2	15	51	14[d,e]	24	25	16[c,e,k]
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)	DMF	R.t.	0.5	29	30	23[d,e]			
9,10-Anthraquinone	DMF	R.t.	5	5	53[d]	*l*	10	38[d]	*l*
Sodium 9,10-anthraquinone-2-sulfonate	DMF	R.t.	10	0	60	23[d]	0	48	21[d]
Sodium 9,10-anthraquinone-1-sulfonate	DMF	R.t.	10	0	69	18[d]			
Sodium 9,10-anthraquinone-1-sulfonate	DMSO	R.t.	10	0	80	1[d]	0	54	18[d,g]
Sodium 9,10-anthraquinone-1-sulfonate	DMSO	50	4	0	92	0[g,i]	0	64	14[g,i]
Sodium 9,10-anthraquinone-1-sulfonate	DMSO	50	6				0	68	11[g,i]
Sodium 9,10-anthraquinone-1-sulfonate	DMSO	50	12				0	72	7[g,i]
Sodium 9,10-anthraquinone-1,5-disulfonate	DMSO	R.t.	10	6	51	12[d]	0		
9,10-Phenanthraquinone	DMF	R.t.	5	0	90	0[d]	22	56	0[g,i]
Potassium nitrosodisulfonate (Fremy's salt)	DMF	R.t.	4	24	12	39[c]			
Crystal violet	DMF	R.t.	2.5	37	12	18[c,e]			

[a] Measured from the time the hydrocarbon, sodium cyanide, and oxidizing agent are all present together. [b] Room temperature of 24°. [c] 1:2 molar mixture of hydrocarbon and oxidizing agent. [d] 1:1 molar mixture of hydrocarbon and oxidizing agent. [e] Oxidizing agent added dropwise in solution. [f] Large excess of oxidizing agent. [g] Sodium cyanide added to hydrocarbon with oxidizing agent already present. [h] 1:3 molar mixture of hydrocarbon and oxidizing agent. [i] 1:1.3 molar mixture of hydrocarbon and oxidizing agent. [j] Not separated from the formazan. [k] Large excess of sodium cyanide. [l] Not separated from anthraquinone.

oxidations, and good yields of the cyanation products were obtained. Similar yields were also achieved when sodium cyanide was added to the hydrocarbon in the presence of the quinone, and in these reactions the usual intense green (hydrocarbon Ia) or black color (hydrocarbon IIa) was not observed, the deep magenta color developing immediately upon the addition of the sodium cyanide. Phenanthraquinone, a stronger oxidizing agent than anthraquinone,[15] was also very effective under conditions where cyanation of the hydrocarbons Ia or IIa had proceeded before the addition of the oxidizing agent.

The cyanation of 9-(*p*-bromobenzylidene)fluorene (IIc) with either sodium anthraquinone-1-sulfonate or phenanthraquinone was achieved with success similar to that with hydrocarbon IIa, the lack of any halogen replacement illustrating the selectivity of the cyanide ion attack under these mild conditions.

Cyanation reactions of 9-ethylidenefluorene (IIe) led even in the best case, *i.e.*, with sodium anthraquinone-1-sulfonate oxidant, to only 23% of nitrile IIf, along with 35% of hydrocyanation product VIIc. In all cases, by-product formation was serious and no starting material was recovered. Low molecular weight polymers formed in the absence of an oxidant or when the hydrocarbon was treated with sodium cyanide prior to addition of the oxidant. The nmr spectrum of a trimer isolated was complex, but a distinctive triplet near τ 3.0, which appeared in place of the quartet absorption associated with the vinyl proton of the monomeric hydrocarbon, is possible evidence for the α,β-unsaturated methylene linkage, which would be present in a trimer formed from polymerization of the hydrocarbon, following proton abstraction from its methyl group.

The efficiency of the cyanation reactions with sodium anthraquinone-1-sulfonate was markedly improved by the addition of potassium *t*-butoxide[16] to the DMSO solutions. The undesired hydrocyanation product was thereby converted into more cyanation product by proton loss and subsequent oxidation of the incipient carbanion. In the case of the 10-hr reaction listed in Table I for 9-benzylidenefluorene (IIa), the yield of the cyanation product (IIb) was raised to 78% by the addition of 1 molar equiv of potassium *t*-butoxide to the reaction mixture just prior to work-up; and, in the cyanation reaction of 9-ethylidenefluorene (IIe), the yield of cyanation product IIf was increased to 34%. A reaction in which the hydrocyanation product (VIIa) of 9-benzylidenefluorene (IIa) was itself treated with potassium *t*-butoxide, in the presence of sodium anthraquinone-1-sulfonate, resulted in a 57% conversion to the cyanation product (IIb).

Hydrocyanation of the hydrocarbons is effected when the colored cyanide–hydrocarbon mixtures are treated, in the absence of air, with such protonating agents as hydrogen cyanide,[2a] water, and ammonium chloride. The addition of 1 molar equiv of ammonium chloride, in solid form, to the colored DMF solutions caused fading of the color; and 76% of nitrile VI, 96% of nitrile VIIa, and 70% of nitrile VIIb were obtained from their respective parent compounds.

(15) W. Mansfield Clark, "Oxidation–Reduction Potentials," Williams and Wilkins, Baltimore, Md., 1960, p 386.

(16) The bulky *t*-butoxide ion is noted to be a very strong base in DMSO and has advantages if carbon substitution is to be avoided [A. J. Parker, *Advan. Org. Chem.*, **5**, 1 (1965)].

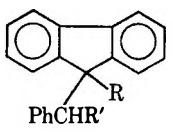
Apart from the high-yield protonation reactions, other attempts at trapping carbanion intermediates IVa and IVb were unsuccessful. Carbonation of the cyanide–hydrocarbon IIa mixture with gaseous carbon dioxide led to the isolation of only nitrile VIIa, in 46% yield. As in a similar attempt[2a] to trap carbanion III, the protonated product may be formed as a result of the reaction of sodium cyanide with carbon dioxide to give sodium cyanoformate, followed by protonation of the carbanion in the neutralized reaction solution by moisture present. Other reagents used in attempts to trap the carbanion intermediates included benzyl chloride, allyl bromide, dimethyl sulfate, sulfur dioxide, and cyanogen bromide; although all of these reagents caused fading of the colored cyanide–hydrocarbon mixtures, in no case was the anticipated product obtained.

The reversibility of cyanide ion attack (reaction 1) is considered to be the cause of the failure of the carbanion-trapping reactions, the reagent reacting with sodium cyanide and reversing the process by which the carbanion is formed. Earlier speculation[2a] on this reversibility, in the case of Ia, has now been substantiated by isolation of hydrocarbon Ia in 40% yield from its hydrocyanation derivative (VI) when a basic solution of the latter was evaporated to dryness under vacuum.

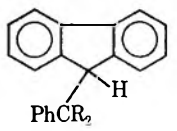
Reactions run between the hydrocarbons and sodium cyanide, in DMF under nitrogen, for extensive periods of time, in the absence of an added oxidizing agent, were anomalous. Although protonation of intermediates after 1 hr gives exclusively hydrocyanation products, cyanation products are isolated if the reactions are left for 40 hr before the ammonium chloride is added. In view of the fact that there was no apparent oxidation by the solvent, for no formaldehyde could be detected, a process of electron transfer and disproportionation of the incipient radical would appear necessary to explain the formation of a cyanation product. An electron lost from the carbanion may be transferred either to a molecule of unreacted hydrocarbon (reaction 2) or to a molecule of the unsaturated nitrile (reaction 3), once it is formed. The anion radicals so formed are then further able to disproportionate (reactions 5 and 6). If it is assumed that the hydrocarbon regenerated in reaction 5 reacts with more sodium cyanide, which is always present in excess, the over-all effect of reactions 1–6, upon final protonation, is to give rise to products from cyanation (reactions 4 and 6), hydrocyanation (reactions 4 and 6), and reduction (reaction 5) of the hydrocarbon. In the case of hydrocarbon Ia, the cyanation product (Ib) was formed in 74% yield and the hydrocyanation product (VI) in only 9% yield. A similar reaction with hydrocarbon IIa gave 13% of the cyanation product (IIb), 23% of the hydrocyanation product (VIIa), and 24% of a dinitrile. The rather high yield of cyanation product (Ib) from hydrocarbon Ia is undoubtedly due to the already mentioned ability of the hydrocyanation product (VI) to re-form carbanion III in the presence of sodium cyanide. Our inability to find any reduced hydrocarbons among the products of these reactions would be explained if reactions 2 and 5 were to take place to only a very small extent and the unsaturated nitrile itself, once formed, were to act as the principal electron acceptor (reactions

3 and 6). Indeed, the cyanation product might be expected to possess a greater electron affinity than the hydrocarbon, since it contains in its structure an extra component of conjugation in the form of the nitrile group.

The dinitrile, isolated from prolonged treatment of hydrocarbon IIa with sodium cyanide, followed by ammonium chloride, was shown to have either structure VIIIa or IX by its preparation, in 81% yield, from hydrocyanation of nitrile IIb. Under vigorous acid

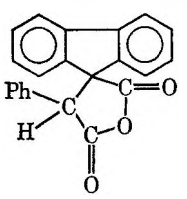


VIIIa, R = R′ = CN
b, R = R′ = CO_2H
c, R = R′ = CH_2OH

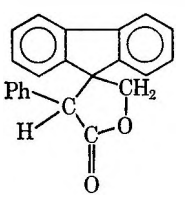


IX, R = CN

hydrolysis, a dicarboxylic acid was isolated from the dinitrile in 91% yield. The acid formed a 1:1 inclusion complex with benzene, and sublimation of this complex afforded an anhydride, in 92% yield, showing strong maxima at 1865 and 1780 cm^{-1}, in close agreement with the carbonyl absorption peaks of five-membered cyclic anhydrides.[17a] The acid and anhydride were therefore given the structures VIIIb and X, respectively, and in consequence the structure VIIIa was assigned to the dinitrile. Additional proof of the



X



XI

dinitrile structure was furnished when the dicarboxylic acid was reduced with lithium aluminium anhydride, and the glycol (VIIIc) so formed (in 56% yield) was subsequently oxidized with Sarrett's reagent. A product was obtained in 27% yield, whose analysis, infrared spectrum (carbonyl absorption[17b] at 1770 cm^{-1}), and nmr spectrum (no aldehydic protons, but an AB quartet centered at τ 5.24 and a one-proton singlet at 5.44) were compatible with a γ-lactone having the spiro structure XI.

The structures of the nitriles IIb, IId, IIf, and VIIa–c were assigned on the basis of their infrared, nmr, and mass spectra. Nitrile IIb was also independently synthesized from 9-benzylidenefluorene by the method of Koelsch.[18] The nmr spectrum of nitrile VIIa in deuteriochloroform is anomalous; it shows, in addition to the absorption for the aromatic protons, a sharp two-proton singlet at τ 5.70. The spectrum in acetone-d_6, however, shows the four-line pattern expected for an AB system, centered at τ 5.17, with a coupling constant of 5 cps. In order to establish conclusively the identity of this nitrile, both nitrile VIIa and 9-benzyl-9-cyanofluorene were independently prepared. Catalytic hydrogenation of nitrile IIb gave a colorless nitrile, identical with nitrile VIIa, whereas benzylation of 9-cyanofluorene, by the method of Anet and Bavin,[19] gave a product whose melting point and spectra were quite different from those of nitrile VIIa. The nmr spectrum of nitrile IIf, in deuteriochloroform, contains a three-proton singlet at τ 7.53 corresponding to the vinyl methyl group, and the spectrum of nitrile VIIc contains a three-proton doublet at τ 9.21, with coupling constant 7 cps, a one-proton octet at τ 6.63, with coupling constant 3.5 cps, and a one-proton doublet at τ 5.77, also with coupling constant 3.5 cps. These spectra are in agreement with structures IIf and VIIc. The structure of nitrile VIIc was also verified by its preparation from nitrile IIf upon catalytic hydrogenation.

(17) (a) L. J. Bellamy in "The Infra-Red Spectra of Complex Molecules," Methuen and Co., Ltd., London, 1957, p 128; (b) p 186.

(18) C. F. Koelsch, *J. Amer. Chem. Soc.*, **58**, 1328 (1936); **64**, 3384 (1932).

Experimental Section[20]

Materials.—Commercially available analytical grade solvents were employed, after they had been stored over Linde Type 4a Molecular Sieves for at least 2 weeks. Sodium cyanide (98%) was dried for 24 hr at 110°, in a vacuum oven, and stored over calcium sulfate in a tightly closed container. All gas streams were dried by sulfuric acid.

9-Benzylidenefluorene (Ia).—Colorless 9-benzylidenefluorene, mp 77–79° (lit.[21] mp 75–76°), was prepared by treatment of fluorene with benzyl alcohol and benzaldehyde in the presence of potassium hydroxide, according to the method of Sprinzak.[21]

9-(*p*-Bromobenzylidene)fluorene (IIc).—The preparation of 9-(*p*-bromobenzylidene)fluorene, mp 148–149° (lit.[22] mp 147–148°), from fluorene and *p*-bromobenzaldehyde in the presence of sodium methoxide was carried out by the method of Allen and his coworkers.[22]

9-Ethylidenefluorene (IIe).—A methanolic solution of Aldrich 9-ethylidenefluorene was treated with decolorizing charcoal and crystallized to give crystals, mp 105.5–106.5° (lit.[23] mp 103–104°).

4a-Methyl-1,3,9-triphenyl-4aH-fluorene (Ia).—The preparation of this hydrocarbon was the same as that described in a previous paper.[2a]

Reaction of 9-Benzylidenefluorene (IIa) with Sodium Cyanide. A. In DMF, in the Presence of Air.—A mixture of the hydrocarbon (1.02 g, 0.004 mol), sodium cyanide (1.96 g, 0.040 mol), and 20 ml of DMF became nearly black within 1 min when stirred under air at room temperature. After 30 min, air was led into the flask for 1.5 hr. The resulting intensely red mixture was poured into 50 ml of water, and the yellow precipitate which separated was dissolved in benzene–cyclohexane (1:1) and chromatographed through a column of neutral alumina. A benzene–cyclohexane (1:1) eluent gave 0.06 g (6%) of unchanged 9-benzylidenefluorene, mp 72–75°, and a benzene eluent gave 0.31 g (28%) of the yellow 9-(α-cyanobenzylidene) fluorene (IIb), mp 193–195°, ir 2200 cm^{-1} (CN) (lit.[18] mp 188–189°), after recrystallization of the residue from ethanol.

B. In DMF, Followed by Treatment with Air.—A mixture differing from that of A only in having two molecular equivalents of sodium cyanide (0.39 g, 0.008 mol) was stirred under nitrogen at room temperature for 30 min. Treatment of the black mixture for 2 hr with air afforded 0.08 g (7%) of nitrile IIb and 0.10 g of a colorless compound. The latter was eluted from the alumina column with ethanol and recrystallized from benzene to constant melting point (254–256° dec).

Anal. Calcd for $C_{21}H_{15}NO_2$: C, 80.48; H, 4.83; N, 4.47; mol wt, 313. Found: C, 80.05; H, 4.73; N, 4.77; mol wt, 313 (mass spectrum).

An infrared spectrum of the compound shows strong absorption at 3370 and 1685 cm^{-1}. The nmr spectrum, in DMF-d_7, shows,

(19) F. A. L. Anet and P. M. G. Bavin, *Can. J. Chem.*, **34**, 991 (1956).

(20) Melting points are uncorrected and were determined with a Kofler microstage apparatus. Microanalyses were performed by Mr. J. Nemeth and his associates, and mass spectra were obtained by Mr. J. Wrona, with an Atlas CH4 spectrometer. A Perkin-Elmer 521 infrared spectrophotometer was employed for infrared spectra, which were run in potassium bromide disks, and nmr spectra were run on a Varian A-60 spectrometer, with tetramethylsilane as an internal reference.

(21) Y. Sprinzak, *J. Amer. Chem. Soc.*, **78**, 466 (1956).

(22) R. E. Allen, E. L. Schumann, W. C. Day, and M. G. Van Campen, *ibid.*, **80**, 591 (1958).

(23) J. L. Kice, *ibid.*, **80**, 350 (1958).

in addition to the complex aromatic absorption, a doublet at τ 3.95, with coupling constant 8 cps. The ratio of the areas is 14:1 (multiplet–doublet).

In a similar experiment in which the cyanide–hydrocarbon mixture was treated with oxygen instead of air, comparable yields of nitrile IIb and the compound of molecular formula $C_{21}H_{15}NO_2$ were obtained. When a cyanide–hydrocarbon mixture in DMSO was treated with air, a 19% yield of fluorenone was obtained as the sole product.

General Procedure for the Cyanation of 4a-Methyl-1,3,9-triphenyl-4aH-fluorene (Ia) and 9-Benzylidenefluorene (IIa) by Sodium Cyanide in the Presence of Oxidizing Agents Other than Molecular Oxygen (Table I).—A solution of hydrocarbon Ia (0.41 g, 0.001 mol) or hydrocarbon IIa (0.51 g, 0.002 mol) in 80 ml of the chosen solvent was placed in a 100-ml three-necked flask equipped with magnetic stirrer, a gas inlet tube dipping into the liquid, and a calcium sulfate drying tube. (In experiments with chromium trioxide, chloranil, DDQ, and ceric salts as the oxidizing agent, 30 ml of solvent was employed.) This solution was stirred under nitrogen for at least 45 min before two molecular equivalents of finely powdered sodium cyanide were added. The color of the resulting mixture was then allowed to develop for 1 hr before the oxidizing agent was added, either in solid form or as a solution in 10 ml of solvent, portionwise over a period of 30 min. (The solid ceric sulfate was added in three portions at hourly intervals, the crystal violet solution was added in two portions, with a 30-min interval between the additions, and the chloranil solution, in the case of hydrocarbon IIa, was added likewise in two portions.) At the termination of the reaction, 10 ml of water was added to the reaction mixture, the nitrogen stream was cut off, and the contents of the flask were poured into 300 ml of water. The hot aqueous mixture was agitated and acidified with a saturated solution of ammonium chloride. If a precipitate separated, it was filtered, washed with cold water, and dried, but, if an oil or an emulsion resulted, the mixture was extracted three times with benzene, the benzene fractions were combined, washed with water, dried over magnesium sulfate, and then evaporated *in vacuo*. The product from the reaction was finally dissolved in a minimum of benzene and added to a column containing silica gel (0.05–0.2 mm) suspended in cyclohexane. Elution with cyclohexane, followed by evaporation of the solvent *in vacuo*, separated any unchanged hydrocarbon present. Elution with cyclohexane and benzene (5:1) gave the unsaturated nitrile (cyanation product), and elution with benzene alone separated any saturated nitrile (hydrocyanation product) present. These compounds were isolated in a pure state from the column (as determined by their infrared spectra and melting points), and the yields quoted in Table I are calculated on the amount of material obtained directly from column chromatography, prior to any recrystallization.

The cyanation and hydrocyanation products of 4a-methyl-1,3,9-triphenyl-4aH-fluorene,[2a] and the cyanation product of 9-benzylidenefluorene,[18] have been reported. An analysis of 9-(α-cyanobenzyl)fluorene was obtained from a sample of the column product which had been recrystallized from 95% ethanol, as colorless crystals, mp 158–160°, ir 2240 cm^{-1} (CN).

Anal. Calcd for $C_{21}H_{15}N$: C, 89.64; H, 5.37; N, 4.98; mol wt, 281. Found: C, 89.57; H, 5.57; N, 4.88; mol wt, 281 (mass spectrum).

Oxidation of 4-Cyano-4a-methyl-1,3,9-triphenyl-3,4-dihydro-4aH-fluorene (VI) by Sodium 9,10-Anthraquinone-1-sulfonate in the Presence of Sodium Cyanide.—A solution of the nitrile (0.22 g, 0.0005 mol), in 80 ml of DMSO, was stirred under nitrogen for 45 min at 50°. Powdered sodium cyanide (0.10 g, 0.002 mol) was added and the mixture became faintly green after 1 hr. The quinone (0.40 g, 0.0013 mol) was then added, and the reaction mixture immediately developed a magenta color which became very intense after 30 min. After 3.5 hr, the mixture was diluted with water and acidified. The resulting yellow solid was filtered (0.21 g) and recrystallized from cyclohexane to afford orange crystals (0.19 g, 87%) of 4-cyano-4a-methyl-1,3,9-triphenyl-4aH-fluorene (Ib), mp 193–195°.

Oxidation of 9-(α-Cyanobenzyl)fluorene (VIIa) by Sodium 9,10-Anthraquinone-1-sulfonate in the Presence of (A) Sodium Cyanide.—The preceding reaction was repeated with 0.14 g (0.0005 mol) of nitrile VIIa, 0.20 g (0.00066 mol) of the quinone, and 0.05 g (0.001 mol) of sodium cyanide, but this time the sodium cyanide was added to a mixture of both the nitrile and the quinone, in 40 ml of DMSO. The yellow solid reaction product was chromatographed according to the general procedure and 0.03 g (24%) of nitrile IIb and 0.07 g (50%) of unchanged nitrile VIIa were isolated.

(B) Potassium *t*-Butoxide.—A reaction similar to A, with potassium *t*-butoxide (0.11 g, 0.001 mol) as the base, was run at room temperature for 30 min in 50 ml of DMSO containing 12 ml of *t*-butyl alcohol. Nitrile IIb was isolated in 57% (0.08 g) yield.

Cyanation of 9-(*p*-Bromobenzylidene)fluorene (IIc) by Sodium Cyanide in the Presence of (A) 9,10-Phenanthraquinone.—A solution of 9-(*p*-bromobenzylidene)fluorene (0.33 g, 0.001 mol) and phenanthraquinone (0.27 g, 0.0013 mol), in 80 ml of DMF, was stirred under nitrogen for 1 hr. Powdered sodium cyanide (0.10 g, 0.002 mol) was added, and the reaction mixture became dark red within 5 min. After 5 hr, the mixture was diluted with water and acidified. The yellowish brown precipitate was chromatographed according to the general procedure to give 0.01 g (3%) of unchanged starting material, mp 147.5–148°, and 0.26 g (74%) of 9-(α-cyano-*p*-bromobenzylidene)-fluorene (IId), mp 166–168°. Elution with more polar solvents gave a yellow gum containing phenanthraquinone. An analytical sample of nitrile IId [mp 167–169°, ir 2185 cm^{-1} (CN)] was recrystallized from 95% ethanol.

Anal. Calcd for $C_{21}H_{12}BrN$: C, 70.39; H, 3.38; N, 3.91; Found: C, 70.47; H, 3.39; N, 3.61.

(B) Sodium 9,10-Anthraquinone-1-sulfonate.—A reaction similar to A was run for 9 hr with 0.66 g (0.002 mol) of 9-(*p*-bromobenzylidene)fluorene, 0.20 g (0.004 mol) of powdered sodium cyanide, and 0.62 g (0.002 mol) of sodium anthraquinone-1-sulfonate, in 80 ml of DMSO at 50°. Chromatography of the resulting yellow solid according to the general procedure yielded 0.41 g (58%) of nitrile IId and 0.10 g (14%) of nitrile VIIb. No starting material was recovered.

Cyanation of 9-Ethylidenefluorene (IIe) by Sodium Cyanide in the Presence of Sodium 9,10-Anthraquinone-1-sulfonate.—A solution of the hydrocarbon (0.58 g, 0.003 mol) and the quinone (0.93 g, 0.003 mol), in 80 ml of DMSO, was stirred under nitrogen for 1 hr at room temperature. Powdered sodium cyanide (0.29 g, 0.006 mol) was added and the reaction mixture became magenta within 5 min. After 5 hr, the mixture was diluted with water and acidified. Evaporation of benzene extracts at 40° gave a dark oil, which was chromatographed according to the general procedure to give 0.15 g (23%) of 9-(α-cyanoethylidene)fluorene (IIf) as a pale yellow solid and 0.23 g (35%) of 9-(α-cyanoethyl)-fluorene (VIIc) as a colorless solid.

An analytical sample of nitrile IIf was recrystallized from 60–68° hexane in the form of pale yellow elongated prisms [mp 144–145°, ir 2200 cm^{-1} (CN)].

Anal. Calcd for $C_{16}H_{11}N$: C, 88.43; H, 5.10; N, 6.45; mol wt, 217. Found: C, 88.26; H, 5.18; N, 6.47; mol wt, 217 (mass spectrum).

An analytical sample of nitrile VIIc was recrystallized from 60–68° hexane in the form of colorless needles [mp 97.0–97.5°, ir 2238 cm^{-1} (CN)].

Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.97; N, 6.39; mol wt, 219. Found: C, 87.67; H, 6.09; N, 6.51, mol wt, 219 (mass spectrum).

Polymerization of 9-Ethylidenefluorene (IIe) by Sodium Cyanide.—A solution of the hydrocarbon (0.58 g, 0.003 mol) in 80 ml of DMSO was stirred under nitrogen for 45 min. Powdered sodium cyanide (0.30 g, 0.006 mol) was added and the reaction mixture became quite black after 30 min. It lightened in color to become reddish orange after 1 hr, but it then darkened and was black again by the end of the 48-hr reaction. Ammonium chloride crystals (0.159 g, 0.003 mol) were added, and the reaction mixture turned dark green. After 5 hr, the mixture was quenched with water and acidified. A pale yellow precipitate (0.58 g, mp 120–300°) was collected, dissolved in a minimum of benzene, and put on a silica gel column. Elution with cyclohexane gave no trace of unchanged hydrocarbon, but elution with cyclohexane and benzene (5:1) afforded an off-white solid (0.31 g). Benzene elution gave a yellow gum. The solid was digested with three 50-ml portions of 60–68° hexane, and the colorless residue was filtered off (0.12 g). Recrystallization from 60–68° hexane–chloroform yielded colorless, irregular prisms (0.10 g, mp 305–311°), whose analysis and molecular weight indicated a compound of molecular formula $C_{70}H_{58}N_2$. An infrared spectrum of this compound showed no nitrile absorption.

Anal. Calcd for $C_{70}H_{58}N_2$: C, 90.67; H, 6.30; N, 3.02; mol

wt, 927. Found: C, 90.76; H, 6.15; N, 3.00; mol wt, 1004 (chloroform solution).

Evaporation of the 60–68° hexane solution to half-volume gave on refrigeration a crop of off-white, elongated prisms (0.03 g, mp 242–246°). An analysis and molecular weight determination of this compound were in agreement with those calculated for a trimer of the original hydrocarbon.

Anal. Calcd for $(C_{15}H_{12})_3$: C, 93.71; H, 6.29; mol wt, 577. Found: C, 93.20; H, 6.43; mol wt, 577 (mass spectrum) and 550 (chloroform solution).

Reaction of 9-Benzylidenefluorene (IIa) with Sodium Cyanide Followed by Treatment with (A) Ammonium Chloride Crystals. Preparation of 9-(α-Cyanobenzyl)fluorene (VIIa).—A solution of the hydrocarbon (1.02 g, 0.004 mol) in 80 ml of DMF was stirred under nitrogen at room temperature for 1 hr. Powdered sodium cyanide (0.80 g, 0.016 mol) was added, and the reaction mixture became black within 5 min. After 1 hr, ammonium chloride crystals (0.22 g, 0.004 mol) were added and the reaction mixture became yellow within 1 hr. After 4 hr, the mixture was diluted with water to yield 1.08 g (96%) of nitrile VIIa in the form of colorless crystals, mp 156–158°.

(B) Carbon Dioxide.—A mixture of the hydrocarbon (0.15 g, 0.002 mol) and sodium cyanide (0.98 g, 0.020 mol), in 20 ml of DMF, was stirred under nitrogen at room temperature. The mixture became black within 2 min. After 3 hr, stirring was interrupted and the flask was gently swept with carbon dioxide. When stirring was resumed, the mixture turned orange within 10 min and gradually became deep red. After 19 hr under carbon dioxide, the reaction mixture was diluted with water. The tan precipitate was collected and chromatographed according to the general procedure to give 0.26 g (46%) of nitrile VIIa, mp 156–158°.

(C) Allyl Bromide.—A mixture of the hydrocarbon (0.51 g, 0.002 mol) and sodium cyanide (0.98 g, 0.020 mol), in 20 ml of DMF, was stirred at room temperature under nitrogen. The reaction mixture became black within 4 min and was stirred under nitrogen for 30 min. The solution was then siphoned into a separatory funnel and added dropwise over a 10-min period to a stirred solution of allyl bromide (15 ml, 0.23 mol) in 10 ml of DMF. Distillation of the solvent and excess allyl bromide under reduced pressure and Soxhlet extraction of the resulting residue with benzene for 4 hr gave, after evaporation of the benzene, a reddish orange residue. Recrystallization of this residue from ethanol afforded 0.17 g (33%) of unchanged hydrocarbon, mp 75–76°.

Similar experiments were run in which mixtures of the hydrocarbon and sodium cyanide in DMF were treated with excesses of benzyl chloride and cyanogen bromide. In the case of benzyl chloride, 0.06 g (12%) of unchanged hydrocarbon was isolated as the only product, and, with cyanogen bromide, 0.28 g (55%) of unchanged hydrocarbon was recovered, together with 0.07 g (13%) of nitrile IIb.

Reaction of 9-(*p*-Bromobenzylidene)fluorene (IIc) with Sodium Cyanide Followed by Treatment with (A) Ammonium Chloride Crystals. Preparation of 9-(α-Cyano-*p*-bromobenzyl-fluorene (VIIb).—In an experiment similar to the hydrocyanation of hydrocarbon IIa, 0.25 g (70%) of nitrile VIIb was obtained from 0.33 g (0.001 mol) of bromo compound IIc in the form of colorless crystals, mp 200–202°. A second recrystallization of the nitrile from 95% ethanol afforded an analytically pure sample [mp 202–203°, ir 2230 cm^{-1} (CN)].

Anal. Calcd for $C_{21}H_{14}BrN$: C, 70.00; H, 3.92; 3.89; Found: C, 70.08; H, 3.96; N, 3.80.

(B) Sulfur Dioxide.—Treatment of a mixture of sodium cyanide (0.49 g, 0.010 mol) and 9-(*p*-bromobenzylidene)fluorene (0.67 g, 0.002 mol) in 15 ml of DMF, at room temperature under nitrogen, after 3.5 hr, with gaseous sulfur dioxide for 5 hr gave 0.10 g (15%) of starting material and 0.09 g (12%) of nitrile IId.

(C) Dimethyl Sulfate.—From a reaction similar to B, in which compound IIc in DMF was treated with sodium cyanide and then 1 ml of freshly distilled dimethyl sulfate, 0.41 g (61%) of unchanged hydrocarbon was recovered, together with 0.04 g (6%) of nitrile VIIb.

Reaction of 4a-Methyl-1,3,9-triphenyl-4aH-fluorene (Ia) with Sodium Cyanide Followed by Treatment with Ammonium Chloride. Preparation of 4-Cyano-4a-methyl-1,3,9-triphenyl-3,4-dihydro-4aH-fluorene (VI).—In an experiment similar to the hydrocyanation of hydrocarbon IIa, 0.41 g (0.001 mol) of hydrocarbon Ia yielded 0.33 g (76%) of nitrile VI, mp 274–276°.

Reaction of 4-Cyano-4a-methyl-1,3,9-triphenyl-3,4-dihydro-4aH-fluorene (VI) with Potassium *t*-Butoxide in DMF, Followed by Vacuum Evaporation of the Solvent.—A solution of the nitrile (0.33 g, 0.00075 mol) in 50 ml of DMF, contained in a flask equipped with a condenser set for distillation, was flushed with nitrogen for 1 hr. Potassium *t*-butoxide (0.165 g, 0.0015 mol) was added, and the intensely green color of the reaction mixture was developed for 3 hr. A receiving flask, immersed in Dry Ice–isopropyl alcohol and connected to a vacuum line, was then attached to the condenser, and the DMF was evaporated under nitrogen at 40° over a 25-hr period, leaving a dark residue. The residue was treated with an excess of water and an orange-yellow solid separated, which was completely soluble in cyclohexane (indicating the absence of any starting material). Chromatography of this solution on silica gel afforded 0.13 g (40%) of 4a-methyl-1,3,9-triphenyl-4aH-fluorene (Ia) as the only identifiable product.

Prolonged Reaction of 4a-Methyl-1,3,9-triphenyl-4aH-fluorene (Ia) with Sodium Cyanide in DMF.—A solution of the hydrocarbon (0.41 g, 0.001 mol) in 80 ml of DMF was stirred under nitrogen, at room temperature, for 2 hr before powdered sodium cyanide (0.20 g, 0.004 mol) was added. The green reaction mixture was stirred under nitrogen for 42 hr, and then ammonium chloride crystals (0.053 g, 0.001 mol) were added. Stirring was resumed and the reaction mixture became reddish brown within 2 min. After 5 hr, the reaction mixture was diluted and acidified to give a copious yellow precipitate which was chromatographed according to the general procedure; 0.32 g (74%) of nitrile Ib, mp 193–194°, and 0.04 g (9%) of nitrile VI, mp 273–274°, were isolated.

In an attempt to detect any possible formation of formaldehyde during this experiment, outflowing gases from the stirred mixture of hydrocarbon Ia and sodium cyanide in DMF were passed through a trap containing a dimedone solution. The DMF was then removed from the reaction mixture and treated with alkaline phloroglucinol (Jorissen's test[24]). In each case a negative result was obtained. (Jorissen's test was found satisfactory in DMF solutions by tests with trace amounts of formaldehyde.)

Prolonged Reaction of 9-Benzylidenefluorene (IIa) with Sodium Cyanide in DMF.—In a reaction similar to the preceding one, hydrocarbon IIa (0.51 g, 0.002 mol) in 80 ml of DMF was treated with powdered sodium cyanide (0.40 g, 0.008 mol) for 35 hr. Ammonium chloride crystals (0.11 g, 0.002 mol) were then added. Six hours later, 100 ml of degassed benzene was run into the dark brown reaction mixture. The reaction mixture was finally diluted with water and the two layers were allowed to separate. The benzene extract was chromatographed according to the general procedure to give 0.075 g (13%) of nitrile IIb, 0.13 g (23%) of nitrile VIIa, recrystallized from 95% ethanol, in the form of colorless fluffy needles, mp 156–158°, and 0.15 g (24%) of 9-cyano-9-(α-cyanobenzyl)fluorene (VIIIa) recrystallized from 95% ethanol as colorless prisms, mp 163–164°, ir 2250 cm^{-1} (CN).

Anal. Calcd for $C_{22}H_{14}N_2$: C, 86.26; H, 4.61; N, 9.15; mol wt, 306. Found: C, 86.07; H, 4.70; N, 9.17; mol wt, 306 (mass spectrum).

Reaction of 9-(α-Cyanobenzylidene)fluorene (IIb) with Sodium Cyanide in DMF Followed by Treatment with Ammonium Chloride. Preparation of 9-Cyano-9-(α-cyanobenzyl)fluorene (VIIIa).—A solution of the nitrile (0.84 g, 0.003 mol) in 200 ml of DMF was stirred under nitrogen for 1 hr. Powdered sodium cyanide (0.60 g, 0.012 mol) was added, and the reaction mixture became dark orange after 4 hr. Ammonium chloride crystals (0.32 g, 0.006 mol) were then added, and the reaction mixture was left stirring under nitrogen at room temperature. After 27 hr, the reaction mixture was diluted with water and acidified to give an off-white precipitate which was chromatographed on silica gel. Elution with cyclohexane and benzene (5:1) gave 0.025 g (3%) of unchanged nitrile IIb, and elution with benzene alone afforded 0.74 g (81%) of dinitrile VIIIa, mp 161–163°. This reaction was carried out on ten times the scale without loss of yield.

Hydrolysis of 9-Cyano-9-(α-cyanobenzyl)fluorene (VIIIa). Preparation of 9-Carboxy-9-(α-carboxybenzyl)fluorene (VIIIb) and Its Anhydride X.—A suspension of the dinitrile (0.30 g, 0.001 mol) in a mixture of concentrated sulfuric acid (5.0 ml), glacial acetic acid (3.0 ml), and water (5.0 ml) was refluxed at 130° for 5 hr. On dilution of the reaction mixture with water, 0.31 g (91%) of 9-carboxy-9-(α-carboxybenzyl)fluorene, mp 208–210°, was obtained. Recrystallization of the dicarboxylic

(24) M. Jorissen, *J. Pharm. Chim.*, **6**, 167 (1897).

acid, from petroleum ether (bp 90–110°)–acetone, gave an analytical sample in the form of colorless elongated prisms [0.28 g, mp 212–213°, ir 1700 cm^{-1} (CO)].

Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.70; H, 4.68; mol wt, 344. Found: C, 76.62; H, 4.65; mol wt, 344 (mass spectrum).

A sample of the dicarboxylic acid (mp 208–210°) was recrystallized from benzene–acetone, and the analysis of the crystalline product (mp 207–210°) was in agreement with that calculated for a 1:1 inclusion complex between the acid and benzene.

Anal. Calcd for $C_{22}H_{16}O_4 \cdot C_6H_6$: C, 79.60; H, 5.25. Found: C, 79.91; H, 5.25.

Sublimation of this inclusion complex (0.04 g) at 125° and 3.00 mm, yielded a sublimate of the acid anhydride (X) in the form of colorless crystals (0.035 g, 92%, mp 183.5–185°).

Anal. Calcd for $C_{22}H_{14}O_3$: C, 80.97; H, 4.32; mol wt, 326. Found: C, 80.67; H, 4.31; mol wt, 326 (mass spectrum).

Reduction of 9-Carboxy-9-(α-carboxybenzyl)fluorene (VIIIb). Preparation of 9-Hydroxymethyl-9-(α-hydroxymethylbenzyl)-fluorene (VIIIc).—A solution of the dicarboxylic acid (1.40 g, 0.004 mol) in anhydrous ether (100 ml) was added dropwise, over a period of 1 hr, to a stirred suspension of lithium aluminum hydride (1.60 g, 0.04 mol) in anhydrous ether (250 ml). The reaction mixture was refluxed for 4 hr. It was then cooled in an ice and salt bath and treated carefully with 20 ml of water and 200 ml of a 10% hydrochloric acid solution; the layers were separated. The aqueous layer was extracted three times with ether and the extracts were combined with the ether layer. Evaporation of the ether left a colorless semisolid gum which, on trituration with 60–68° hexane containing a trace of benzene, afforded a white crystalline solid, 0.84 g. This solid was recrystallized from hexane (bp 60–68°)–benzene to give 0.72 g (56%) of 9-hydroxymethyl-9-(α-hydroxymethylbenzyl)fluorene (VIIIc) as colorless irregular prisms [mp 123–125°, ir 2925 and 2880 cm^{-1} (CH_2)].

Anal. Calcd for $C_{22}H_{20}O_2$: C, 83.49; H, 6.37; mol wt, 316. Found: C, 83.67; H, 6.53; mol wt, 316 (mass spectrum).

Oxidation of 9-Hydroxymethyl-9-(α-hydroxymethylbenzyl)-fluorene (VIIIc). Preparation of 9-(α-Carboxybenzyl)-9-hydroxymethylfluorene Lactone (XI).—A solution of the glycol (0.30 g, 0.00095 mol) in anhydrous pyridine (3 ml) was added dropwise to a slurry of Sarett's reagent (5 ml), prepared from chromium trioxide and anhydrous pyridine.[25] The mixture was stirred at room temperature for 10.5 hr; then it was treated with 20 ml of water to complete the separation of the product. The resulting tan solid had very little solubility in a wide range of organic solvents. It was extracted with boiling chloroform and a nearly colorless gum was obtained upon evaporation of the solvent. The gum crystallized from hexane (bp 60–68°)–benzene, and the product was recrystallized from the same solvent mixture to give colorless crystals, 0.08 g (27%), of the lactone (XI), mp 172–175°.

(25) W. J. Hickinbottom in "Reactions of Organic Compounds," Longmans, Green and Co., London, 1959, p 132.

Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.55; H, 5.16; mol wt, 312. Found: C, 84.38; H, 5.26; mol wt, 312 (mass spectrum).

Catalytic Hydrogenation of 9-(α-Cyanobenzylidene)fluorene (IIb).—The nitrile (0.28 g, 0.001 mol), in 100 ml of ethanol, was stirred in a 125-ml hydrogenation flask and hydrogenated at atmospheric pressure with 30% palladium–charcoal as catalyst (0.015 g) for 3.5 hr. The filtered solution afforded a colorless residue, on evaporation, which was recrystallized from ethanol to give 0.14 g (50%) of nitrile VIIa, mp 157–159°.

Benzylation of 9-Cyanofluorene with Benzyl Chloride and Sodium Methoxide. Preparation of 9-Benzyl-9-cyanofluorene.—The procedure used is that described by Anet and Bavin[19] for the benzylation of methyl fluorene-9-carboxylate.

To a stirred solution prepared from sodium (0.68 g, 0.030 g-atom) and 25 ml of methanol was added, at room temperature, 9-cyanofluorene (1.91 g, 0.010 mol), prepared according to the method of King and his coworkers.[26] Benzyl chloride (6 ml, 0.052 mol) was added dropwise over a 5-min period to the orange-brown solution, and the reaction mixture was stirred at room temperature for 12 hr. It was then poured into 60 ml of a mixture of ice and 5% hydrochloric acid solution. The mixture was extracted twice with chloroform and the extracts were washed with 5% sodium bicarbonate solution and evaporated. The liquid residue was then dissolved in ether and the solution washed with 15% aqueous ammonia solution. Evaporation of the ether solution gave crystals which were washed with acetone and recrystallized from ethanol to give 1.70 g (61%) of the colorless 9-benzyl-9-cyanofluorene, mp 120–122°. A second recrystallization from ethanol gave an analytically pure sample [mp 122–123°, ir 2230 cm^{-1} (CN)].

Anal. Calcd for $C_{21}H_{15}N$: C, 89.63; H, 5.37; N, 4.98; mol wt, 281. Found: C, 89.53; H, 5.64; N, 4.95; mol wt, 281 (mass spectrum).

An nmr spectrum of the compound in deuteriochloroform shows a singlet at τ 6.66, for the two methylene protons.

Catalytic Hydrogenation of 9-(α-Cyanoethylidene)fluorene (IIf). Preparation of 9-(α-Cyanoethyl)fluorene (VIIc).—A solution of the nitrile (0.10 g, 0.00046 mol) in ethanol (50 ml) was hydrogenated at 20 lb/$in.^2$ for 2 hr, in the presence of 30% palladium on charcoal (0.02 g). The filtered solution afforded a brown, oily residue, on evaporation, which was charcoaled in hexane (bp 60–68°). The hexane solution was then concentrated and 9-(α-cyanoethyl)fluorene (VIIc) separated in the form of colorless crystals (0.05 g, 50%, mp 96–96.5°).

Registry No.—Ib, 19656-46-3; IIb, 19656-47-4; IId, 19656-48-5; IIf, 19656-49-6; VI, 10229-35-3; VIIa, 19656-51-0; VIIb, 19656-52-1; VIIc, 19656-53-2; VIIIa, 19656-54-3; VIIIb, 19656-55-4; VIIIc, 19656-56-5; X, 19656-57-6; XI, 19656-58-7; 9-benzyl-9-cyanofluorene, 19656-59-8.

(26) J. A. King, R. I. Meltzer, and J. Doczi, *J. Amer. Chem. Soc.*, **77**, 2217 (1955).

Phosphorus Derivatives of Nitrogen Heterocycles. I. Preparation and Chemistry of 9,10-Dihydroacridinephosphonic Acid Derivatives

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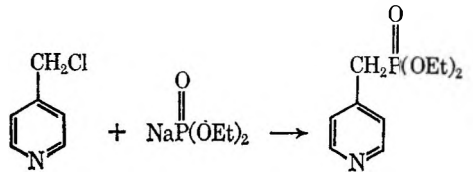
The reaction of N-methylacridinium quaternaries or acridinium salts with diethyl sodiophosphonate gives diethyl 10-methyl-9,10-dihydroacridine-9-phosphonate (**10**) and diethyl 9,10-dihydroacridine-9-phosphonate (**14**). Dehydrogenation of **14** yields diethyl acridine-9-phosphonate (**22**). Dihydroacridinephosphonate **10** forms an anion which is alkylated with alkyl halides and which undergoes the Wadsworth–Emmons reaction with aryl aldehydes to produce olefins **15**, **16**, and **17**. Upon reaction with Grignard reagents, **10** undergoes an unusual rearrangement reaction to produce ethyl hydrogen 9-ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (**28**).

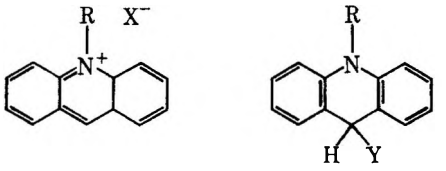
Very few compounds are known in which phosphorus is attached directly to a nitrogen heterocycle as a ring substituent. Diethyl acridine-9-phosphonate has been described as the product from the Arbusov reaction between 9-chloroacridine and triethyl phosphite.[1] The Arbusov reaction of 2,4-diamino-6-chloro-1,3,5-triazine with triethyl phosphite is reported to give the corresponding 6-phosphonate.[2] Closely related phosphonic acid derivatives are the products of the reactions between halomethylpyridines and quinolines with diethyl sodiophosphonate.[3-5] For example, 4-chloromethylpyridine on reaction with diethyl sodiophosphonate yields diethyl (4-pyridyl)methylphosphonate (**1**).[4]



1

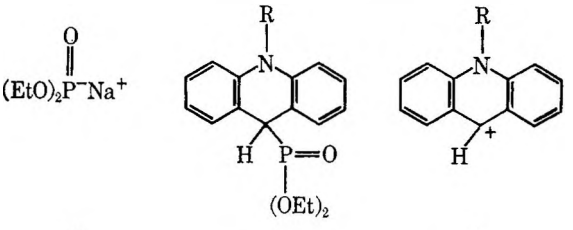
The present paper describes part of a study designed to produce additional examples of phosphorus derivatives of nitrogen heterocycles.

It has long been known[6-8] that N-alkyl- or N-arylacridinium salts, such as halides, when treated with nucleophilic anions are converted into nonionic compounds. Thus, an aqueous solution of N-phenylacridinium iodide (**2**) when treated with sodium hydroxide gives the nonionic 9-hydroxy compound **3**. The dihydroacridine **3** can be reconverted into the ionic form (**2**) by reaction with dilute hydrochloric acid. 9-Cyanodihydroacridines **5** can be prepared from N-alkylacridinium salts **4** with aqueous potassium cyanide. The cyano compounds **5** are more stable than the hydroxy compounds **3** necessitating heating with strong acid in order to be converted to the ionic derivative **4**. It therefore appeared that the strong nucleophile **6**, the anion from diethyl hydrogen phosphonate, should react with an acridinium quaternary salt to form a stable dihydroacridine-9-phosphonate **7**. In terms of Pearson's concept of hard and soft acids and bases the structure **7** should be stable, being a combination of the acridine cation **8**, a soft acid, and the anion **6**, a soft base.[9]



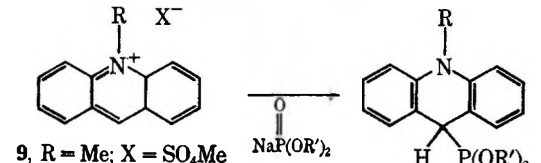
2, R = Ph; X = Cl
4, R = alkyl; X = Cl

3, R = Ph; Y = OH
5, R = alkyl; Y = CN



6 **7** **8**

When N-methylacridinium methosulfate (**9**) was treated with diethyl sodiophosphonate, diethyl 10-methyl-9,10-dihydroacridine-9-phosphonate (**10**) was formed in good yield. The assigned structure was fully confirmed by the spectroscopic data obtained and by the chemical properties. In particular the nuclear magnetic resonance (nmr) spectrum of **10** showed absorption for the phosphonate ester groups at δ 1.13 and 3.83, the N-methyl group at 3.32, and H at C_9 as a doublet at 4.5 (J_{PCH} = 26 Hz). The relative peak areas and additional absorption from the aryl protons were in accord with the structural assignment. The infrared (ir) spectrum showed characteristic phosphonate absorptions at 1250 (P=O) and 1030–1040 cm^{-1} (POC). The ultraviolet (uv) spectrum with absorption at 287 mμ was fully consistent with a dihydro-



9, R = Me; X = SO_4Me
11, R = H; X = I
13, R = H; X = Br

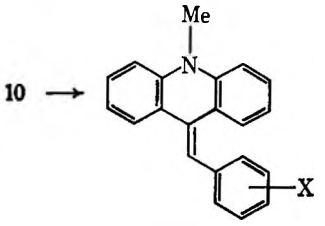
10, R = Me; R′ = Et
12, R = Me; R′ = *i*-Pr
14, R = H; R′ = Et

(1) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **69**, 1002 (1947).
(2) G. F. D'Alelio, U. S. Patent 3,011,998 (1961).
(3) P. Bednarek, R. Bodalski, J. Michalski, and S. Musierowicz, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **11**, 507 (1963).
(4) E. Maruszewska-Wieczorkowska and J. Michalski, *Rocz. Chem.*, **38**, 625 (1964).
(5) R. Bodalski, A. Malkiewicz, and J. Michalski, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, **13**, 139 (1965).
(6) A. Albert, "The Acridines," 2nd ed, Edward Arnold, Ltd., London, 1966, p 332.
(7) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons, Ltd., London, 1953, pp 575–586.
(8) A. Hantzsch and M. Kalb, *Chem. Ber.*, **32**, 3109 (1899).
(9) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967).

acridine chromophore. The phosphonate **10** showed good thermal stability being recovered unchanged after heating at 200° for 1 hr. In an analogous manner the acridinium salt **9** yielded diisopropyl 10-methyl-9, 10-dihydroacridine-9-phosphonate (**12**) when treated with diisopropyl sodiophosphonate.

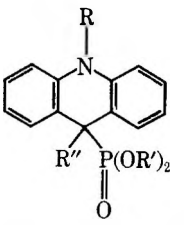
Acridine hydrobromide **13** or hydroiodide **11** underwent the same reaction as the quaternary salts to produce diethyl 9,10-dihydroacridine-9-phosphonate (**14**) in 70% yield. The nmr spectrum of **14** was very similar to that of the homolog **10** except for the absence of the N-methyl peak. The ir spectrum showed NH absorption (3230 cm^{-1}) and weakly hydrogen-bonded P=O (1230 cm^{-1}). It appears that the reaction of the acridine salts and quaternaries with dialkyl sodiophosphonates to produce dihydroacridinephosphonates is quite general, the availability of the acridine quaternaries being the main limitation.

These compounds undergo reactions typical of phosphonic acid esters, thereby providing further support for the structural assignments made above. The hydrogen at C_9 is particularly acidic, being activated by the phosphonate ester group and being at the same time doubly benzylic. The anion is thus readily formed by treatment with base. The phosphonate **10** yields the expected anion with sodium hydride in dimethoxyethane, and the anion reacts with benzaldehyde in a Wadsworth–Emmons reaction[10] to give 10-methyl-9-benzylidene-9,10-dihydroacridine (**15**). The structure of this product was confirmed by an independent synthesis, involving reaction of N-methylacridone with benzyl magnesium bromide.[11] *m*-Nitrobenzaldehyde and *p*-methoxybenzaldehyde likewise give substituted benzylidene derivatives of 9,10-dihydroacridines **16** and **17**. These compounds appear



15, X = H
16, X = *m*-NO_2
17, X = *p*-OMe

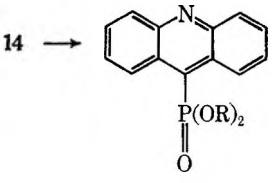
to be more stable in moist air than the earlier literature indicates.[12] However, when pyridine-2-carboxaldehyde was allowed to react with the anion of the phosphonate **10** N-methylacridone was the main product, presumably arising from hydrolytic degradation of the olefin during work-up.[12] The carbanions of the phosphonates **10** and **14** were alkylated by standard procedures.[13] Thus the anion of **10** reacted readily with methyl iodide to give diethyl 9,10-dimethyl-9,10-dihydroacridine-9-phosphonate (**18**). With the NH dihydroacridines the possibility of forming dianions exists so that **14** treated with 2 equiv of butyllithium followed by excess methyl iodide gave the dimethylated



18, R = Me; R′ = Et; R″ = Me
19, R = CH_2Ph; R′ = Et; R″ = CH_2Ph
20, R = H; R′ = Et; R″ = CH_2Ph
21, R = Me; R′ = Et; R″ = Et

product **18** identical with that prepared from the N-methyl compound **10**. This same dianion upon reaction with exactly 2 equiv of benzyl bromide afforded two products in 47 and 20% yields, respectively. The minor product was readily shown to be the 9,10-dibenzyl derivative **19** from the analytical data and particularly the nmr spectrum. The major product was shown to be the mono-C-benzylated compound **20** by its analysis and nmr spectrum. In the nmr spectrum of **20** the benzyl protons appeared as a doublet (J_{PH} = 8 Hz), while the characteristic doublet for H at C_9 was absent confirming C-benzylation. The ir spectrum of this monobenzyl compound showed the expected N—H stretching absorption. It was not possible to detect any N-monobenzylated material in the reaction product.

Further chemical characterization of these dihydroacridine derivatives is provided by the results of the dehydrogenation of **14**. Upon heating in benzene with tetrachloro-*p*-benzoquinone, the dihydroacridine **14** afforded, after chromatography on alumina, diethyl acridine-9-phosphonate (**22**), mp 95–96°. The nmr



22, R = Et
23, R = H

spectrum, Figure 1, is particularly informative, providing substantiation for the assigned acridine phosphonic acid structure. The multiplet centered at δ 4.25 is assigned to the ester methylene protons and arises from spin coupling with both the methyl protons and phosphorus and is fairly typical of phosphonate ethyl esters.[14,15] The other assignments are straightforward and are indicated in Figure 1. The uv spectrum with maxima at 269, 255, and 210 mμ indicates the presence of the acridine chromophore.[16] This structure had previously been assigned to the product, mp 165–167°, of the Arbusov reaction between 9-chloroacridine and triethyl phosphite.[1] Characterization of the product previously reported was not complete, however, and the product may not, in fact, contain phosphorus. Hydrolysis of the acridine phosphonate **22** with 18% hydrochloric acid gave acridine-9-phosphonic acid (**23**). The acid was insoluble in

(10) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

(11) E. D. Bergmann, M. Rabinovitz, and A. Bromberg, *Tetrahedron*, **24**, 1289 (1968); H. Decker and R. Pschorr, *Chem. Ber.*, **37**, 3396 (1904).

(12) Reference 6, p 340.

(13) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, pp 203–212.

(14) See, for example, J. D. Baldeschwieler, F. A. Cotton, B. D. Nageswara Rao, and R. A. Schunn, *J. Amer. Chem. Soc.*, **84**, 4454 (1962).

(15) The methylene protons in all the dihydroacridinephosphonic acid ethyl esters examined in this work give the more typical approximate quintets in their nmr spectra.

(16) Reference 6, p 188.

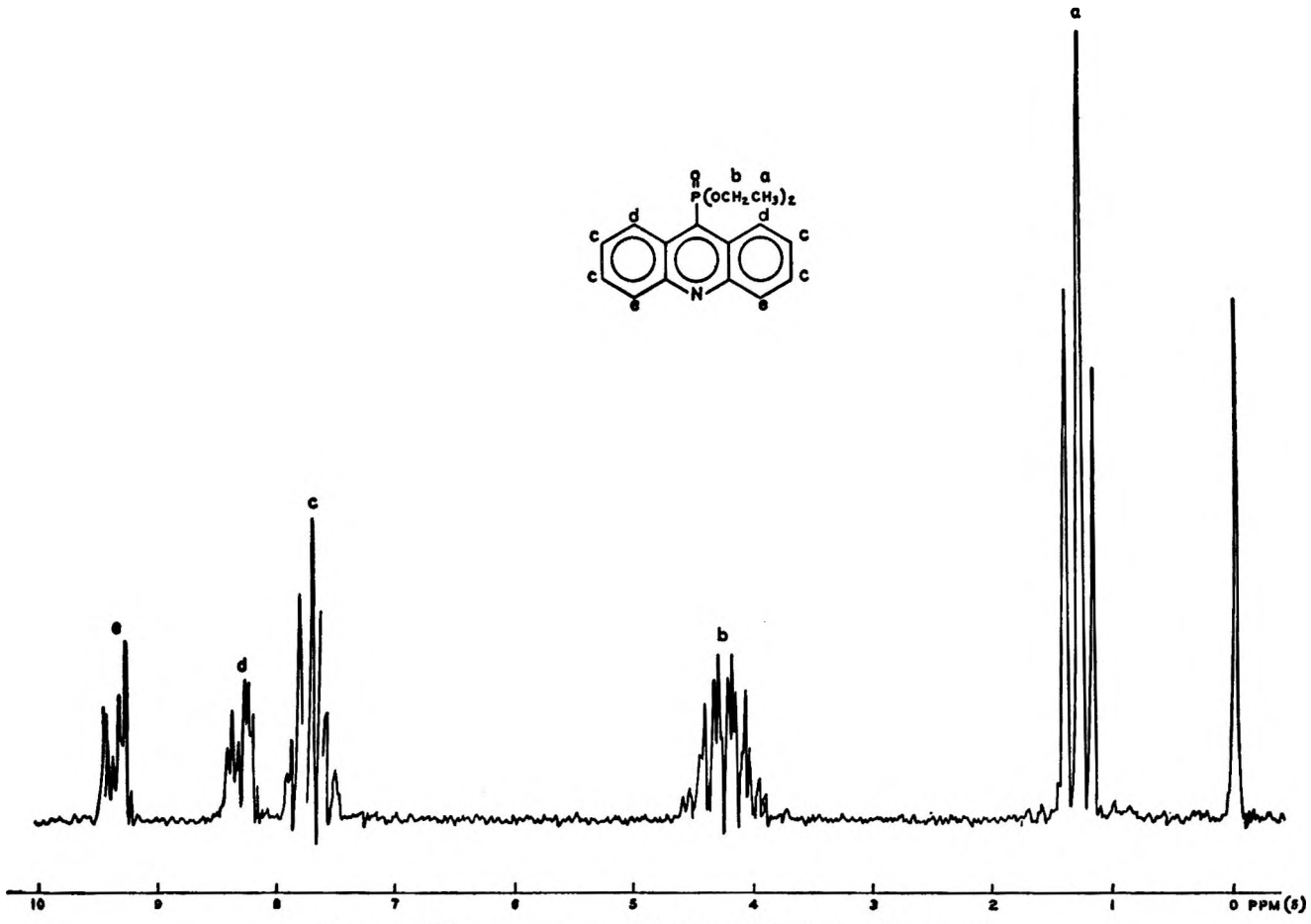
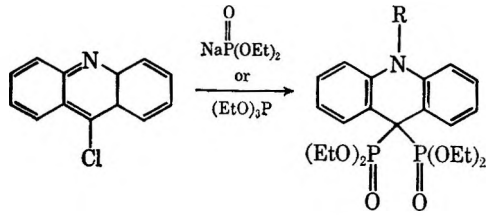


Figure 1.—The nmr spectrum of diethyl acridine-9-phosphonate (22).

common organic solvents but dissolved readily in aqueous base and was reprecipitated upon acidification.

An attempt was made to repeat the Arbusov reaction of 9-chloroacridine and triethyl phosphite under the conditions described by Kosolapoff.[1] No product corresponding to that described by Kosolapoff (mp 165–167°) could be isolated from the reaction. The only materials obtained, after chromatography on alumina, were unreacted chloroacridine and a solid containing phosphorus, mp 211–213°. This compound was the sole product isolated from the reaction of 9-chloroacridine and diethyl sodiophosphonate in dimethylformamide. The ir spectrum of this product showed NH absorption and the uv spectrum suggested the presence of a dihydroacridine chromophore (λ max, 209, 238, 292, and 332 mμ). The nmr spectrum and elementary analysis together with the above spectral data suggest that this compound is tetraethyl 9,10-dihydroacridine-9,9-diphosphonate (24). The compound is readily acetylated to produce the acetate (25).



24, R = H
25, R = COMe

which exhibits spectral data in complete accord with the structure. It seems probable that the acridinephosphonate 22 is an intermediate in the formation of the diphosphonate 24 from 9-chloroacridine since on heating the phosphonate 22 with diethyl sodiophosphonate in dimethylformamide the diphosphonate 24 is formed in 65% yield. The ease of nucleophilic attack at C_9 in the acridinephosphonate 22 is surprising. These results, however, still leave unanswered the question of the structure of Kosolapoff's product.

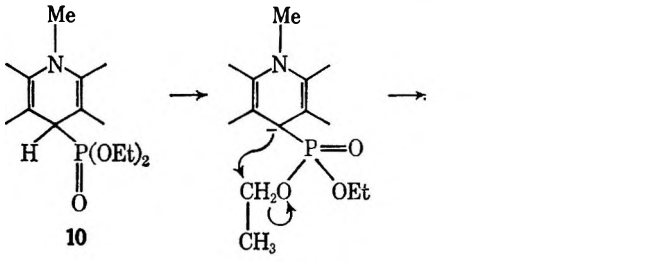
Typical phosphonic acid esters are converted into tertiary phosphine oxides upon treatment with Grignard reagents (eq 1).[17] Upon treatment of the phos-

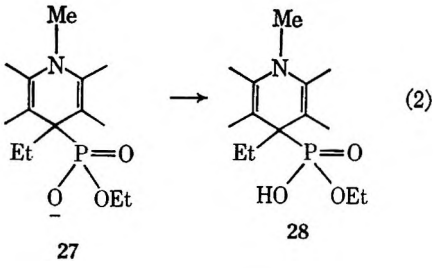
$$\mathrm{R\overset{O}{\overset{\|}{P}}(OR')_2 + 2R''MgX \longrightarrow R\overset{O}{\overset{\|}{P}}R''_2 + 2MgOR'X} \quad (1)$$

phonate ester 10 with a Grignard reagent an unusual and unexpected isomerization reaction was observed. The product from the reaction with methylmagnesium chloride in ether was shown by nmr and ir spectra not to be the expected tertiary phosphine oxide. It was further found that phenylmagnesium bromide gave an identical product, albeit in lower yield, which suggested an isomerization process initiated by the Grignard reagents. Elementary analysis confirmed that the product was isomeric with the starting material, and titration with base established an equivalent weight of 329. An analysis of the nmr spectrum led to the assignment of the structure of this acid as ethyl hydrogen 9-ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (28). The nmr spectrum showed two ethyl

(17) K. D. Berlin, T. H. Austin, M. Peterson, and M. Nagabhushanam in "Topics in Phosphorus Chemistry," Vol. 1, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, New York, N. Y., 1964, pp 39–43.

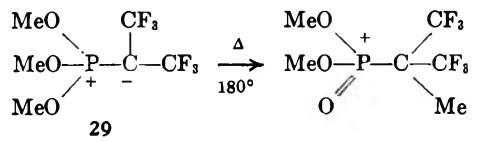
groups in slightly different envionments, and most significantly the characteristic doublet for H at C_9 was absent. The acidic proton appeared at low field (δ 11.50). The pathway for this isomerization is not certain but probably involves formation of a carbanion at C_9 (26) followed by rearrangement (eq 2). The





(2)

driving force here could derive from the greater stability of anion 27 over the anion 26. The fact that the anion 26 derived by treatment of 10 with Grignard reagent rearranges to 27, whereas 26 formed from 10 with sodium hydride or butyllithium does not rearrange can be explained by a combination of two factors: (a) the external electrophiles (aryl aldehydes and alkyl halides) added to the sodium- and lithium-derived anions are stronger than the internal phosphonate ester as electrophiles and (b) carbanions show a greater tendency to rearrange in the presence of magnesium salts than in presence of sodium or lithium.[18] This type of rearrangement is almost without precedent, the closest example being the thermal rearrangement of the ylide 29.[19] The monoester 28 was readily converted into the diethyl ester 21 upon heating with triethyl orthoformate.[20]



29

Experimental Section

Melting points are uncorrected and were measured on a Fisher-Johns hot stage melting point apparatus. The elemental analyses were by Clark Analytical Laboratory and Dr. F. J. Ludwig, Petrolite Corp., Physical-Analytical Section. Nmr spectra were obtained with a Varian Associates A-60 spectrometer, using a tetramethylsilane internal standard. Infrared spectra were determined on a Beckman IR-4 spectrometer.

Diethyl 10-Methyl-9,10-dihydroacridine-9-phosphonate (10).—To a stirred suspension of N-methylacridinium methosulfate, derived from acridine (100 g, 0.56 mol) and dimethyl sulfate (70.5 g, 0.56 mol) in toluene (200 ml) was added diethyl sodiophosphonate in dioxane (200 ml) [derived from sodium (12.9 g, 0.56 g-atom) and diethyl phosphite (77.5 g, 0.56 mol)] during 30 min. During the addition, which was carried out under an argon blanket, the reaction temperature rose to 55°. The reaction mixture was heated at 85–90° for 2 hr and, after cooling, water (150 ml) was added. The organic layer was separated, and the aqueous layer was extracted with two 50-ml portions of benzene. The combined organic extracts were dried ($MgSO_4$) and evaporated to yield a green oil. Crystallization from benzene–hexane gave diethyl 10-methyl-9,10-dihydroacridine-9-phosphonate (10), yield 130 g (68%), mp 85–88°. Recrystallization gave an analytically pure sample: mp 89–91°; nmr ($CDCl_3$) δ 1.13 (t, 6, J = 7 Hz, CH_3CH_2), 3.32 (s, 3, NCH_3), 3.83 (m, 4, J = 7 Hz, CH_3CH_2O), 4.5 (d, 1, J = 26 Hz, HCP), 7.4–6.8 (m, 8, Ar-H); ir (Nujol) 1250 (P=O) and 1030–1040 cm^{-1} (P–O–C); uv max (MeOH) 287 mμ (log ϵ 4.16) and 210 (4.72).

Anal. Calcd for $C_{18}H_{22}NO_3P$: C, 65.24; H, 6.69; N, 4.23; P, 9.35. Found: C, 65.04; H, 6.73; N, 4.24; P, 9.32.

Diethyl 9,10-Dihydroacridine-9-phosphonate (14).—To a stirred suspension of acridine hydrobromide (26 g, 0.1 mol) in toluene (100 ml) was added diethyl sodiophosphonate (16 g, 0.1 mol) in dioxane (50 ml) during 15 min under an argon blanket. The reactants were heated under reflux for 2 hr and after cooling water (75 ml) was added. Chloroform (100 ml) was added, and the organic layer was separated. The aqueous layer was extracted with two 50-ml portions of chloroform, and the combined organic fractions were evaporated. Crystallization from benzene–hexane gave diethyl 9,10-dihydroacridine-9-phosphonate (14): yield 20 g (63%); mp 189–190°; nmr ($CDCl_3$) δ 1.16 (t, 6, J = 7 Hz, CH_3CH_2O), 3.90 (m, 4, J = 7 Hz, CH_3CH_2O), 4.55 (d, 1, J = 25.5 Hz, H–C–P), 7.5–6.5 (m, 9, ArH + NH); ir (Nujol) 3230 (N–H) and 1230 cm^{-1} (P=O).

Anal. Calcd for $C_{17}H_{20}NO_3P$: C, 64.35; H, 6.31; N, 4.42; P, 9.78. Found: C, 63.95; H, 6.46; N, 4.51; P, 9.79.

Diethyl 10-Acetyl-9,10-dihydroacridine-9-phosphonate.—Diethyl 9,10-dihydroacridine-9-phosphonate (14, 2 g) was dissolved in acetic anhydride (5 ml), treated with sulfuric acid (1 drop), and warmed on a steam bath for 30 min. The mixture was immediately poured into warm water and extracted with chloroform. Evaporation of the chloroform and crystallization from benzene–hexane gave diethyl 10-acetyl-9,10-dihydroacridine-9-phosphonate, mp 157–158°.

Anal. Calcd for $C_{19}H_{22}NO_4P$: C, 63.51; H, 6.13; N, 3.90; P, 8.64. Found: C, 63.25; H, 6.17; N, 3.70; P, 8.48.

Diisopropyl 10-Methyl-9,10-dihydroacridine-9-phosphonate (12).—Diisopropyl sodiophosphonate (18.8 g, 0.1 mol) was allowed to react with N-methylacridinium methosulfate (30.5 g, 0.1 mol) using the method described above. Crystallization of the product from benzene–hexane gave diisopropyl 10-methyl-9,10-dihydroacridine-9-phosphonate (12): yield 14.4 g (40%); mp 124–125.5°; nmr ($CDCl_3$) δ 1.04 (t, 12, J = 6.5 Hz, CH_3–CH–), 3.26 (s, 3, N–CH_3), 4.24 (m, 2, J = 6.5 Hz, CH_3CHO), 4.24 (d, 1, J = 26 Hz, H–C–P), 6.65–7.35 (m, 8, ArH).

Anal. Calcd for $C_{20}H_{26}NO_3P$: C, 66.85; H, 7.24; N, 3.90; P, 8.64. Found: C, 67.28; H, 7.24; N, 3.86; P, 8.39.

9-Benzylidene-10-methyl-9,10-dihydroacridine (15).—To a solution of diethyl 10-methyl-9,10-dihydroacridine-9-phosphonate (10, 3.3 g, 0.01 mol) and benzaldehyde (1.1 g, 0.01 mol) in 1,2-dimethoxyethane (30 ml) was added 50% sodium hydride (0.5 g, 0.01 mol). The reaction mixture was maintained at 70–75° for 40 min, poured into ice–water, and extracted with benzene. Crystallization of the residue from the benzene evaporation yielded 9-benzylidene-10-methyl-9,10-dihydroacridine (15): yield 2 g (70%); mp 148–149° (lit.[11] mp 143°); nmr ($CDCl_3$) δ 3.34 (s, 3, N–CH_3), 6.70 (s, 1, HC=C), 6.80–8.0 (m, 13, Ar-H).

Anal. Calcd for $C_{21}H_{17}N$; C, 89.04; H, 6.00; N, 4.95. Found: C, 89.27; H, 6.17; N, 4.80.

A sample of this compound prepared from N-methylacridone and benzylmagnesium bromide according to the method of Decker and Pschorr[11] was identical in all respects with that prepared above.

9-(*m*-Nitro)benzylidene-10-methyl-9,10-dihydroacridine (16).—*m*-Nitrobenzaldehyde was treated with phosphonate 10 in the manner used for benzaldehyde. The 9-(*m*-nitro)benzylidene-10-methyl-9,10-dihydroacridine (17) was obtained in 40% yield after crystallization from benzene–methanol: mp 182–185°; nmr ($CDCl_3$) δ 3.57 (s, 3, N–CH_3), 6.6–8.3 (m, 15, C=CH, ArH + $0.33C_6H_6$).

Anal. Calcd for $C_{21}H_{16}N_2O_2 \cdot 0.33C_6H_6$: C, 77.97; H, 5.08; N, 7.91. Found: C, 78.01; H, 5.30; N, 7.86.

9-(*p*-Methoxy)benzylidene-10-methyl-9,10-dihydroacridine (17) was prepared from *p*-methoxybenzaldehyde and phosphonate

(18) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 220–221.

(19) W. J. Middleton, U.S. Patent 3,067,233 (1962).

(20) J. Preston and H. G. Clark, U. S. Patent 2,928,859 (1960).

10 by the procedure above. Crystallization from benzene–methanol gave an analytically pure sample in 50% yield: mp 155–156°; nmr ($CDCl_3$) δ 3.44 (s, 3, N-CH_3), 3.78 (s, 3, O-CH_3), 7.0–8.0 (m, 15, C=CH, ArH + 0.33C_6H_6).

Anal. Calcd for $C_{22}H_{19}NO \cdot 0.33C_6H_6$: C, 84.96; H, 6.19; N, 4.13. Found: C, 85.09; H, 6.38; N, 4.17.

Diethyl 9,10-Dimethyl-9,10-dihydroacridine-9-phosphonate (18).—To phosphonate 10 (3.3 g, 0.01 mol) in 1,2-dimethoxyethane (50 ml) was added a 1.6 *M* solution of butyllithium in hexane (6.5 ml, 0.01 mol) under an argon blanket. To the resulting deep red solution was added methyl iodide (2.28 g, 0.016 mol), and the reaction mixture was heated at 60° for 20 min. After cooling to room temperature, the mixture was poured into water. Extraction with benzene and crystallization from benzene–hexane gave diethyl 9,10-dimethyl-9,10-dihydroacridine-9-phosphonate (18): yield 1.7 g (50%); mp 112–113.5°; nmr ($CDCl_3$) δ 1.10 (t, 6, J = 7 Hz, CH_3CH_2O), 2.96 (d, 3, J = 15 Hz, CH_3CP), 3.24 (s, 3, N-CH_3), 3.68 (m, 4, J = 7 Hz, CH_3CH_2O) 6.7–7.5 (m, 8, ArH).

Anal. Calcd for $C_{19}H_{24}NO_3P$: C, 66.09; H, 6.96; N, 4.06; P, 8.99. Found: C, 66.08; H, 6.90; N, 3.95; P, 8.94.

Methylation of Diethyl 9,10-Dihydroacridine-9-phosphonate (14).—Diethyl 9,10-dihydroacridine-9-phosphonate (14) (6.34 g, 0.02 mol) suspended in 1,2-dimethoxyethane (50 ml) was treated with a 1.6 *M* solution of butyllithium in hexane (12.5 ml, 0.02 mol). To the resultant red solution methyl iodide (2.8 g, 0.02 mol) was added dropwise. After stirring at ambient temperature for 30 min, water (50 ml) was added, the organic layer was separated, and the aqueous portion was extracted with benzene. Evaporation of the combined organic fractions and crystallization from benzene–hexane gave unreacted starting material, yield 2.1 g (33%), mp 186–188°. The mother liquors were concentrated and chromatographed on alumina from benzene. Elution with chloroform, concentration, and crystallization from benzene–hexane yielded diethyl 9,10-dimethyl-9,10-dihydroacridine-9-phosphonate (18, 2 g, 30%, mp 110–111°), identical with the sample prepared above. No monoalkylated products were isolated although tlc suggested the presence of other products in the reaction.

Benzylation of Diethyl 9,10-Dihydroacridine-9-phosphonate (14).—To a stirred suspension of phosphonate 14 (6.34 g, 0.02 mol) in 1,2-dimethoxyethane (100 ml) was added a 1.6 *M* solution of butyllithium in hexane (25 ml, 0.04 mol) with cooling to keep the temperature below 10°. To the resulting lithio derivative was added benzyl bromide (7.7 g, 0.045 mol) in dimethoxyethane (10 ml) at 10°. After stirring 2 hr at 10–20° the mixture was poured into water (200 ml). Extraction with benzene and crystallization from benzene–hexane gave diethyl 9-benzyl-9,10-dihydroacridine-9-phosphonate (20): yield 3.9 g (47%); mp 201–204°; nmr ($CDCl_3$) δ 1.16 (t, 6, J = 7 Hz, CH_3CH_2O), 4.84 (m, 4, J = 7 Hz, CH_3CH_2O), 4.96 (d, 2, J = 8 Hz, $PhCH_2$–CP), 6.5–8.0 (m, 16, ArH + NH + 0.33C_6H_6); ir (Nujol) 3200 (N-H) and 1200 cm^{-1} (P=O).

Anal. Calcd for $C_{24}H_{26}NO_3P \cdot 0.33C_6H_6$: C, 72.06; H, 6.47; N, 3.23; P, 7.16. Found: C, 72.06; H, 6.67; N, 3.29; P, 7.31.

Crystallization of the mother liquors from monobenzyl compound 20 gave (benzene–hexane) diethyl 9,10-dibenzyl-9,10-dihydroacridine-9-phosphonate (19): yield 2 g (20%); mp 172–174°; nmr ($CDCl_3$) δ 1.15 (t, 6, J = 7 Hz, CH_3CH_2O), 3.9 (m, 6, CH_3CH_2O + $PhCH_2N$), 5.03 (s, 2, $PhCH_2CP$), 6.5–8.0 (m, 18, ArH).

Anal. Calcd for $C_{31}H_{32}NO_3P$: C, 74.85; H, 6.44; N, 2.82; P, 6.24. Found: C, 74.49; H, 6.54; N, 2.73; P, 6.39.

Diethyl Acridine-9-phosphonate (22).—Diethyl 9,10-dihydroacridine-9-phosphonate (14) (2 g, 0.0095 mol) and tetrachlorobenzoquinone (2.5 g, 0.0095 mol) were heated under reflux in benzene (50 ml) for 1 hr. The solid which separated on cooling was filtered off and discarded (tetrachlorohydroquinone). The benzene solution was concentrated to 25 ml and chromatographed on alumina. Elution with chloroform and evaporation yielded a yellow solid. Crystallization from benzene–hexane gave diethyl acridine-9-phosphonate (22): yield 2 g (66%); mp 95–96°; nmr ($CDCl_3$) δ 1.23 (t, 6, J = 7 Hz, CH_3CH_2O), 4.25 (m, 4, J = 7 Hz, CH_3CH_2O), 7.74 (m, 4, H at $C_{2,3,6,7}$), 8.30 (m, 2, H at $C_{4,5}$), 9.35 (m, 2, H at $C_{1,8}$); uv max (MeOH) 369 mμ (log ϵ 4.06), 255 (4.20), and 210 (4.18).

Anal. Calcd for $C_{17}H_{18}NO_3P$: C, 64.76; H, 5.71; N, 4.44; P, 9.84. Found: C, 64.64; H, 5.78; N, 4.20; P, 9.56.

Acridine-9-phosphonic Acid (23).—Diethyl acridine-9-phosphonate (22, 750 mg) was heated under reflux with 18% hydrochloric acid (25 ml) for 3 hr. After 2 hr an orange-yellow solid began to separate. After cooling the solid was filtered, washed with water, and dried. The acid was purified by dissolving in 3 *N* sodium hydroxide and precipitation with hydrochloric acid. The precipitate of acridine-9-phosphonic acid (23) was filtered, washed with water, and dried: mp >300°; ir (Nujol) 1165 cm^{-1} (P=O).

Anal. Calcd for $C_{13}H_{10}NO_3P \cdot 2H_2O$: C, 52.88; H, 3.39; N, 4.76; P, 10.51; H_2O, 12.2. Found: N, 4.85; P, 10.84; H_2O, 10.9.

Ethyl Hydrogen 9-Ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (28).—To a solution of diethyl 10-methyl-9,10-dihydroacridine-9-phosphonate (10, 16.6 g, 0.05 mol) in dry benzene (200 ml) was added a 3 *M* solution of methylmagnesium chloride in tetrahydrofuran (51 ml, 0.15 mol) during 20 min. After stirring at room temperature for 2 hr dilute hydrochloric acid was added to the reaction. The organic phase was separated and the aqueous portion was extracted with chloroform. Evaporation of the combined organic layers and crystallization from ethanol gave ethyl hydrogen 9-ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (28): yield 11 g (80%); mp 217–219° dec; nmr ($CDCl_3$) δ 0.74 (t, 3, J = 7 Hz, CH_3CH_2C), 0.93 (t, 3, J = 7 Hz, CH_3CH_2O), 2.48 (q, 2, J = 7 Hz, CH_3CH_2C), 3.30 (s, 3, N-CH_3), 3.57 (q, 2, J = 7 Hz, CH_3CH_2O), 6.7–7.8 (m, 8, ArH), 11.50 (s, 1, O-H).

Anal. Calcd for $C_{18}H_{22}NO_3P$: C, 65.26; H, 6.65; N, 4.23; P, 9.37; equiv wt, 331.4. Found: C, 65.34; H, 7.02; N, 4.19; P, 9.56; equiv wt, 329 (KOH titration).

Diethyl 9-Ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (21).—Ethyl hydrogen 9-ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (28, 2 g) was heated at 140–150° with triethyl orthoformate (3 ml) for 20 hr. The solid phosphonate (28) gradually dissolved as reaction proceeded. Upon cooling crystals separated which were filtered and recrystallized from benzene–hexane to yield analytically pure diethyl 9-ethyl-10-methyl-9,10-dihydroacridine-9-phosphonate (21): yield 1.8 g (82%); mp 112–113°; nmr ($CDCl_3$) δ 0.78 (t, 3, J = 7 Hz CH_3CH_2C), 1.08 (t, 6, J = 7 Hz, CH_3CH_2O), 2.67 (q, 2, J = 7 Hz, CH_3–CH_2C), 3.37 (s, 3, N-CH_3), 3.77 (q, 4, J = 7 Hz, CH_3CH_2O), 6.8–7.6 (m, 8, ArH).

Anal. Calcd for $C_{20}H_{26}NO_3P$: C, 66.85; H, 7.24; N, 3.90; P, 8.64. Found: C, 66.94; H, 7.29; N, 4.13; P, 8.64.

Tetraethyl 9,10-Dihydroacridine-9,9-diphosphonate (24).—Diethyl sodiophosphonate (4 g, 0.025 mol) in dioxane (20 ml) was added during 20 min to 9-chloroacridine (5 g, 0.023 mol) in dimethylformamide (45 ml). The temperature of the reaction mixture rose to 55° during the addition. After stirring overnight at ambient temperature, the mixture was poured into water (200 ml) and the solid which precipitated was filtered and dried (3 g, 51%). Recrystallization from benzene–hexane gave tetraethyl 9,10-dihydroacridine-9,10-diphosphonate (24): yield 2 g (34%); mp 211–213°; nmr ($CDCl_3$) δ 1.07 (t, 12, J = 7 Hz, CH_3CH_2O), 4.10 (q, 8, J = 7 Hz, CH_3CH_2O), 7.05–6.55 (m, 6, H at $C_{1,2,3,6,7,8}$), 7.70 (s, 1, N-H), 8.06 (m, 2, H at $C_{4,5}$); uv max (MeOH) 332 mμ (log ϵ 3.94), 292 (4.11), 282 (4.13), and 209 (4.61); ir (Nujol) 3300 (N-H), 1240 (P=O), 1225 (P=O), 1040 cm^{-1} (P-O-C); ir (benzene) 3460 (N-H), 1250 cm^{-1} (P=O).

Anal. Calcd for $C_{21}H_{29}NO_6P_2$: C, 55.63; H, 6.48; N, 3.09; P, 13.69. Found: C, 56.09; H, 6.46; N, 3.0; P, 13.52.

Reaction of Diethyl Acridine-9-phosphonate (22) with Diethyl Sodiophosphonate.—Sodium (0.1 g) was added to diethyl phosphite (2 g) in dimethylformamide (5 ml) to give diethyl sodiophosphonate. To this reagent was added diethyl acridine-9-phosphonate (1.3 g) and the mixture was heated at 50–55° for 30 min. After cooling, the reaction mixture was poured into water and the precipitated solid was filtered and dried. Crystallization of the solid from benzene–hexane gave tetraethyl 9,10-dihydroacridine-9,9-diphosphonate (24), yield 1.4 g (65%), mp 211–213°. This compound gave identical spectral data as the sample from 9-chloroacridine.

Tetraethyl 10-Acetyl-9,10-dihydroacridine-9,10-diphosphonate (25).—Tetraethyl 9,10-dihydroacridine-9,10-diphosphonate (24) (500 mg) was heated at 80° for 10 min in acetic anhydride (5 ml) containing 1 drop of sulfuric acid. The crude acetyl derivative was obtained by pouring the reaction mixture into warm water and extraction with ether. The ether extract was evaporated and the residue crystallized from benzene–hexane to yield tetraethyl 10-acetyl-9,10-dihydroacridine-9,10-diphosphonate (25), yield 400 mg, mp 120–122°.

Anal. Calcd for $C_{23}H_{31}NO_7P_2$: C, 55.76; H, 6.26; N, 2.83; P, 12.53. Found: C, 56.45; H, 6.39; N, 2.80; P, 12.40.

Registry No.—**10**, 19656-30-5; **12**, 19656-31-6; **14**, 19656-32-7; **15**, 19656-33-8; **16**, 19656-34-9; **17**, 19656-35-0; **18**, 19656-36-1; **19**, 19656-37-2; **20**, 19656-38-3; **21**, 19656-39-4; **22**, 19656-40-7; **23**, 19656-41-8; **24**, 19656-42-9; **25**, 19656-43-0; **28**, 19656-44-1; diethyl 10-acetyl-9,10-dihydroacridine-9-phosphonate, 19656-45-2.

Acknowledgment.—The author wishes to thank Professor C. D. Gutsche and Dr. F. E. Mange for helpful discussions during the course of this work.

Dual Formation of β Diketones from Methylene Ketones and Acetic Anhydride by Means of Boron Trifluoride. Improved Method of Synthesis of Certain β Diketones[1]

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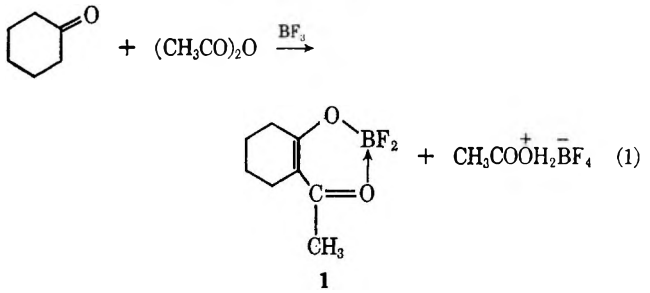
Evidence is presented that the formation of β diketones from methylene ketones and acetic anhydride by means of boron trifluoride involves, not only direct C acetylation of the ketone, but also O acetylation of the ketone and C acetylation of the resulting ketone enol ester. The O acetylation is catalyzed by proton acid formed as the by-product in the C acetylation of the ketone. Certain intermediate ketone enol esters, β diketone enol esters, and boron difluoride complexes were isolated. Acetophenone, however, apparently undergoes only C acetylation. The relative proportions of the methyl and methylene derivatives of methyl methylene ketones were found to be dependent, not only on the structure of the ketone, but also on the conditions employed for effecting the acetylation. Several β diketones were prepared conveniently by use of the boron trifluoride–diacetic acid complex which is available commercially.

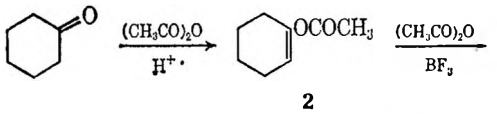
In 1954,[2] the acylation of a ketone with an aliphatic anhydride by boron trifluoride to form a β diketone was suggested to involve, not only C acylation of the ketone, but also O acylation of the ketone followed by C acylation of the resulting ketone enol ester.

We now present evidence for such dual formation of β diketones from certain methylene ketones and acetic anhydride. Thus cyclohexanone and this anhydride were found to be converted by boron trifluoride into boron difluoride complex **1**, not only by direct C acetylation of the ketone (eq 1), but also indirectly through ketone enol acetate **2** and β diketone enol acetate **3** (eq 2). Although the second course of reaction is dependent on formation of proton acid as by-product in the first course (see eq 1 and 2), the O acetylation may be initiated soon after the boron trifluoride is added, since only a catalytic amount of the proton acid is required. The boron difluoride complex **1** was subsequently treated with hot sodium acetate solution to liberate the β diketone.

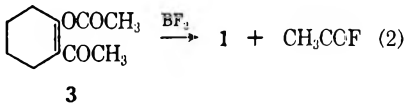


(1)

1



2

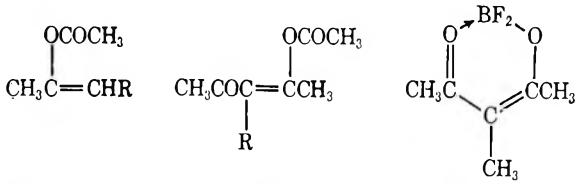


(2)

3

In support of the O acetylation course of reaction (eq 2), the intermediate ketone enol acetate **2** and the β diketone enol acetate **3** were isolated from the reaction mixture of cyclohexanone and acetic anhydride and subsequently converted into the boron difluoride complex **1** or 2-acetylcyclohexanone under similar conditions. In the further reaction of the β diketone enol acetate **3**, acetyl fluoride was shown to be formed as by-product (see eq 2).

Similarly, ketone enol acetates **4a** and **b** and β diketone enol acetates **5a** and **b** were isolated from the reaction mixtures of the appropriate ketones, acetic anhydride and boron trifluoride, and certain of them were subsequently converted into β diketones or their boron difluoride complexes such as **6**. Previously, certain ketone enol esters and β diketone enol esters have been converted into β diketones or their difluoride complexes; benzoyl fluoride was shown to be eliminated from a β diketone enol benzoate.[3]



4a, R = CH_3 **5a**, R = CH_3 **6**

b, R = n-C_4H_9 **b**, R = n-C_4H_9

(1) Supported by the National Science Foundation.

(2) *Org. Reactions*, **8**, 98 (1954).

(3) See C. R. Hauser, F. C. Frostick, Jr., and E. H. Man, *J. Amer. Chem. Soc.*, **74**, 3231 (1952).

TABLE I
RELATIVE PROPORTIONS OF METHYL (12) AND METHYLENE (13) DERIVATIVES OF KETONES OBTAINED WITH ACETIC ANHYDRIDE BY BORON TIFLUORIDE DETERMINED BY VPC

Ketone	Fast saturation —with BF_3 gas, %—		Slow saturation ——with BF_3 gas, %——		Use of BTDA[a] ——complex, %——	
	12	13	12	13	12	13
$CH_3COCH_2CH_3$	14	86	0	100	0	100
$CH_3COCH_2CH_2CH_3$	26	74	8.3 (0)[b]	91.7 (100)[b]	5 (0)[b]	95 (100)[b]
$CH_3CO(CH_2)_4CH_3$	36	64	8.4 (0)[b]	91.6 (100)[b]	0	100
$CH_3COCH_2CH(CH_3)_2$	80	20	49	51	25 (25)[b]	75 (75)[b]
$CH_3COCH(CH_3)_2$	70[c]	30[d]	37[c]	63[d]	2 (0)[b,c]	98 (100)[b,d]

[a] Boron trifluoride–diacetic acid complex. [b] Percentage obtained in the presence of catalytic amount of *p*-toluenesulfonic acid. [c] Methyl derivative **15**. [d] Methinyl derivative **16**.

That formation of the ketone enol acetates **2** and **4a** and **b** requires the presence of proton acid (see eq 2) is supported, not only by Bedoukian's[4] preparation of such compounds from methylene ketones and acetic anhydride by means of *p*-toluenesulfonic acid, but also by our observation that the relative extent of O acetylation accompanying C acetylation of methyl methylene ketones by means of boron trifluoride is dependent upon the strength and/or amount of proton acid present (see next section).

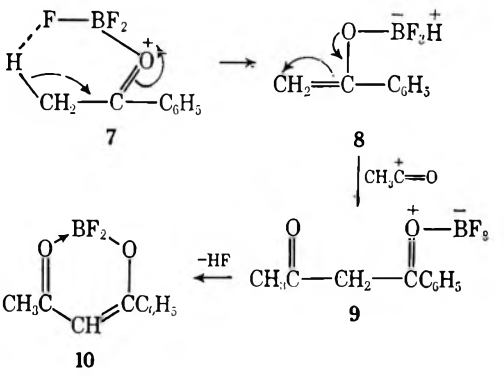
In contrast to cyclohexanone and the other methylene ketones considered above, acetophenone underwent C acetylation with acetic anhydride in the presence of boron trifluoride apparently without appreciable O acetylation. Thus none of the enol acetate of acetophenone was isolated from, nor could any be detected by vpc in, the product obtained from this methyl ketone, acetic anhydride, and the reagent under the conditions that afforded the enol acetates of the methylene ketones **2** and **4a** and **b**. Moreover, Bedoukian[4] was unable to prepare the enol acetate of acetophenone with acetic anhydride in the presence of *p*-toluenesulfonic acid under the conditions that produced the enol acetates of certain methylene ketones.

The mechanism of direct C acetylation of acetophenone, as well as that of other ketones, probably involves the conversion of both the anhydride and ketone into reactive intermediates. The intermediate from the anhydride would presumably be a carbonium ion (as in a Friedel–Crafts acylation) and that from the ketone is suggested to be an enol-type complex such as **8**, the formation of which is perhaps initiated by hydrogen bonding as indicated in **7**. Condensation of the enol-type complex **8** with the carbonium ion would form the boron trifluoride complex of the β diketone (**9**), which eliminates hydrogen fluoride to give the boron difluoride complex **10** (Scheme I).[5]

That acetophenone was converted by boron trifluoride into an enol-type intermediate such as **8** was supported by α bromination of this ketone in the presence of this reagent but not in its absence. That the β diketone boron trifluoride complex **9** was produced as an intermediate was indicated by evolution of some hydrogen fluoride (etching of glass) from the crude reaction product to afford the relatively stable boron difluoride complex **10** (see Experimental Section).

Since boron trichloride and aluminum chloride have failed to effect acetylations of ketones,[6] success with

SCHEME I



boron trifluoride is suggested to be associated with a greater tendency for hydrogen bonding in the boron trifluoride complex **7** and/or a less tendency for loss of hydrogen fluoride from the enol-type complex **8** compared with those of corresponding complexes from the boron and aluminum chlorides. The presence of the negative charge on the boron in **8** should make **8** a better donor in its condensation with the carbonium ion than a neutral complex that might arise through loss of hydrogen halide.

Acetylation of Methyl Methylene Ketone.—Acetylation of methyl methylene ketones **11** by means of boron trifluoride may form the methyl and methylene derivatives **12** and **13**, and that of methyl isopropyl ketone (**14**) the methyl and methinyl derivatives **15** and **16**, respectively. The relative yields of the isomeric products obtained under various conditions are summarized in Table I.

CH_3COCH_2R **11** $CH_3COCH_2COCH_2R$ **12** $CH_3COCHRCOCH_3$ **13**

$CH_3COCH(CH_3)_2$ **14** $CH_3COCH_2COCH(CH_3)_2$ **15**

$CH_3COC(CH_3)_2COCH_3$ **16**

Table I shows that the relative proportion of the methyl and methylene derivative produced on acetylation of a methyl methylene ketone is dependent, not only on the structure of the ketone as previously observed,[7] but also on the conditions employed. Thus, with a particular methyl methylene or methyl methinyl ketone (**11** or **14**, respectively), relatively more of the methyl derivative (**12** or **15**) and relatively less of the methylene or methinyl derivative (**13** or **16**) were produced by fast saturation of the reaction mixture

(4) P. Z. Bedoukian, *J. Amer. Chem. Soc.*, **67**, 1430 (1945).

(5) Since little etching of the glass apparatus occurred, the eliminated hydrogen fluoride was apparently converted by boron trifluoride into HBF_4, which was neutralized by the oxygen compounds to form oxonium salts.

(6) B. M. Perfetti and R. Levine, *ibid.*, **75**, 626 (1953); H. G. Walker, J. J. Sanderson, and C. R. Hauser, *ibid.*, **75**, 4109 (1953).

(7) C. R. Hauser and J. T. Adams, *ibid.*, **66**, 345 (1944).

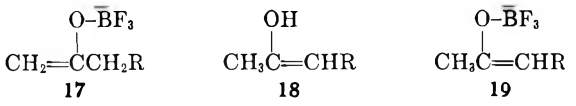
TABLE II
YIELDS OF β-DIKETONES FROM KETONES AND ACETIC ANHYDRIDE BY BORON TRIFLUORIDE–DIACETIC ACID COMPLEX (BTDA)

Ketone	β Diketones	Registry no.	Bp (mm) or mp, °C	Yield, %	Previous methods, % BF_3[a]	Previous methods, % Bases[b]
2-Butanone	3-Methyl-2,4-pentanedione	815-57-6	92–93 (68)	48[c]	32	9
2-Pentanone	3-Ethyl-2,4-pentanedione	1540-34-7	85–87 (21)	57[c,d]	31	2
2-Heptanone	3-*n*-Butyl-2,4-pentanedione	1540-36-9	94–96 (9)	74[c]	74–77	<1
Phenylacetone[e]	3-Phenyl-2,4-pentanedione	5910-25-8	56–58	68[d]	41–63	10–23
3-Methyl-2-butanone	3,3-Dimethyl-2,4-pentanedione	3412-58-3	93 (40)	40–47[c,d]	19	
Cyclohexanone	2-Acetylcyclohexanone	874-23-7	115–117 (20)	73[c]	75–86	35
Cyclopentanone	2-Acetylcyclopentanone	1670-46-8	101–103 (24)	80[c]	59–76	
Diethyl ketone	3-Methyl-2,4-hexanedione	4220-52-4	98–100 (30)	81[c]	62	16–45
Dibenzyl ketone	1,3-Diphenyl-2,4-pentanedione	19588-08-0	64–66	72		
Acetophenone	Benzoylacetone	93-91-4	55–57	70	70–83	65–70

[a] See ref 2, pp 131, 133, and 186. [b] See ref 2, pp 136–139. [c] Vpc pure. [d] Obtained in the presence of 5–10 mol % of *p*-toluenesulfonic acid. [e] Purified through its sodium bisulfite addition product.

with boron trifluoride gas than by slow saturation[8] or when the boron trifluoride–diacetic acid complex (BTDA) was employed; this was especially true when the two latter procedures were used in the presence of a catalytic amount of *p*-toluenesulfonic acid (see footnote *b*, Table I). Moreover, when the fast saturation procedure was employed with methyl *n*-amyl ketone and acetic anhydride and the reaction mixture worked up after only 15 min, the proportion of methyl derivative was considerably greater (40%) than that (26%) obtained after the usual 2-hr period.

These results are explained by the dual formation of β diketones considered above. Evidently, all of the methyl derivative **12** from each of the three methyl *n*-alkyl ketones listed in Table I was produced by direct C acetylation through the boron trifluoride–enol-type complex **17**, since only the methylene derivative **13** should be expected by the indirect O acetylation of such ketones which are known to undergo proton-catalyzed enolization of only methylene hydrogen to form enols **18** as intermediates.[4] Although some of the methylene derivative **13** may have been produced by direct C acetylation through the boron trifluoride–enol complex **19**, most of **13** probably arose by O acetylation through enols **18** especially in the slow saturation and BTDA procedures.



17 **18** **19**

Interestingly, to the extent that the methyl derivative **12** was formed from the methyl *n*-alkyl ketones, and this amounted to 14–36% in the fast saturation procedure (see Table I), the presumably less stable boron trifluoride–enol complex **17** was the intermediate. A possible explanation for this is that hydrogen bonding with fluorine initiates some ionization of an α hydrogen of the methyl group (see **7**, Scheme I). Presumably, such hydrogen bonding also initiates some ionization of an α hydrogen of the methylene group to form the more stable complex **19** but the extent of its formation was not evident since the methylene derivative **13** probably arose by both courses of reaction. The above observation that the proportion of methyl derivative **12** (R = n-C_4H_9) was greater in the fast saturation procedure after 15 min than after 2 hr may be explained by occurrence of relatively more direct C acetylation during the shorter period before generation of much by-product proton acid, which promoted O acetylation leading to methylene derivative **13** (R = n-C_4H_9). Also, some isomerization of intermediate complex **17** to the more stable complex **19** may have occurred during the longer period.

With regard to the influence of the structure of the ketone on the relative proportions of the isomeric β diketone form the methyl methylene ketones, the percentage of the methyl derivative in both the fast and slow saturation procedures increased and that of the methylene derivative decreased as the number of β hydrogens on the methylene side of the ketone was decreased as in the ketone series: methyl ethyl, methyl *n*-alkyl, methyl isobutyl, and methyl neopentyl. The last ketone afforded exclusively the methyl derivative (see Experimental Section). A similar effect of structure of the ketone on the proportions of the methyl and methylene derivatives has previously been observed in O acetylations of methyl methylene ketones with isopropenyl acetate to form ketone enol acetates.[9]

When methyl *n*-amyl ketone was acylated with propionic or butyric anhydride by means of boron trifluoride (slow saturation) in the presence of a catalytic amount of *p*-toluenesulfonic acid, both the methyl and methylene derivatives were produced, the approximate ratio being 25:75. Apparently, the O acylation of the ketone was slower with these higher anhydrides than with acetic anhydride, with which only the methylene derivative was obtained under similar conditions (see Table I).

Improved Method of Synthesis for Certain β Diketones.—Although boron trifluoride gas produces good yields of many β diketones from ketones and acetic anhydride especially when this reagent is first coordinated with ethyl acetate or acetic acid (as monoacid complex),[10] the commercially available boron trifluoride–diacetic acid complex (BTDA) is recommended, since it generally affords equally good or better yields and is more convenient to employ. In Table II are summarized the yields of β diketones obtained using BTDA (in some cases in the presence of *p*-toluene-

(8) For similar relative proportions of the methyl methylene or methyl methinyl derivatives obtained previously employing slow saturation, and an alkali extraction procedure for separation of the isomers, see ref 7.

(9) E. H. Man, F. C. Frostick, Jr., and C. R. Hauser, *J. Amer. Chem. Soc.*, **74**, 3228 (1952).

(10) R. M. Manyik, F. C. Frostick, Jr., J. J. Sanderson, and C. R. Hauser, *ibid.*, **75**, 5030 (1953); see also ref 2, pp 129–134.

sulfonic acid) and also the yields realized previously with boron trifluoride or a base.

Table II shows that, with the exception of the acetylation of acetophenone, the acetylations listed in Table II have been realized in poorer yields by means of a basic reagent, with which ethyl acetate is generally employed. Whereas boron trifluoride (as gas or BTDA) produces the methylene or methinyl derivatives of the methyl methylene or methyl methinyl ketones listed in Table II, bases produce mainly the methyl derivatives.[11]

BTDA was found unsatisfactory for effecting the propionylation of methyl *n*-amyl ketone with propionic anhydride because of accompanying anhydride–acetic acid exchange leading to formation of a mixture of the propionyl and acetyl methylene derivatives of the ketone; the relative proportions of these two derivatives and of unchanged ketone were 60:33:7 (by vpc). Propionylation could presumably be realized satisfactorily, however, with a complex of boron trifluoride and propionic acid.

Experimental Section[12]

Isolation of Ketone Enol Acetates. A. From Cyclohexanone.—A stirred mixture of 0.3 mol of cyclohexanone and 0.6 mol of acetic anhydride at 0° was treated, during 15 min, with about 14 mol % of boron trifluoride gas (determined by increase in weight of the reaction flask and contents). After stirring and cooling for 2 hr, the reaction mixture was poured into sodium acetate solution at room temperature, and the resulting mixture was extracted with ether. The combined ethereal extract was washed free of acid with saturated sodium bicarbonate solution, followed by water, and dried (Drierite). The solvent was removed, and the residue was distilled to give 3.1 g (22%) of cyclohexenyl acetate (**2**), bp 74–77° (17 mm) [lit.[4] bp 74–76° (17 mm)].

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.46; H, 8.27.

In another experiment, a mixture of 0.1 mol of cyclohexanone, 0.2 mol of acetic anhydride, and 0.015 mol of boron trifluoride–diacetic acid complex (BTDA)[13] was stirred at 0–10° for 2 hr. The reaction mixture was then treated with water and worked up as described above to give 2.1 g (15%) of **2**, bp 73–76° (17 mm); the vpc retention time of this product was identical with that of an authentic sample of enol acetate **2**.[4]

A mixture of this product **2** (1.4 g, 0.01 mol) and acetic anhydride (0.02 mol) was saturated with boron trifluoride at 0–10°, and the reaction mixture decomposed with hot sodium acetate[2,10] to give 0.75 g (76%) of 2-acetycyclohexanone, bp 94–96° (10 mm) [lit.[9] bp 95–98° (10 mm)]; the vpc retention time of this product was identical with that of an authentic sample.

B. From Methyl Ethyl Ketone.—To a stirred mixture of 0.3 mol of this ketone and 0.6 mol of acetic anhydride at 0–10° was added 10 mol % of boron trifluoride gas as described under A to give 1.1 g (3%) of ketone enol acetate **4a**, bp 117–121° (750 mm) [lit.[14] bp 118–120° (751 mm)].

This product was treated with acetic anhydride and excess boron trifluoride at 0–10°, followed by sodium acetate solution, to give boron difluoride complex **6** of 3-methyl-2,4-pentanedione, mp and mmp 93.5–94.5° (lit.[3] mp 94–94.5°).

C. From Methyl *n*-Amyl Ketone.—A mixture of 0.3 mol of methyl *n*-amyl ketone and 0.6 mol of acetic anhydride was treated with boron trifluoride gas as described under A to give 2.35 g (5%) of enol acetate **4b**, bp 60–64° (10 mm) [lit.[4] bp 75–76° (17 mm)].

This product was treated with acetic anhydride and boron trifluoride, followed by sodium acetate, to afford 3-*n*-butyl-2,4-pentanedione, bp 104–106° (20 mm), which gave the gray copper chelate, mp 184–185° (lit.[7] mp 185–186°).

Isolation of β Diketone Enol Acetates. A. From Cyclohexanone.—A stirred mixture of 0.5 mol of cyclohexanone and 1.0 mol of acetic anhydride at −30 to −20° was saturated, during 40 min, with boron trifluoride gas. After stirring for 80 min longer at the same temperature, the reaction mixture was hydrolyzed with hot sodium acetate solution and worked up. There was isolated, besides recovered cyclohexanone, 16.5 g (16%) of the enol acetate of 2-acetylcyclohexanone (**3**), bp 130–135° (12 mm).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C 66.01; H, 7.80.

In another experiment, 0.25 mol of the ketone and 0.5 mol of the anhydride were used to give 8% of the enol acetate of 2-acetylcyclohexanone (**3**), bp 126–129° (10 mm).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.82; H, 8.01.

When the reaction was carried out at 0°, none of the β diketone enol acetate **3** was isolated; instead, some 2-acetylcyclohexanone was obtained.

A sample (0.025 mol) of β-diketone enol acetate **3** was added, during 3 min, to stirred boron trifluoride diacetaic acid complex (BTDA)[13] (0.03 mol) cooled in an ice bath. After 30 min, the reaction mixture was warmed to 50–70° and the evolved gas was collected in a trap cooled in a Dry Ice–acetone bath. The liquid in the trap was identified as acetyl fluoride: bp *ca.* 20° (lit.[15] bp 20–21°); ir (gas) 1870 (C=O) [lit.[15] 1869 and 1180 cm^{-1} (CF)]. This product reacted readily with aniline to give acetanilide, mp and mmp 113–115°.

The colored semisolid remaining in the flask was decolorized with activated charcoal and recrystallized from glacial acetic acid to give boron difluoride complex 1 of 2-acetylcyclohexanone, mp and mmp 77–79°, yield about 35%.

B. From Methyl Ethyl Ketone.—A stirred mixture of 0.25 mol of this ketone and 0.5 mol of acetic anhydride at 0–10° was saturated, during 10 min, with boron trifluoride gas. After 1 hr at the same temperature, the reaction mixture was worked up to give 3.8 g (10%) of the enol acetate of 3-methyl-2,4-pentanedione (**5a**), bp 115–117° (30 mm) [lit.[3] bp 115–117° (30 mm)].

This compound (**5a**) was added to excess boron trifluoride–monoacetic acid complex[10] at 0°. After stirring for 2 hr, the reaction mixture was heated on the steam bath until the vapor temperature reached 50°. The material which had collected in a trap cooled in a Dry Ice–acetone bath was redistilled to give acetyl fluoride, bp 22°, in about 50% yield.

C. From Methyl *n*-Amyl Ketone.—A mixture of this ketone (0.2 mol) and acetic anhydride (0.4 mol) at 0–10° was saturated during 10–15 min, with boron trifluoride gas, and the reaction mixture was worked up to give 6.4 g (16%) of the enol acetate of 3-*n*-butyl-2,4-pentanedione (**5b**), bp 114–117° (10 mm).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.96; H, 8.88.

This product was treated with boron trifluoride, followed by sodium acetate, to give 3-*n*-butyl-2,4-pentanedione, bp 104–106° (20 mm) [lit.[16] bp 102–106° (20 mm)], in 42% yield.

Isolation of Boron Difluoride Complexes of β Diketones from Methylene Ketones. A. From Cyclohexanone.—To a stirred mixture of 0.1 mol of cyclohexanone and 0.2 mol of acetic anhydride at 0° was added 0.2 mol of boron trifluoride–diacetic acid complex.[13] After being allowed to warm to room temperature during 1 hr, the reaction mixture was poured onto 300 ml of cold water. The resulting precipitate was collected, washed with water, and recrystallized from glacial acetic acid to give 8.2 g (70%) of the boron difluoride complex of 2-acetylcyclohexanone (**1**), mp 79–81°.

Anal. Calcd for $C_8H_{11}BF_2O_2$: C, 51.10; H, 5.90; B, 5.75; F, 20.20. Found: C, 51.29; H, 6.21; B, 5.72; F, 20.27.

(11) See R. Levine, J. A. Conroy, J. T. Adams, and C. R. Hauser, *J. Amer. Chem. Soc.*, **67**, 1510 (1945); also see ref 2, pp 60–88.

(12) Boiling points and melting points are uncorrected. Analyses were by Clark Microanalytic Laboratory, Urbana, Ill., Arlington Laboratories, Fairfax, Va., and Crobaugh Laboratories, Charleston, W. Va. Vpc determinations were made on an F & M Model 500 gas chromatograph using a 15-ft silicone rubber column. Ketones and anhydrides were purified by distillation.

(13) This liquid coordination complex ($BF_3 \cdot 2CH_3COOH$), which contained 36% by weight BF_3, was obtained from Harshaw Chemical Co., Cleveland, Ohio.

(14) B. H. Gwynn and E. F. Degering, *J. Amer. Chem. Soc.*, **64**, 2216 (1942).

(15) J. Overend and J. Scherer, *Spectrochim. Acta*, **16**, 773 (1960).

(16) F. G. Young, F. Frostick, Jr., J. Sanderson, and C. R. Hauser, *J. Amer. Chem. Soc.*, **72**, 3635 (1950).

Similarly, difluoride complex 1 was obtained by treatment of a mixture of cyclohexanone and acetic anhydride with boron trifluoride gas, and the product recrystallized from glacial acetic acid. A sample of the complex was converted into 2-acetylcyclohexanone by means of hot sodium acetate solution.

Also, boron difluoride complex 1 was prepared from 2-acetylcyclohexanone and boron trifluoride gas, and found to be identical with that obtained as described above.

B. From Methyl Ethyl Ketone.—A stirred mixture of 0.25 mol of this ketone and 0.5 mol of acetic anhydride was saturated with boron trifluoride at 0–10°. After 4 hr, the reaction mixture was poured into a solution of 42 g of sodium acetate in 300 ml of water. After cooling in an ice bath for 30 min, the solid was collected and recrystallized from methanol, giving 10.5 g (26%) of the boron difluoride complex of 3-methyl-2,4-pentanedione (6), mp 93.5–94.5° (lit.[3] mp 94–94.5°).

This complex (0.059 mol) was refluxed for 15 min with sodium acetate solution to give 5.0 g (75%) of 3-methyl-2,4-pentanedione, bp 77–79° (30 mm) [lit.[16] bp 75–80° (30 mm)].

Acetylation of Acetophenone. A. Nonformation of Enol Acetate of Ketone.—Attempts to isolate the enol acetate of acetophenone employing acetophenone, acetic anhydride, and either gaseous boron trifluoride or BTDA under the conditions described above for the isolation of enol acetate of cyclohexanone were unsuccessful. In the experiment with BTDA, the material obtained on working up the reaction mixture was shown by vpc to consist of only recovered acetophenone (85%) and benzoylacetone (8%); no third peak in the appropriate region for the enol acetate of acetopheone was observed, indicating that not even a trace of this product was produced.

B. Evidence for Enol-Type Complex 8.—A stirred solution of 6.0 g (0.05 mol) of acetophenone in 40 ml of ethylene chloride at 0–10° was saturated with boron trifluoride gas to produce a white precipitate. After 10 min, 3.0 ml (0.06 mol) of bromine in 10 ml of ethylene chloride was added during 5 min. The brown color was discharged and part of the precipitate was dissolved during the addition of the first few milliliters of the bromine solution. The brownish reaction mixture was refluxed with aqueous sodium acetate (0.1 mol) for 2 hr. After cooling, the resulting mixture was extracted with ether. The ethereal extracts were combined and dried (Drierite), and the solvent was removed. The brownish residue was distilled under vacuum to give 3.0 g (34%) of phenacyl acetate, bp 115–120° (1.5 mm), mp 37–39 and 43–45° after recrystallization from ethanol–petroleum ether (bp 30–60°) (lit.[17] mp 40°). This melting point was not depressed on admixture with authentic phenacyl acetate (mp 44–46°) prepared in 56% yield from phenacyl bromide and sodium acetate. The infrared spectra of the two samples were identical.

A blank experiment carried out with acetophenone and bromine in the absence of boron trifluoride failed to give phenacyl acetate, and 90% of the ketone was recovered.

C. Formation of Boron Trifluoride and Difluoride Complexes of Benzoylacetone.—A solution of 1.0 mol of acetophenone and 2.0 mol of acetic anhydride in 100 ml of ethylene chloride was saturated with boron trifluoride gas at 10° during 2.5 hr. The solid was filtered, washed thoroughly with ether, and dried in air. The product, mp 140–146°, slowly etched glass on standing at room temperature, indicating that it consisted partly of the boron trifluoride complex of benzoylacetone (9). Recrystallization of the product from glacial acetic acid afforded 67.4 g (32%) of the boron difluoride complex of benzoylacetone (10), mp 154–155.5° (lit.[18] mp 154–155°).

Boron trifluoride complex 9 is readily converted into boron difluoride complex 10, especially in the presence of oxygen compounds. When produced from benzoylacetone and boron trifluoride etherate[19] at 0°, crude trifluoride complex 9, mp 136–140°, evolved hydrogen fluoride readily (etched glass) and afforded a difluoride complex 10, mp 154–155°, after recrystallization from glacial acetic acid. When produced in ether at 10–22° or in benzene at 14–20° (but warmed to 35°), the trifluoride complex 9 was converted directly into difluoride complex 10. Even when a solution of 0.3 mol each of benzoylacetone and acetophenone and 0.6 mol of acetic anhydride in 250 ml of ligroin (bp 90–120°) was saturated with boron trifluoride gas below 0°, the solid obtained evidently consisted mainly of difluoride complex 10 with only a little of trifluoride complex 9 since it etched glass very slowly. Recrystallization from glacial acetic acid afforded 10, mp 154–155°.

In an experiment employing BTDA, the pure boron difluoride complex 10, mp 153–155°, was isolated in 39% yield, and converted into benzoylacetone, mp 55–57°, with hot sodium acetate solution.

Relative Proportions of Methyl and Methylene Derivatives from Acetylation of Methyl Methylene Ketones.—In Table I are summarized the relative proportions of isomeric β diketones from acetylation of methyl methylene (or methyl methinyl) ketones obtained under various conditions and determined by vpc. The three procedures employed are indicated below.

A. Fast Saturation Procedure.—A mixture of the ketone (0.1 mol) and acetic anhydride (0.2 mol) was saturated as rapidly as possible (15–20 min) with boron trifluoride gas as described previously.[10] The product was distilled and the distillate analyzed by vpc.[12]

B. Slow Saturation Procedure.—A mixture of the ketone (0.1 mol) and acetic anhydride (0.2 mol) was slowly saturated (during 3–4 hr) with boron trifluoride gas as described previously.[7] The product was distilled and the distillate analyzed by vpc.[12]

Certain of the ketones listed in Table I were also acetylated by this procedure in the presence of 10 mol % or less of *p*-toluenesulfonic acid monohydrate.

Similarly, a mixture of 0.1 mol of methyl neopentyl ketone, 0.2 mol of acetic anhydride, and 0.01 mol of *p*-toluenesulfonic acid monohydrate was stirred for 5–10 min at room temperature, then cooled to 0–10° and saturated slowly with boron trifluoride to give 7.5 g (48%) of 2,2-dimethyl-4,6-heptanedione, bp 97–102° (40 mm) [lit.[9] bp 99° (40 mm)], and copper chelate, mp 117–118° (lit.[9] mp 117–118°). None of the methylene derivative was isolated.

C. Procedure Using BTDA.[13]—To a stirred mixture of 0.1 mol of the ketone and 0.2 mol of acetic anhydride cooled in a water bath at room temperature was added rapidly 0.2 mol of BTDA.[13] Some heat was generated. After stirring at room temperature overnight (about 12 hr), the reddish brown reaction mixture was poured onto a solution of 0.4 mol of sodium acetate in 300 ml of water, and the resulting mixture was refluxed for 1–3 hr. The product was extracted three times with ether and the extracts were combined. The ethereal solution was washed free of acid with saturated sodium bicarbonate solution and dried (Drierite). The solvent was removed and the residue was distilled under vacuum. The distillate was analyzed by vpc.[12]

Improved Method of Synthesis of Acetyl Derivatives of Methylene or Methinyl Ketones.—In Table II are summarized the yields of β diketones obtained from acetylation of methylene or methinyl ketones and acetophenone employing boron trifluoride–diacetic acid complex (BTDA),[13] as described in the preceding section C. These yields were based on products that were pure by vpc.[12] The products were identified by agreement of the boiling point or melting point with reported values and/or by vpc.

Although a reaction period of about 12 hr was generally employed, shorter reaction periods afforded only about 8–13% lower yields in the acetylation of cyclohexanone; thus the yields of 2-acetylcyclohexanone after 5 min, 30 min, and 1 hr were 60, 62, and 65%, respectively. Also, acetylation of phenylacetone to form 3-phenyl-2,4-pentanedione was realized in about 50% yield after 4 hr, compared with the 68% yield after 12 hr. However, acetylation of methyl *n*-amyl ketone during 1 hr produced 3-*n*-butyl-2,4-pentanedione in only 10% yield (see Table II).

Registry No.—Acetic anhydride, 108-24-7; boron trifluoride, 7637-07-2; **1**, 19613-66-2; **3**, 14768-84-4; **5b**, 19588-00-2.

(17) J. B. Ruther and E. E. Reid, *J. Amer. Chem. Soc.*, **41**, 75 (1919).
(18) G. Morgan and R. Tunstall, *J. Chem. Soc.*, **125**, 1963 (1924).
(19) See H. Meerwein and D. Vossen, *J. Prakt. Chem.*, **141**, 149 (1934).

Use of Ketoxime Derivatives to Prepare α-Acetoxy Ketones[1a]

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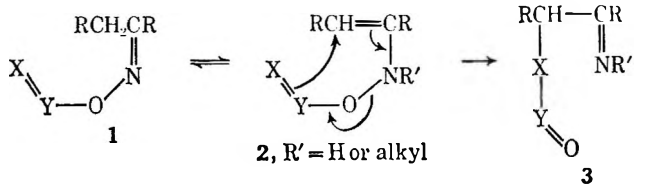
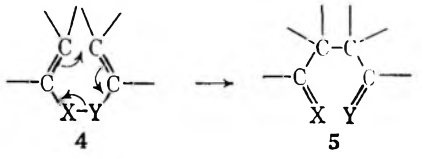
The O-acetyl derivatives of oximes from 4-heptanone (**10**), deoxybenzoin (**11**), dibenzyl ketone (**12**), cyclohexanone (**13**), 2-methylcyclohexanone (**38**), and *p*-nitrobenzyl *p*-methoxybenzyl ketone (**37**) have been prepared. Successive reactions of each of these oxime acetates with trimethyloxonium fluoroborate, triethylamine, and aqueous acid yielded an α-acetoxy ketone. Evidence is presented to support the idea that these transformations proceed *via* a facile Claisen-type rearrangement of an intermediate N-acetoxyenamine. In the cases of cyclohexanone and 2-methylcyclohexanone, a related rearrangement was effected by reaction of the ketones with the hydrochloride salt of O-acetyl-N-methylhydroxylamine (**28**). With unsymmetrical ketones, the proportions of structurally isomeric α-acetoxy ketones produced were not influenced by the stereochemistry of the starting oxime acetate.

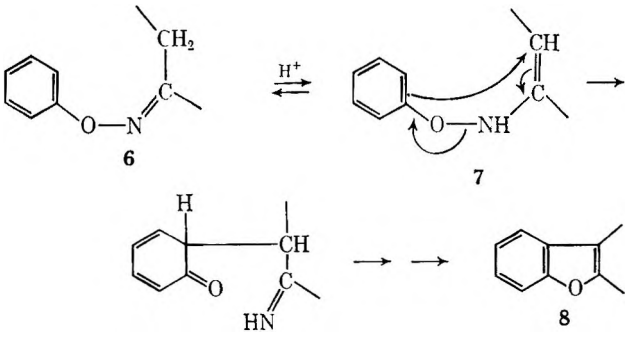
In earlier studies of the reactions of oxime arylsulfonates,[2] the formation of α-sulfonoxy ketones as by-products in several reactions suggested the possibility of a general rearrangement of O-substituted oximes **1** by way of the corresponding enamines **2** to form α-substituted imines **3**. Such rearrangements (**2** → **3**) would



be examples of the general rearrangement **4** → **5** of 1,5-dienes and analogous compounds of which the Claisen and Cope rearrangements are best known.[3] Studies[3] of



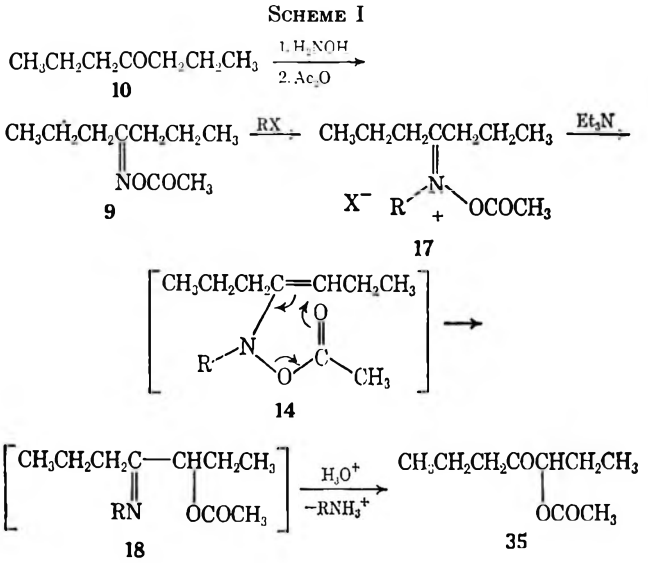
this concerted rearrangement **4** → **5** have indicated that any factors which will diminish the strength of the X–Y single bond in **4** will also facilitate rearrangement. Consideration of the average bond energy values[4] of pertinent single bonds [C–C (83 kcal/mol), C–N (70 kcal/mol), C–O (84 kcal/mol), N–N (38 kcal/mol), N–O (48 kcal/mol)] supports the idea that the rearrangement **4** → **5** will be especially favorable when the X–Y bond is either N–O or N–N. Examples of ready rearrangement involving N–N bond cleavage are presumably provided by the Fischer synthesis of indoles and by the related reaction of N,N′-divinylhydrazine derivatives.[5] Examples of rearrangement with concurrent N–O bond cleavage have been provided by recent studies of the acid-catalyzed



rearrangement of aryl ethers of oximes (*e.g.*, **6**) to form benzofurans **8**[6] in a reaction analogous to the Fischer indole synthesis.

We elected to study the reaction with O-acetyl derivatives of oximes (*e.g.*, **9**) since the anticipated reaction sequence (Scheme I) offered a potentially useful syn-

SCHEME I



thetic method for converting a ketone into the corresponding α-acetoxy ketone. Furthermore, the possibility existed the the configuration of an unsymmetrical ketone oxime could be used to determine the position of substitution by the acetoxyl group. For our initial studies we used ketones **10**–**13** which either were symmetrical or possessed only a single α-carbon atom capable of undergoing substitution.

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(2) (a) H. O. House and W. F. Berkowitz, *J. Org. Chem.*, **28**, 307, 2271 (1963); (b) for a recent review, see C. O'Brien, *Chem. Rev.*, **64**, 81 (1964).

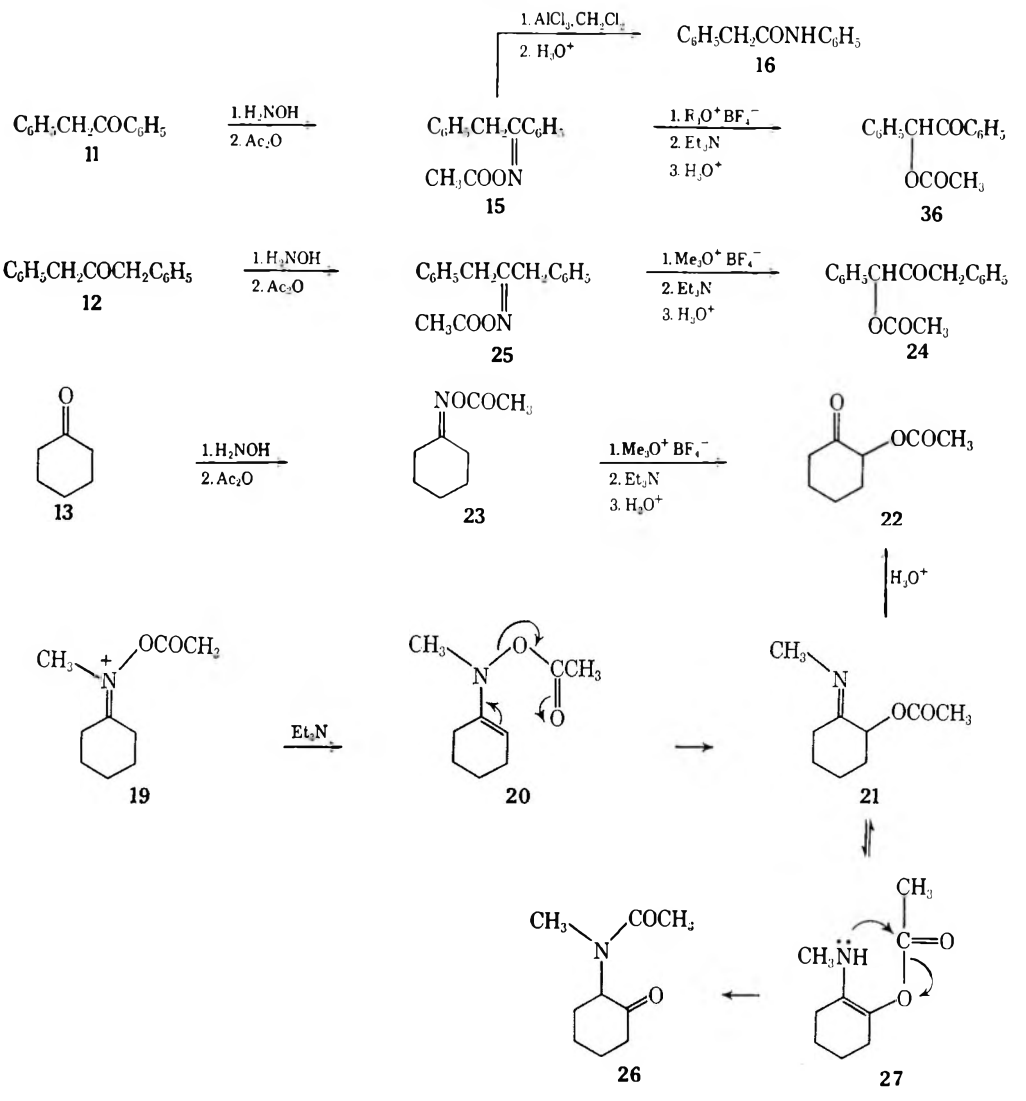
(3) For recent reviews, see (a) S. J. Rhoads, "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, pp 655–706; (b) E. Vogel, *Angew. Chem, Intern. Ed. Engl.*, **2**, 1 (1963); (c) G. Schröder, J. F. M. Oth, and R. Merenyi, *ibid.*, **4**, 752 (1965).

(4) Data from F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience Publishers, New York, N. Y., 1962, p 88.

(5) N. V. Sidgwick, I. T. Millar, and H. D. Springall, "The Organic Chemistry of Nitrogen," 3rd ed, Clarendon Press, Oxford, 1966, pp 623, 644–647.

(6) (a) T. Sheradsky, *Tetrahedron Lett.*, 5225 (1966); (b) A. Mooradian, *ibid.*, 407 (1967); (c) D. Kaminsky, J. Shavel, Jr., and R. I. Meltzer, *ibid.*, 859 (1967); (d) A. Mooradian and P. E. Dupont, *ibid.*, 2867 (1967).

Scheme II



To permit rearrangement, it was apparent that the starting oxime acetate (*e.g.*, **9**) must be converted into an enamine (*e.g.*, **14**). Although this conversion might in principle be accomplished by an acid- or base-catalyzed tautomerization of the oxime acetate to an enamine structure (*e.g.*, **14**, R = H), the use of aqueous or alcoholic solutions of acids or bases to accomplish this change would be complicated by the ready hydrolysis (or alcoholysis) of the oxime acetates to form the oximes. Treatment of oxime acetate **15** with aluminum chloride promoted not the desired rearrangement, but rather a Beckman rearrangement to form amide **16** (Scheme II). We therefore examined reactions of the oxime acetates **9** and **15** with alkylating agents to form the corresponding imminium salts (*e.g.*, **17**) since deprotonation of these salts should yield the enamines (*e.g.*, **14**). Although reactions of these oxime acetates with methyl iodide, methyl tosylate, and dimethyl sulfate were very slow even at elevated temperatures, the alkylation could be effected with the very reactive triethyloxonium and/or trimethyloxonium fluoroborate salts[7] in methylene chloride or nitromethane. The progress of the alkylation reaction could be followed in the infrared by observing the replacement of the band at 1760–1775 cm^{-1} (C=O of oxime acetate) by a new band at 1820 cm^{-1} which we attribute to the carbonyl stretching vibration of an acetoxyimminium salt.[8] From these measurements we concluded that the alkylations were accomplished most efficiently with solutions of trimethyloxonium fluoroborate in nitromethane, a reaction time of 2–3 hr at 25° being sufficient.

The direct addition of solutions of these imminium salts (*e.g.*, **17**) to water produced a small amount of rearranged α-acetoxy ketone; however, the major product was the starting ketone from competing hydrolysis rather than deprotonation of the imminium salt. This difficulty was overcome by adding the solution of imminium salt to anhydrous triethylamine and then hydrolyzing the reaction mixture with aqueous acid. By use of this procedure the desired enamine (*e.g.*, **14**) was apparently produced in the triethylamine solution and then underwent rapid rearrangement to form the intermediate α-acetoxyimine (*e.g.*, **18**). In an effort to learn how rapidly the rearrangement **20** → **21** occurred, solutions of imminium salt **19** were quenched in triethylamine at 0–10° and then hydrolyzed after relatively short reaction periods. As summarized in Table

(7) H. Meerwein in Houben-Weyl's "Methoden der organischen Chemie," Vol. 6, part 3, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, Germany, 1965, p 329.

(8) The carbonyl stretching frequency for N-acetoxypyridinium salts is found at 1804–1830 cm^{-1}: V. J. Traynelis, A. I. Gallagher, and R. F. Martello, *J. Org. Chem.*, **26**, 4365 (1961); C. W. Muth and R. S. Darlak, *ibid.*, **30**, 1909 (965).

TABLE I

VARIATION IN PRODUCT YIELDS WITH REACTION CONDITIONS FOR DEPROTONATION AND SUBSEQUENT HYDROLYSIS OF THE PRODUCTS FROM IMMINIUM SALT 19

Reaction time and temperature before hydrolysis	Products, % yield[a]		
	Cyclohexanone	Acetoxy ketone 22	Amide 26
1 min at 5–10°	4	38	<1
10 min at 5–10°	4	30	<1
30 min at 5–10°	3	46	17
45 min at 5–25°	3	51	16
150 min at 25°	2	13	41
240 min at 25°	*b*	*b*	44[b]
Direct hydrolysis without Et_3N treatment	55	3	<1

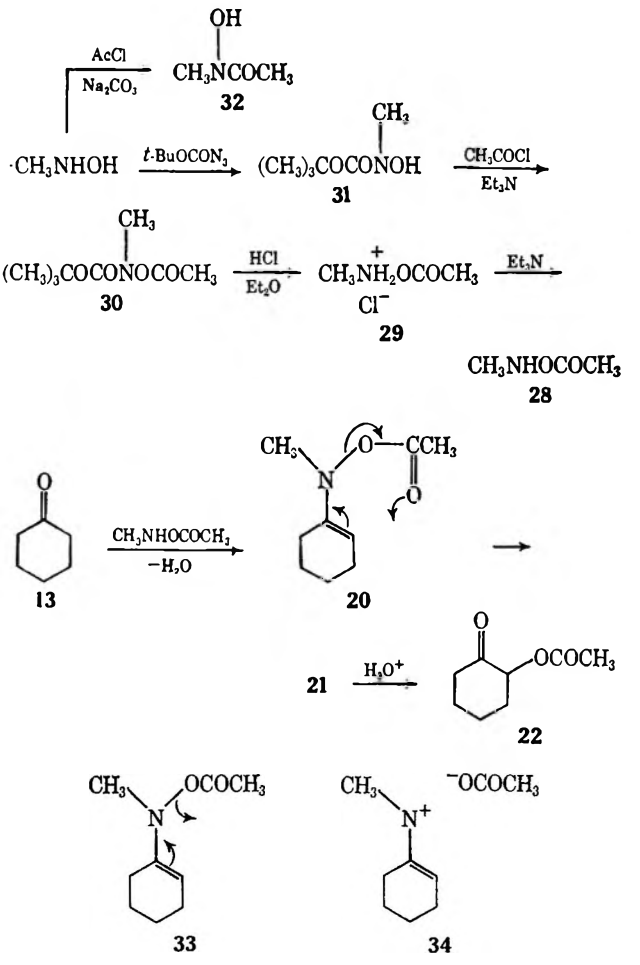
[a] Unless otherwise noted, the yields were determined by gas chromatographic analysis. [b] In this case the product was fractionally distilled to isolate keto amide 26 and the isolated yield is tabulated.

I, the half-life for rearrangement of the acetoxyenamine **20** at 5–10° is less than 30 sec. If the rearrangement is assumed to be a first-order process with a normal frequency factor, the maximum activation energy for rearrangement is approximately 20 kcal/mol. Of incidental interest was the observation that use of relatively long reaction periods prior to hydrolysis yielded significant amounts of a by-product, keto amide **26**. As indicated in Scheme II, we believe this by-product arises from an intramolecular O → N acetyl transfer (structure **27**) which becomes a serious side reaction if the initially formed acetoxyimine **21** is not hydrolyzed promptly. The formation of this by-product provides support for the intermediacy of acetoxyimine **21** in the formation of acetoxy ketone **22**.

Since it was not practical to follow the reaction of the imminium salts (*e.g.*, **19**) with triethylamine by spectrometric methods, we sought to obtain evidence for the intermediacy of acetoxyenamine **20** by generating this structure in a different way. For this purpose, O-acetyl-N-methylhydroxylamine (**28**) and the corresponding salt **29** were prepared as indicated in Scheme III.[9] Although O-acetyl derivative **28** underwent the characteristic[9] transacetylation to form N-acetyl derivative **32**, the corresponding hydrochloride salt **29** was relatively stable permitting a study of the reaction of O-acetyl salt **29** with cyclohexanone (**13**) in the presence of molecular sieves to remove water. The probable intermediate, enamine **20**, presumably rearranges as previously indicated (**20** → **21**) since acetoxy ketone **22** was formed upon hydrolysis. This combination of data therefore argues strongly that the rearrangement of acetoxyenamines (*e.g.*, **14** and **20**) occurs rapidly and can form the basis for the synthesis of α-acetoxy ketones. Our data, which do not include ^{18}O-labeling studies, do not provide compelling evidence that the rearrangement has occurred by a six-centered process (*e.g.*, **20**) rather than by a four-centered rearrangement (*e.g.*, **33**) or by an ionization–recombination sequence (*e.g.*, **34**). However, we regard these possibilities as distinctly less probable especially in view of the earlier cited behavior of O-aryl oximes **6** which apparently rearrange by a six-centered transition state **7** even at the expense of losing the resonance energy of a benzene ring.

(9) This preparative route is an adaptation of the route described by L. A. Carpino, C. A. Giza, and B. A. Carpino, *J. Amer. Chem. Soc.*, **81**, 955 (1959).

SCHEME III



To examine the selectivity of this acetoxylation procedure with unsymmetrical ketones, we chose ketones **37** and **38** (Scheme IV) for study. The stereoisomeric oximes **39a** and **40a** had been separated and characterized previously.[2a] Only one crystalline oxime of ketone **38** had been reported previously;[10] this material is believed to be the less-hindered isomer **41a** based on its Beckmann rearrangement to form lactam **46** when treated with concentrated H_2SO_4.[11] We have repeated this rearrangement (**41a** → **46**) under milder conditions (PCl_5 in methylene chloride) as additional support[12] for the stereochemistry **41a** assigned to this oxime, mp 43–44°, and to the derived oxime acetate **41b**. Following a procedure used earlier for the isomerization of the more stable stereoisomer of benzaldoxime to the less stable isomer,[13] oxime **41a** was converted into a mixture of the hydrochloride salts of oximes **41a** and **42a**. The mixture of oximes obtained from these salts was acetylated to yield a mixture of oxime acetates **41b** and **42b**. Although we were unsuccessful in efforts to isolate a sample of the oxime acetate **42b** from this mixture, its composition was readily determined from the nmr spectrum of the mixture.

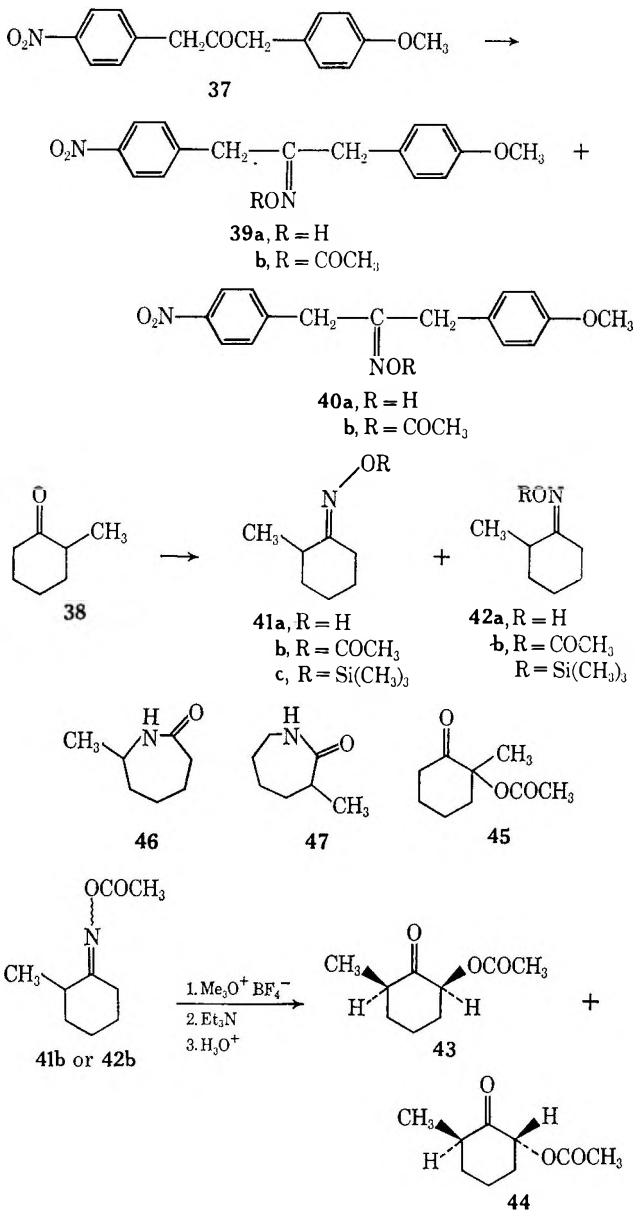
(10) (a) E. Müller, D. Fries, and H. Metzger, *Chem. Ber.*, **88**, 1891 (1955); (b) O. Wallach, *Ann.* **346**, 249 (1906); (c) A. J. N. Hope and S. Mitchell, *J. Chem. Soc.*, 4125 (1954).

(11) (a) J. von Braun and A. Heymans, *Ber.*, **63**, 502 (1930); (b) J. G. Hildebrand and M. T. Bogert, *J. Amer. Chem. Soc.*, **58**, 650 (1936); (c) A. Schaffler and W. Ziegenbein, *Chem. Ber.*, **88**, 1374 (1955).

(12) L. G. Donamura and W. Z. Heldt, *Org. Reactions*, **11**, 1 (1960).

(13) (a) E. Beckmann, *Ber.*, **22**, 429 (1889); (b) O. L. Brady and F. P. Dunn, *J. Chem. Soc.*, 1783 (1923).

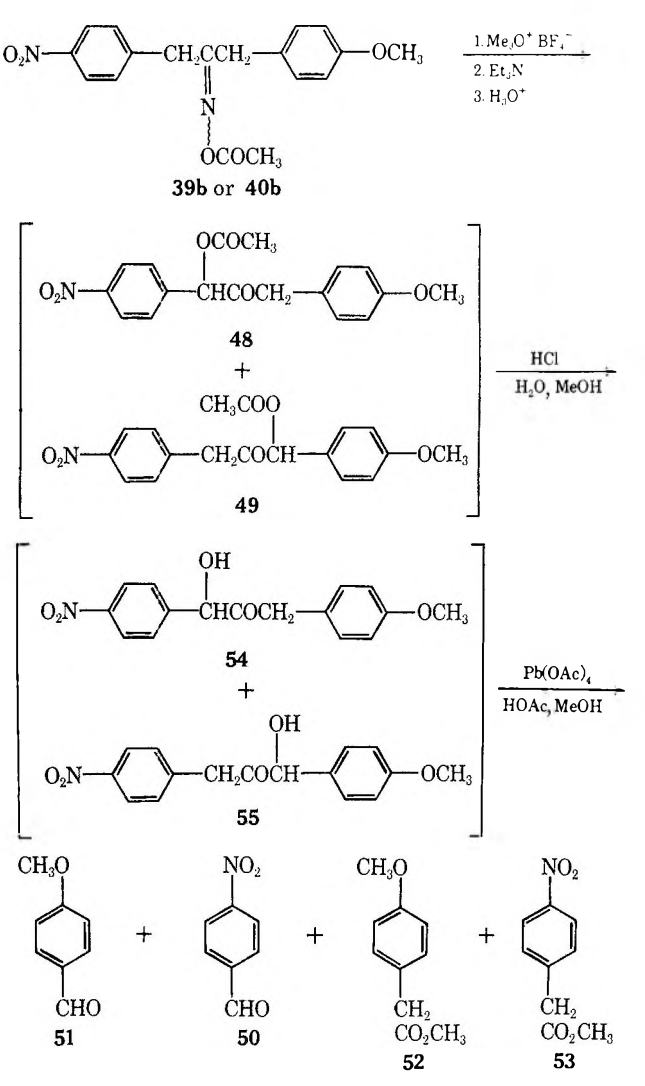
Scheme IV



Application of the usual alkylation–rearrangement sequence either to the pure oxime acetate **41b** or to the mixture of oxime acetates **41b** and **42b** produced, in 41–51% yield, mixtures of stereoisomeric secondary acetoxy ketones **43** and **44** which contained less than 1% of the tertiary acetate **45**. This result is to be contrasted with the acetoxylation of the ketone **38** by reaction with $Pb(OAc)_4$ in benzene[14] which produced a mixture containing 23% of the tertiary acetate **45** and 77% of the secondary acetates **43** and **44**. The reaction of 2-methylcyclohexanone (**38**) with the hydroxylamine salt **29** also produced (25% yield) a mixture containing 56% of the tertiary acetate **45** and 44% of the secondary acetates **43** and **44**.

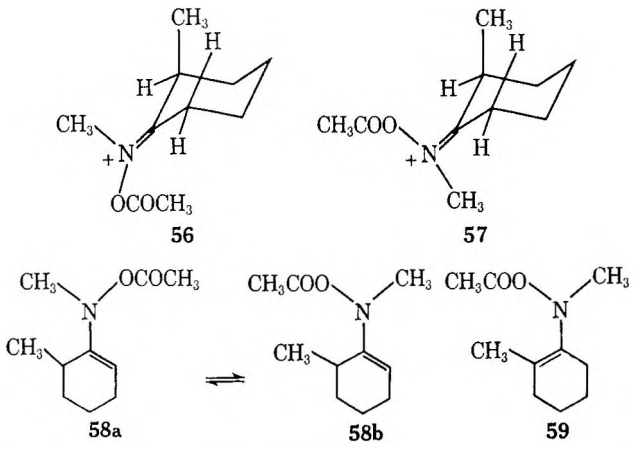
The oxime acetates **39b** and **40b**, obtained from the previously described[2a] oximes **39a** and **40a**, were also subjected to the usual alkylation–rearrangement sequence (Scheme V). Since we were unsuccessful in separating the initial products **48** and **49** from the relatively complex reaction mixture, a hydrolysis and cleavage procedure developed with the related acetoxy ketone **24** was applied to the reaction mixtures to produce mixtures of **50** and **52** from **48** and **54** and mixtures of **51** and **53** from **49** and **55**. Comparable mixtures of these four products, **50–53**, were obtained in low over-all yield (9–16%) irrespective of which oxime acetate isomer **39b** or **40b** served as the starting material.

Scheme V



These latter studies allow us to conclude that the stereochemistry of the starting oxime acetate does not control the position of acetoxylation of an unsymmetrical ketone in the reaction sequence studied here. Instead the position of attack is apparently determined by the position at which the enamine double bond is formed. For example, the addition of either of the salts **56** or **57** (from oxime acetates **41b** and **42b**) to an excess of the base, triethylamine, apparently resulted in the formation of the less highly substituted enamine **58**, which subsequently rearranged to the imine derivative of acetoxy ketones **43** and/or **44**. We attribute the selective formation of a single enamine (**58** not **59**) in this case to the kinetically controlled abstraction of the stereoelectronically favored axial proton from salts **56** and **57** by the relatively basic reaction medium. To minimize steric interactions between the nitrogen substituents and the 2-methyl group, salts **56** and **57** are

(14) The procedure of G. W. K. Cavill and D. H. Solomon, *J. Chem. Soc.*, 4426 (1955). Also see H. B. Henbest, D. N. Jones, and G. P. Slater, *ibid.*, 4472 (1961); J. D. Cocker, H. B. Henbest, G. H. Phillipps G. P. Slater, and D. A. Thomas, *ibid.*, 6 (1965).



56 57

58a 58b 59

expected[15a] to exist very largely in the indicated conformations **56** and **57**.

Exposure of salts **56** and **57** to a weakly acidic medium where equilibration between enamines and immonium salts is rapid[15a,b] would be expected to produce an equilibrium mixture of enamines **58** and **59**. It seems likely that this equilibrium mixture would contain comparable amounts of the two structural isomers as is found with the dimethylaminoenamine of 2-methylcyclohexanone.[15c] In agreement with these expectations, the enamines generated from 2-methylcyclohexane (**38**) and the hydroxylamine salt **29** under weakly acidic conditions afforded the previously noted mixture of structurally isomeric acetates **45** (56% of mixture) and **43** and **44** (44% of mixture).

In the foregoing discussion, it has been assumed that the barrier to rotation about the enamine C–N bond is sufficiently low[16] to permit interconversion of conformations **58a** and **58b** prior to rearrangement of conformation **58a**.

Experimental Section[17]

Preparation of the Oxime Acetates 9, 15, 23, and 25.—The oximes were prepared by reaction of the ketones with a solution obtained from $HONH_3Cl$ and $NaHCO_3$, Na_2CO_3, or KOAc in aqueous MeOH or EtOH. 4-Heptanone oxime was isolated as a colorless liquid: bp 65–65.5° (1.0 mm) or 86–87° (9 mm); $n^{23}D$ 1.4468 [lit.[18] bp 93–94° (15 mm), $n^{20}D$ 1.4486]; ir (CCl_4) 3600, 3260 (free and associated OH), and 1645 cm^{-1} (C=N); nmr (CCl_4) δ 9.50 (1 H, br, OH), 1.9–2.6 (4 H, m, CH_2C=N), and 0.8–1.9 (10 H, m, aliphatic CH); mass spectrum, abundant fragments at *m/e* 98, 70, 57, and 43. 1,3-Diphenyl-2-propanone oxime crystallized from EtOH as white needles: mp 119–122° (lit.[19] mp 120–121°); ir ($CHCl_3$) 3580, 3260 (free and associated OH), and 1655 cm^{-1} (C=N); uv (95% EtOH) series of weak bands in the region 245–270 mμ (ε 305–455); nmr [$(CD_3)_2SO$] δ 6.8–7.5 (10 H, m, aryl CH), 3.56 (2 H, s, $ArCH_2$ *cis* to OH), and 3.38 (2 H, s, $ArCH_2$ *trans* to OH);[20] mass spectrum, weak molecular ion *m/e* 225, abundant fragments *m/e* 210, 182, 107, 106, 91, and 90.

Deoxybenzoin oxime (*syn* benzyl group)[2a,21] separated from EtOH as white needles: mp 94–96° (lit. mp 96–97°,[22] 98°[21]); ir ($CHCl_3$) 3580 and 3270 cm^{-1} (free and associated OH).

A solution of 8.926 g (69.5 mmol) of 4-heptanone oxime, 20.0 ml (21.7 g, 213 mmol) of Ac_2O, and 25 ml of Et_2O was refluxed for 1.4 hr, poured onto ice, and then neutralized with solid $NaHCO_3$. After Et_2O extraction, distillation afforded 10.38 g (87.5%) of the oxime acetate **9** as a colorless liquid, bp 46–47° (0.06 mm), $n^{26}D$ 1.4427, which exhibited only a single component on glpc[23] and tlc;[24] ir (CCl_4) 1775 (ester C=O) and 1640 cm^{-1} (C=N); nmr (CCl_4) δ 2.08 (*ca.* 3 H, s, CH_3CO) superimposed on a 2.0–2.5 m (*ca.* 4 H, CH_2C=N) and 0.7–2.0 (10 H, m, aliphatic CH); mass spectrum, abundant fragments at *m/e* 70, 45, 43, 41, 39, and 29.

Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.00; N, 8.18. Found: C, 63.15; H, 10.00; N, 7.95.

The same procedure with 5.00 g (22.2 mmol) of 1,3-diphenyl-2-propanone oxime, 3.0 ml (3.3 g, 31 mmol) of Ac_2O, and 40 ml of Et_2O (reaction time 2.25 hr) afforded 5.74 g (95.5%) of a crude product, extracted with methylene chloride, which crystallized on standing, mp 34–37°. Recrystallization (Et_2O–pentane) separated 4.366 g (72%) of oxime acetate **25** as colorless prisms: mp 37–39.5°; mp 38–40 after sublimation under reduced pressure; ir ($CHCl_3$) 1765 (ester C=O) and 1635 cm^{-1} (C=N); uv (95% EtOH) series of weak peaks in the region 245–270 mμ (ε 270–485); nmr ($CDCl_3$) δ 7.2–8.0 (10 H, m, aryl CH), 3.80 (2 H, s, $ArCH_2$ *cis* to OAc), 3.74 (2 H, s, $ArCH_2$ *trans* to OAc),[20] and 2.27 (3 H, s, CH_3CO); mass spectrum, abundant fragments at *m/e* 209, 182, 117, 116, 91, 90, 60, 45, and 43.

Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.57; H, 6.40; N, 5.09.

A similar procedure with 8.992 g (79.3 mmol) of cyclohexanone oxime and 10.2 g (100 mmol) of Ac_2O in 50 ml of Et_2O for 16 hr at ambient temperature yielded oxime acetate **23** as 11.58 g (94%) of colorless liquid: bp 73.5–74° (0.25 mm) [lit.[25] bp 130° (20 mm)]; $n^{21}D$ 1.4824, $n^{25}D$ 1.4803; ir (liquid film) 1760 (ester C=O) and 1645 cm^{-1} (C=N); nmr (CCl_4) δ 2.08 (*ca.* 3 H, s, CH_3CO) superimposed on 1.3–2.8 (10 H, m, aliphatic CH).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.74; H, 8.39; N, 9.23.

After reaction of 5.00 g (23.6 mmol) of deoxybenzoin oxime with 7.93 g (75 mmol) of Ac_2O in 60 ml of refluxing Et_2O for 2 hr, distillation at 45–50° (0.1 mm) gave 5.727 g (95.5%) of crude acetate which solidified, mp 44–47°. Recrystallization (Et_2O–hexane) separated 5.457 g (91.5%) of oxime acetate **15** as white prisms: mp 48.5–50°; mp 51.5–52.5° after recrystallization [Et_2O–petroleum ether (bp 30–60°)],[26] ir (CCl_4) 1770 (ester C=O) and 1610 cm^{-1} (conjugated C=N); uv (95% EtOH) 246 mμ (ε 13,200); nmr ($CDCl_3$) δ 7.0–7.9 (10 H, m, aryl CH), 4.20 (2 H, s, CH_2C=N), and 2.17 (3 H, s, CH_3CO); mass spectrum, abundant fragments at *m/e* 103, 91, 77, 76, 60, 51, 50, 45, and 43.

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.56; H, 6.01; N, 5.66.

After a solution of 2.00 g (3.95 mmol) of oxime acetate **15** and 4.0 g (30 mmol) of $AlCl_3$ in 45 ml of CH_2Cl_2 had been stirred under N_2 at 25–30° for 1 hr, the mixture was poured onto ice and then extracted with Et_2O. The crude brown oil (1.864 g) recovered, from the Et_2O extract crystallized from EtOH as 818 mg (48.5%) of phenylacetanilide (**16**), mp 114–116° (lit.[21] mp 117.5°),

(15) (a) F. Johnson, *Chem. Rev.*, **68**, 375 (1968); (b) see H. O. House, B. A. Tefertiller, and H. D. Olmstead, *J. Org. Chem.*, **33**, 935 (1968), and references cited therein; (c) W. D. Gurowitz and M. A. Joseph, *ibid.*, **32**, 3289 (1967).

(16) This rotation barrier is estimated to be in the range 12–21 kcal/mol. See (a) A. Mannschreck and U. Koelle, *Tetrahedron Lett.*, 863 (1967); (b) Y. Shvo, E. C. Taylor, and J. Bartulin, *ibid.*, 3259 (1967).

(17) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated magnesium sulfate was employed as a drying agent. The infrared spectra were determined with a Perkin-Elmer Model 237 infrared recording spectrophotometer fitted with a grating. The ultraviolet spectra were determined with a Cary recording spectrophotometer, model 14. The nmr spectra were determined at 60 mc with a Varian Model A-60 nmr spectrometer. The chemical shift values are expressed either in cycles per second or δ values (parts per million) relative to a tetramethylsilane internal standard. The mass spectra were obtained either with a CEC Model 21-130 or with a Hitachi (Perkin-Elmer) mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates.

(18) (a) E. Muller and H. Metzger, *Chem. Ber.*, **88**, 165 (1955); (b) A. I. Vogel, W. T. Cresswell, G. H. Jeffery, and J. Leicester, *J. Chem. Soc.*, 514 (1952).

(19) C. H. DePuy and B. W. Ponder, *J. Amer. Chem. Soc.*, **81**, 4629 (1959).

(20) G. J. Karabatsos and R. A. Taller [*Tetrahedron*, **24**, 3347 (1968)] have noted that the *cis*-α-methylene protons of ketoximes normally have their nmr peaks about 0.2 ppm at lower field than the *trans*-α-methylene protons.

(21) S. S. Jenkins, *J. Amer. Chem. Soc.*, **55**, 703 (1933).

(22) G. Wittig, F. Bangert, and H. Kleiner, *Ber.*, **61**, 1140 (1928).

(23) A gas chromatography column packed with silicone gum, no. SE-30, suspended on Chromosorb P was employed for this analysis.

(24) A plate coated with silica gel was employed for this analysis.

(25) Z. Csuros, K. Zech, G. Dely, and E. Zalay, *Acta Chim. Hung.*, **1**, 66 (1951); *Chem. Abstr.*, **46**, 5003 (1952).

(26) The preparation and characterization of this substance was performed by Dr. William F. Berkowitz [Ph.D. Dissertation, Massachusetts Institute of Technology, 1963].

identified with an authentic sample by a mixture melting point and comparison of ir spectra. Chromatography (SiO_2) of the residual oil (380 mg) from the mother liquid separated an additional 37 mg (2.5%) of amide **16** (eluted with EtOAc–PhH) and 90 mg of crude solid (eluted with PhH) with ir absorption suggesting the presence of the oxime acetate **15** and deoxybenzoin oxime. The crude product from a comparable experiment was analyzed by glpc[23] (diphenylmethane internal standard). The calculated yield of amide **16** (retention time 25 min) was 51% and no peak was observed corresponding to N-benzylbenzamide (retention time 26 min). The formation of primarily, if not exclusively, amide **16** as a Beckmann rearrangement[12] product is consistent with the formulation of the oxime acetate as **15** ($PhCH_2$ and OAc groups *cis*) corresponding to the known[21] stereochemistry of the starting oxime which was acetylated.

Preparation of O-Acetyl-N-methylhydroxylamine (28).—To a cold (0°) stirred mixture of 10.85 g (75.9 mmol) of *t*-butoxylcarbonyl azide and 6.95 g (83.5 mmol) of N-methylhydroxylamine hydrochloride was added, dropwise over 45 min, a solution of 11.4 g (285 mmol) of NaOH in 100 ml of H_2O. The cooling bath was removed and the resulting mixture was stirred for 3 hr and then partitioned between H_2O and Et_2O. The aqueous phase was acidified (pH 5) with aqueous HCl and extracted with Et_2O, and the extract was dried and concentrated. Distillation of the residual liquid (11.60 g) separated 9.104 g (80.5%) of the **N-hydroxy carbamate 31** as a colorless liquid: bp 50–50.5° (0.30 mm); $n^{28}D$ 1.4298; ir (liquid film) 3250 (br, associated OH) and 1702 cm^{-1} (carbamate C=O); nmr (CCl_4) δ 7.94 (1 H, br, OH), 3.08 (3 H, s, CH_3N), and 1.43 [9 H, s, $(CH_3)_3C$]; mass spectrum, abundant fragments at *m/e* 59, 56, 44, 41, and 39.

Anal. Calcd for $C_6H_{13}NO_3$: C, 48.96; H, 8.90. Found: C, 48.94; H, 8.88.

To a cold (0°) solution of 9.104 g (61.8 mmol) of carbamate **31** and 10.5 ml (7.6 g, 75 mmol) of anhydrous Et_3N in 300 ml of CH_2Cl_2 was added, dropwise and with stirring, 5.00 ml (5.80 g, 70.5 mmol) of AcCl. The resulting mixture was stirred for 50 min at 25–30° and then partioned between aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and distilled to separate 11.06 g (95% of the **N-acetoxy carbamate 30**, a colorless liquid: bp 47–48° (0.7 mm): $n^{28}D$ 1.4182; ir (liquid film) 1795 (acetate C=O) and 1725 cm^{-1} (carbamate C=O); nmr (CCl_4) δ 3.16 (3 H, s, CH_3N), 2.06 (3 H, s, CH_3CO), and 1.43 [9 H, s, $(CH_3)_3C$]; mass spectrum, abundant fragments at *m/e* 59, 57, 56, 44, 43, 41, and 39.

Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 50.62; H, 7.95; N, 7.60.

A solution of 2.066 g (10.6 mmol) of the N-acetoxy carbamate **30** in 10 ml of anhydrous Et_2O was treated with 124 mmol of anhydrous HCl in 40 ml of Et_2O. After the resulting solution stood under N_2 for 67 hr, the white needles which separated were collected, washed with anhydrous Et_2O, and dried under reduced pressure. **N-Acetoxyamine hydrochloride 29** amounted to 1.256 g (95%): mp 109–111° dec; ir (KBr pellet) 1805 cm^{-1} (acetate C=O); nmr (D_2O, partial hydrolysis probably occurred 3.18 (t, J = 10 Hz, Me group of $CH_3N^+H_2OR$) and 2.29 (s, CH_3CO).

A suspension of 164 mg (1.31 mmol) of hydrochloride **29** in 2 ml of CH_2Cl_2 was treated with 0.300 ml (0.217 g, 2.14 mmol) of Et_3N, which converted the initial suspension into a pale yellow solution from which a white solid (presumably $Et_3NH^+Cl^-$) separated. The resulting suspension was stirred at 25–30° and aliquots were removed periodically for ir analysis. After either 10 or 30 min the ir spectrum contained a strong peak at 1740 cm^{-1} (N-acetoxy C=O of **28**) and a very weak peak at 1635 cm^{-1} (C=O of hydroxamic acid **32**). After 16 hr the peaks were of comparable intensity and after 24 hr the peak at 1635 cm was more intense.

As described elsewhere,[27] a cold (0°) solution of 5.273 g (63.0 mmol) of N-methylhydroxylamine hydrochloride and 6.67 g (63.0 mmol) of Na_2CO_3 in 50 ml of MeOH was treated with 4.86 g (63.0 mmol) of AcCl to yield 2.44 g (43%) of **N-methylhydroxamic acid 32** as a colorless liquid: bp 60–62° (0.4 mm); $n^{27}D$ 1.4509 [lit.[27] bp 74–76° (0.8 mm), $n^{23}D$ 1.4512]; ir (liquid film) 3150, 2900 (br, associated OH), and 1620 cm^{-1} (amide C=O); nmr (CCl_4) δ 9.87 (1 H, s, OH), 3.20 (3 H, s, CH_3N), and 2.08 (3 H, CH_3CO).

(27) H. Ulrich and A. A. R. Sayigh, *J. Chem. Soc.*, 1098 (1963).

Conversion of 4-Heptanone Oxime Acetate (9) into the Acetoxy Ketone 35. A. Alkylation with Triethyloxonium Fluoroborate.—To 2.5 ml of a CH_2Cl_2 solution containing 2.48 g (13.0 mmol) of triethyloxonium fluoroborate[28] was added 1.71 g (10 mmol) of oxime acetate **9**. The initially heterogeneous mixture (two liquid phases) was stirred at 25–30° under N_2 for 2 hr at which time a single liquid phase was present. The ir spectrum (CH_2Cl_2) of an aliquot had absorptions of approximately equal intensity at 1760 (starting acetate **9**) and at 1820 cm^{-1} (alkylated acetate **17**).[8] From the ir spectra of aliquots, we concluded that the alkylation reaction (**9** → **17**) was complete after 21 hr at which time the solution was separated into three equal aliquots. The first aliquot was quenched with aqueous $NaHCO_3$ and the organic layer was dried, concentrated, and distilled in a short-path still (1.0 mm, 100° bath). The distillate, 357 mg of straw-colored liquid, was mixed with a known weight of anisole (internal standard) and analyzed by glpc.[29,30] The calculated yields of products were 11% 4-heptanone (**10**, eluted first), 4% acetoxy ketone **35** (eluted second), and *ca.* 10% a peak corresponding in retention time to the Beckmann product, N-propylbutyramide. Collected[29] samples of the ketones were identified with authentic samples by comparison of glpc retention times and ir spectra. The second aliquot of the original reaction mixture was cooled to 0°, treated with 2.0 ml of Et_3N, stirred for 15 min, and poured into H_2O. The crude product was partitioned between CH_2Cl_2 and aqueous HCl and the neutral organic phase was subjected to the previously described isolation and analytical procedure. The calculated[29,30] yields of products were <1% ketone **10**, 9% acetate **35**, and *ca.* 9% N-propylbutyramide. The third aliquot of the original reaction mixture was added to cold (0°) Et_3N and then subjected to the isolation procedure just described. The calculated[29,30] yields were 2% ketone **10**, 23% acetate **35**, and *ca.* 8% N-propylbutyramide.

The reaction was repeated with 36 mmol of triethyloxonium fluoroborate and 4.00 g (23.4 mmol) of oxime acetate **9** in 10 ml of CH_2Cl_2. After 16 hr the resulting mixture was added, dropwise and with vigorous stirring over 50-min, to 40 ml of cold, anhydrous Et_3N. The resulting mixture was stirred for 15 min, treated with excess aqueous 6 *M* HCl, stirred for 30 min, and then the crude product was isolated in the usual way. Analysis[29,30] of the distillate indicated the absence of 4-heptanone, a calculated yield of 60% acetate **35** and the presence of 1–2% a minor component with a retention time corresponding to N-propylbutyramide (the Beckmann rearrangement product expected from 4-heptanone oxime).

An authentic sample of **N-propylbutyramide**, prepared from propylamine and butyryl chloride, was isolated as a colorless liquid: bp 125–126° (15 mm); $n^{25}D$ 1.4399 [lit.[31] bp 127–132° (20 mm)]; ir (CCl_4) 1645 (amide C=O) and 1540 cm^{-1} (NH bending); nmr (CCl_4) δ 8.1 (1 H, br, NH), 3.22 (2 H, m, CH_2N), and 0.7–2.5 (12 H, m, aliphatic CH); mass spectrum, molecular ion at *m/e* 129, abundant fragments at *m/e* 71, 44, 43, 41, 30, and 27. Previously described procedures[32] were followed to prepare 3-bromo-4-heptanone, bp 68.5–71° (7 mm) [lit.[32] bp 82–83° (17 mm)], which exhibited a single major component on glpc[23] and had the following spectral properties: ir (CCl_4) 1720 cm^{-1} (C=O); nmr (CCl_4) δ 4.09 (1 H, t, J = 6.5 Hz, BrCHCO), 2.4–2.9 (2 H, m, CH_2CO), and 0.8–2.4 (10 H, m, aliphatic CH); mass spectrum, molecular ion at *m/e* 194 (^{81}Br isotope), abundant fragments at *m/e* 71 ($CH_3CH_2CH_2C{\equiv}O^+$), 43, and 41 with pairs of weak peaks at 121 and 123 ($CH_3CH_2C^+HBr$) and at 149 and 151 ($CH_3CH_2CHBrC{\equiv}O^+$). Solvolysis[32] of this bromo ketone in a solution of NaOAc in HOAc afforded an authentic sample of the **acetoxy ketone 35**: bp 68.5–69.5° (2.3 mm), $n^{24}D$ 1.4252 [lit.[32] bp 98–100° (16 mm), $n^{25}D$ 1.4240]. Analysis by tlc[24] and glpc[23] indicated the product to be homogeneous: ir (CCl_4) 1745 (ester C=O), 1735, and 1720 cm^{-1} (C=O in two conformations of acetoxy ketone); nmr (CCl_4) δ 4.94 (1 H, m, COCHOAc), 2.3–2.8 (2 H, m, CH_2CO), 2.13 (3 H, s, CH_3CO), and 0.7–2.0 (10 H, m, aliphatic CH); nass spectrum, abundant

(28) Prepared by the procedure of H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

(29) A gas chromatography column packed with Apiezon L suspended on Chromosorb G was employed for this analysis.

(30) A programmed increase in column temperature was used in this analysis.

(31) S. I. Gertler and A. P. Yerington, U. S. Department of Agriculture U. S. Government Printing Office, Washington, D. C., ARS-33-31; *Chem. Abstr.*, **50**, 17297 (1956).

(32) J. Colonge and J. C. Dubin, *Bull. Soc. Chim. Fr.*, 1180 (1960).

fragments at *m/e* 129 [$CH_3CH_2CH(OCOCH_3)C{\equiv}O^+$], 101 ($CH_3CH_2CH{=}O^+COCH_3$), 71 ($CH_3CH_2CH_2C{\equiv}O^+$), 43, and 41. Acid-catalyzed hydrolysis (HCl in H_2O–MeOH at 25°) of acetoxy ketone **35** afforded **3-hydroxy-4-heptanone** as a colorless liquid: $n^{24}D$ 1.4301 (lit.[32] $n^{25}D$ 1.4275) which was homogeneous by tlc[24] and glpc[23] analyses: ir (liquid film) 3475 (br, assoc OH) and 1710 cm^{-1} (C=O); nmr (CCl_4) δ 4.13 (1 H, m, OCHCO), 3.47 (1 H, s, OH), 2.3–2.9 (2 H, m, CH_2CO), and 0.8–2.3 (10 H, m, aliphatic CH); mass spectrum, molecular ion at *m/e* 130, abundant fragments at *m/e* 73, 71 ($CH_3CH_2CH_2C{\equiv}O^+$), 59 ($CH_3CH_2CH{=}{}^+OH$), 57, 55, 43, 41, and 31.[33]

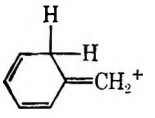
B. Alkylation with Trimethyloxonium Fluoroborate.—A solution of 13.20 g (97 mmol) of trimethyloxonium fluoroborate[34] and 10.59 g (62 mmol) of oxime acetate **9** in 25 ml of CH_3NO_2 was prepared at 0° and then stirred at 25–30° for 1.25 hr. (Preliminary experiments employing the previously described ir analysis established that the reaction was complete in various solvents after the following times: 1.8–3.2 hr for the suspension in CH_2Cl_2; 1 hr for the suspension in 1,2-dimethoxyethane; 20–30 min for the solution in CH_3NO_2.) Gas evolution (presumably Me_2O) was noted as the solution warmed to 25–30°. The resulting solution was added to 40 ml of cold (0°) Et_3N under N_2, and then hydrolyzed and worked up in the usual way. Fractional distillation of the crude liquid product separated 4.295 g (40.3%) of the pure[29,30] acetoxy ketone **35** [bp 87–89° (12 mm), $n^{26}D$ 1.4217], and 0.872 g of a fraction [bp 89–92°, $n^{26}D$ 1.4249] which contained[29,30] 92% acetoxy ketone **35** (total yield 48%) and several minor higher boiling impurities. In comparable small-scale reactions with other solvents used for the alkylation, anisole was added (internal standard) and the crude products were analyzed;[29,30] the calculated yields of acetoxy ketone **35** were 59% with CH_2Cl_2 and 40% with 1,2-dimethoxyethane.

Conversion of Deoxybenzoin Oxime Acetate (15) into Acetoxy Ketone 36.—Attempts to methylate oxime acetate **15** with CH_3I were unsuccessful and reactions with methyl tosylate or with dimethyl sulfate at elevated temperatures (100–160°) produced complex reaction mixtures from which various amounts of deoxybenzoin, benzoin, benzil, and phenylacetanilide were ultimately isolated.

After a solution of 2.895 g (19.3 mmol) of trimethyloxonium fluoroborate and 2.850 g (11.3 mmol) of oxime acetate **15** in 12.5 ml of CH_3NO_2 had been allowed to react for 4 hr (alkylation complete by ir analysis), the reaction solution was added to 12 ml of cold (0°) Et_3N and then stirred at 25–30° for 20 min. After following the previously described hydrolysis and isolation experiments, the crude neutral product was obtained as 3.928 g of brown oil which showed one major spot on tlc[24] corresponding to acetoxy ketone **36**. After chromatography (200 g of SiO_2), the fractions eluted with PhH–Et_2O were recrystallized (hexane–CH_2Cl_2) to separate 922 mg (33.6%) of benzoin acetate (**36**) as tan prisms, mp 79–83°. Recrystallization (EtOH) gave pure benzoin acetate, mp 80–81.5° (lit.[35] mp 81.5–82.5°), identified with an authentic sample by a mixture melting point and by comparison of ir spectra, ir ($CHCl_3$) 1735 (acetate C=O) and 1695 cm^{-1} (conjugated C=O).

Conversion of Diphenylacetone Oxime Acetate (25) into Acetoxy Ketone 24.—After reaction of 7.999 g (53.3 mmol) of trimethyloxonium fluoroborate with 7.152 g (26.8 mmol) of oxime acetate **25** in 25 ml of CH_3NO_2 for 2.1 hr, the mixture was quenched in 80 ml of cold (0°) Et_3N and then stirred at 25–30° for 30 min. The usual hydrolysis and isolation procedure separated the crude product (a brown liquid) which was divided into two equal portions for purification. One aliquot was chromatographed (SiO_2) to separate 2.4 g (68%) of crude acetoxy ketone **24** (identified by ir absorption) in fractions eluted with PhH and with PhH–Et_2O. This material was added to a solution of 5 ml of aqueous 2 *M* HCl in 25 ml of MeOH and allowed to stand at 25–30° for 62 hr. After dilution with water, 1.744 g (57.5%) of 1,3-diphenyl-1-hydroxy-2-propanone was collected as tan needles, mp 112–114°. The second aliquot was distilled in a short-path still (0.02 mm, 150° bath) and the distillate (2.00 g or 56% of crude acetoxy ketone **24**, identified by ir absorption) was hydrolyzed as described above to yield 1.203 g (50.5%) of hydroxy ketone, mp 113–114.5°. After recrystallization (cyclohexane–MeOH) each of these hydroxy ketone samples melted at 114.5–115.5° and was identified with an authentic sample by a mixture melting point.

To obtain authentic samples 1,3-diphenyl-2-propanone (**12**) was brominated according to a published procedure[36] to yield crude 1-bromo-1,3-diphenyl-2-propanone as white needles, mp 44–47° (lit.[37] 47–48°), from pentane–Et_2O followed by sublimation: ir (CCl_4) 1735 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.9–7.7 (10 H, m, aryl CH), 5.57 (1 H, s, BrCHCO), and *ca.* 3.75 1nd 3.97 (2 H, AB pattern, J = 16 Hz, CH_2CO); mass spectrum, molecular ion at *m/e* 290 (^{81}Br isotope), abundant fragments at *m/e* 119 ($C_6H_5CH_2C{\equiv}O^+$) and 91 ($C_7H_7^+$) as well as weak peaks at *m/e* 169 and 171 ($C_7H_6Br^+$). 1,3-Dibromo-1,3-diphenyl-2-propanone (a mixture of diastereoisomers) was isolated as white needles: mp 71–97° (lit.[36] mp 79–97°); ir (CCl_4) 1740 cm^{-1} (C=O of α,α′-dibromo ketone); nmr ($CDCl_3$) δ 7.0–7.7 (10 H, m, aryl CH) and 5.65–5.85 (2 H, m, BrCHCO); mass spectrum, abundant fragments at *m/e* 208, 180, 179, 178, 141, 91, 82, 80, 44, and 40. Reaction of the dibromo ketone with NaI in aqueous acetone[38] yielded 89.5% **1-hydroxy-1,3-diphenyl-2-propanone**, mp 115–116° (lit.[38] mp 114.5–116.5°), or white needles, mp 117–117.5°, after recrystallization (cyclohexane–MeOH): ir ($CHCl_3$) 3470 (associated OH) and 1725 cm^{-1} (C=O); uv (95% EtOH) 253 mμ (ε 405), 259 (473), 264 (422), and 293 (365); nmr [$(CD_3)_2SO$ + D_2O)] δ 6.8–7.8 (10 H, m, aryl CH), 5.23 (1 H s, OCHCO), and 3.83 (2 H, s, CH_2CO); mass spectrum, molecular ion at *m/e* 226 with abundant fragments at *m/e* 208, 121, 107 ($C_7H_6OH^+$), 105, 92 (fragment A),

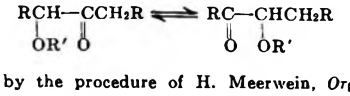


A

91 ($C_7H_7^+$), 79, and 77. Acetylation of this hydroxy ketone with NaOAc and Ac_2O in refluxing Et_2O for 45 hr followed by distillation of the crude neutral product in a short-path still (0.02 mm, 140° bath) formed acetoxy ketone **24** as a pale yellow liquid, $n^{28}D$ 1.5516 [(lit.[39] bp 195° (5 mm)], in 88.6% yield: ir (liquid film) 1745 (ester C=O) and 1735 cm^{-1} (C=O); uv (95% EtOH) 253 mμ (ε 636), 258 (679), 264 (622), and 289 (478); nmr (CCl_4) δ 6.8–7.6 (10 H, m, aryl CH), 5.96 (1 H s, OCHCO), 3.58 (2 H, s, CH_2CO), and 2.03 (3 H, s, CH_3CO); mass spectrum, molecular ion at *m/e* 268 with abundant fragments, *m/e* 177 [$C_6H_5CH(OCOCH_3)C{\equiv}O^+$], 149 ($C_7H_6OC^+CH_3$), 107 ($C_7H_6OH^+$), 91 ($C_7H_7^+$), and 43. After a solution of 690 mg (2.57 mmol) of acetoxy ketone **24** in a mixture of 1.25 ml of aqueous 2 *M* HCl and 6 ml of MeOH had been stirred at 25–30° for 62 hr, dilution with H_2O precipitated 533 mg (92%) of the crude 1-hydroxy-1,3-diphenyl-2-propanone. After recrystallization from cyclohexane–MeOH, the α-hydroxy ketone (433 mg or 74%) was obtained as needles, mp 115.2–116.4°, which was identified with the previously described sample by a mixture melting point and comparison of ir spectra.[32]

In an adaptation of a previously described general procedure,[40] a solution of 1.988 g (4.49 mmol) of anhydrous $Pb(OAc)_4$ and 605 mg (2.67 mmol) of 1-hydroxy-1,3-diphenyl-2-propanone in MeOH–HOAc (1:1 v/v) was heated at 50–55° with stirring under N_2 for 2.1 hr and then treated with 10 ml of H_2O, 0.35 ml (0.63 g, 6.4 mmol) of concentrated H_2SO_4, and 406 mg of *n*-butylbenzene and extracted with CH_2Cl_2. After the organic extract had been washed with aqueous $NaHCO_3$, analysis by glpc[29] indicated the presence of benzaldehyde (yield 82%, retention time 17.0 min), *n*-butylbenzene (36.5 min), and methyl phenylacetate (86%, 54.5 min). Methyl benzoate (38.5 min)

(33) From the mass spectra of the α-bromo ketone, the α-acetoxy ketone, and the α-hydroxy ketone, and from the similarities in the nmr spectra of these three compounds, we conclude that the potential problem with isomerization i ⇌ ii (R′ = H or $COCH_3$) has not complicated the products we have isolated.



(34) Prepared by the procedure of H. Meerwein, *Org. Syn.*, **46**, 120 (1966).

(35) B. B. Corson and N. A. Saliani, "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1943, p 69.

(36) R. Breslow, T. Eicher, A. Krebs, R. A. Peterson, and J. Posner, *J. Amer. Chem. Soc.*, **87**, 1320 (1965).

(37) A. C. B. Smith and W. Wilson, *J. Chem. Soc.*, 1342 (1955).

(38) A. W. Fort, *J. Amer. Chem. Soc.*, **84**, 2620 (1962).

(39) V. I. Veksler, *Zh. Obsch. Khim.*, **20**, 1289 (1950); *Chem. Abstr.*, **45** 1540 (1951).

(40) E. Baer, *J. Amer. Chem. Soc.*, **62**, 1597 (1940).

and phenylacetaldehyde (24.5 min) were not detected. Collected samples of the benzaldehyde and methyl phenylacetate were identified by comparison of ir spectra and glpc retention times.

Conversion of Cyclohexanone Oxime Acetate (23) into 2-Acetoxycyclohexanone (22).—A mixture of 1.637 g (10.9 mmol) of trimethyloxonium fluoroborate, 833 mg (5.37 mmol) of oxime acetate **23**, and 10 ml of CH_2Cl_2 was stirred at 25–30° for 2 hr (alkylation complete by ir analysis) and then added to 7.5 ml of cold (0°) Et_3N and stirred for 45 min. After the usual hydrolysis and isolation procedures, 304 mg of *n*-butylbenzene was added and the CH_2Cl_2 solution of products was analyzed by glpc.[29,30] The calculated yields were 3% cyclohexanone (**13**, eluted first), 51% 2-acetoxycyclohexanone (**27**, eluted second), and 15.5% keto amide **26** (eluted third). Cyclohexanone was identified by its glpc retention time and a collected[29] sample of acetoxy ketone **22** was identified with an authentic sample by comparison of ir spectra and glpc retention times. Reaction of cyclohexanone with $Pb(OAc)_4$ as previously described[14] yielded an authentic sample of the pure[29] acetoxy ketone **22**: bp 99–103° (5 mm); $n^{25}D$ 1.4587 [lit.[14] bp 123–126° (16 mm)]; ir (CCl_4) 1760 (ester C=O) and 1735 cm^{-1} (C=O); nmr (CCl_4) δ 4.8–5.3 (1 H, m, OCHCO) and 2.03 (*ca.* 3 H, s, CH_3CO) superimposed on 1.3–2.7 (*ca.* 8 H, m, aliphatic CH); mass spectrum, molecular ion at *m/e* 156, abundant fragments at *m/e* 113, 67, and 43. A collected[29] sample of keto amide **26** was identified with a subsequently described sample by comparison of ir spectra and glpc retention times.

To examine the effect of reaction time after the alkylated product has been treated with Et_3N, the alkylation reaction was repeated (reaction time 2–4 hr) and the resulting suspension was added to cold (0°) Et_3N. Aliquots of the resulting mixture were removed, hydrolyzed, and analyzed[29,30] periodically. The results of this study are summarized in Table I. In one case the triethylamine solution was allowed to stir for 240 min and then the crude product was fractionally distilled. Keto amide **26** was isolated in 44% yield as a colorless liquid, bp 103–106° (0.20 mm), $n^{25}D$ 1.4923, which contained a single component by glpc[29] ir (CCl_4) lacks absorption in the 3- or 6-μ regions attributable to NH and has peaks at 1725 (ketone C=O) and 1650 cm^{-1} (amide C=O); nmr (C_6D_6) δ 5.0–5.5 (1 H, m, NCHCO), with *ca.* 3 H singlets at 2.57 (CH_3N) and 1.85 (CH_3CO) superimposed on a multiplet at 1.0–3.0 (*ca.* 8 H, aliphatic CH); mass spectrum, molecular ion at *m/e* 169, abundant fragments at *m/e* 126, 98, 74, 70, 43, 42, and 41.

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.63; H, 8.92; N, 8.11.

Reaction of Cyclohexanone with O-Acetyl-N-methylhydroxylamine Hydrochloride (29).—A mixture of 1.9 g of Linde Molecular Sieve No. 5A, 318 mg (2.53 mmol) of hydroxylamine salt **29**, 501 mg (5.11 mmol) of cyclohexanone, and 10 ml of CH_2Cl_2 was stirred at 25–30° for 36 hr. Then 258 mg of *n*-butylbenzene (internal standard) was added and an aliquot of the mixture was washed with water and analyzed by glpc[29,30] indicating a 44% yield of acetoxy ketone **22**. A comparable hydrolysis and analysis after a 64-hr reaction period indicated the yield of acetoxy ketone **22** to be 46% with cyclohexanone as the only other volatile product detected. A collected[29] sample of acetoxy ketone **22** was identified with an authentic sample by comparison of glpc retention times and ir spectra.

Attempts to accomplish the conversion by reaction of cyclohexanone in CH_2Cl_2 with hydroxylamine salt **29** in the presence of excess Et_3N with or without $CaCl_2$[41] resulted in the formation of only small amounts of the acetoxy ketone.

Preparation of the Ketone 37.—Published[2a] procedures were followed to prepare 1-(4-methoxyphenyl)-3-(4-nitrophenyl)-1-propanol. However, the previously noted[2a] difficulty in dehydrating this alcohol to the corresponding olefin led us to use the following procedure. A solution of 17.332 g (59.8 mmol) of 1-(4-methoxyphenyl)-3-(4-nitrophenyl)-1-propanol, 11.71 g (117 mmol) of KOAc, and 50 ml of Ac_2O was heated to 85–95° for 6 hr and then diluted with 150 ml of water. Solid $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2. After the organic extract had been dried and concentrated, the residual pale yellow solid (19.5 g) was recrystallized (Et_2O) to separate 16.73 g (88.5%) of **1-acetoxy-1-(4-methoxyphenyl)-3-(4-nitrophenyl)propane** as pale yellow prisms: mp 61–63.5°; ir (CCl_4) 1740 cm^{-1} (ester C=O); uv (CH_3CN) 222 mμ (ε 16,100), 276 (12,500), and 280 (12,300); nmr ($CDCl_3$) δ 6.7–8.3 (8 H, m, aryl CH), 5.71 (1 H, t, J = 7 Hz, AcOCHAr), 3.79 (3 H, s, OCH_3), 2.04 (3 H, s, CH_3CO), and 1.7–3.0 (4 H, m, aliphatic CH); mass spectrum, abundant fragments at *m/e* 117, 91, 60, 58, 45, 44, and 43.

Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.67; H, 5.54; N, 4.03.

A solution of 5.01 g (15.2 mmol) of this acetate and 80 mg of TsOH in 100 ml of PhH was refluxed for 20 min and then cooled, washed with aqueous $NaHCO_3$, dried, and concentrated. The residual oil, 4.067 g (99%) of **1-(4-methoxyphenyl)-3-(4-nitrophenyl)propene**, crystallized as pale yellow prisms, mp 84–87° (lit.[2a] mp 89.8–90.6°), identified with the previously described[2a] material by comparison of ir spectra. This olefin was converted into ketone **37**, mp 94–95° (lit.[2a] 94–94.5°), by the published[2a] procedure. The reported[2a] nmr data for ketone **37** in $CDCl_3$ solution were complicated by partial overlap of the methoxy peak with the peak for one benzylic methylene group. A more satisfactory spectrum was obtained in $(CD_3)_2CO$ with peaks at 6.7–8.3 (8 H, m, aryl CH), 3.99 (2 H, s, benzylic protons of $-CH_2C_6H_4NO_2$-4), 3.79 (2 H, s, benzylic protons of $-CH_2C_6H_4$-OCH_3-4), and 3.74 (3 H, s, OCH_3). When a solution of 62 mg of ketone **37** in 0.300 ml of acetone-d_6 was treated with 2 drops of 2% DCl in D_2O the respective times for exchange of one-half of the benzylic protons for deuterons were approximately 15 min for the δ 3.99 peak and 45 min for the δ 3.79 peak. When a comparable solution was treated with 2 drops of 20% DCl in D_2O, the approximate times for half-exchange were 2 min for the δ 3.99 peak and 10 min for the δ 3.79 peak. Similar treatment of a solution with 2 drops of 2% NaOD in D_2O resulted in the immediate formation of a deep purple color and essentially complete exchange in 20 sec for the δ 3.99 peak; the approximate time for half-exchange for the δ 3.79 peak was 8 min. Thus, with both acidic and basic catalysts, the benzylic protons adjacent to the *p*-nitrophenyl ring are removed more rapidly than protons at the other benzylic position. It was also of interest to note that, except for the loss of benzylic CH absorption, the nmr spectrum of ketone **37** in the alkaline acetone-d_6 solution was unaltered for at least 15 min indicating the absence of rapid degradation in the basic solution.

Preparation of the Oxime Derivatives 41 and 42 of 2-Methylcyclohexanone (38).—Reaction of 35.2 g (0.314 mol) of ketone **38** with an aqueous solution of $HONH_3Cl$ and NaOAc yielded, after distillation, 32.00 g (80%) of a liquid, bp 66.5° (0.3 mm), which partially crystallized on standing. Successive recrystallizations (Et_2O–hexane and hexane) at Dry Ice temperatures separated 20.74 g (52%) of the **oxime stereoisomer 41a** as white needles, mp 43–44° [lit. mp 42–43°,[10a] 43–44,[10b] bp 104° (15 mm),[10a] 114–115° (16 mm)[10c]]. This isomer, believed to have the configuration indicated in structure **41a**,[11,42] has the following spectral properties: ir ($CHCl_3$) 3570, 3265 (free and associated OH), and 1660 cm^{-1} (C=N); nmr ($CDCl_3$) δ 14.20 (1 H, s, OH), 3.0–3.5 (1 H, m, CHC=N), 1.0–2.7 (8 H, m, aliphatic CH), and 1.13 (3 H, d, J = 6.5 Hz, CCH_3); mass spectrum, molecular ion at *m/e* 127, abundant fragments at *m/e* 110, 95, 67, 55, 41, 39, and 27. The crude liquid oxime (believed to be a mixture of **41a** and **42a**) recovered from the recrystallization mother liquors had ir and nmr absorption very similar to that of the pure crystalline isomer.

To a solution of 3.71 g (17.8 mmol) of PCl_5 in 40 ml of CH_2Cl_2 was added, portionwise with stirring, 2.135 g (16.8 mmol) of oxime **41a** (mp 43–44°). The reaction mixture was stirred for 5 min, then poured with stirring into 100 ml of boiling H_2O, neutralized (pH 8) with $NaHCO_3$, and concentrated, and the residual solid was extracted with CH_2Cl_2. Drsing and concentration of the organic extract left 1.621 g (76%) of crude lactam **46**, mp 60–77°. Recrystallization from hexane gave 1.074 g (50%) of lactam **46** as white needles melting within the range 82–88°: mp 89–91° after recrystallization [lit. mp 90–91°,[11b] 91–92°[11c,42a]]; ir (CCl_4) 3390, 3280, 3190 (free and associated NH), and 1665 cm^{-1} (amide C=O); nmr ($CDCl_3$) δ 3.50 (1 H, m, >NCH<), 2.44 (2 H, m, CH_2CO), 1.0–2.2 (8 H, m, aliphatic CH), and 1.24 (2 H, d, J = 6.8 Hz, CH_3C); mass spectrum, molecular ion at *m/e* 127, abundant fragments at *m/e* 112, 85, 55, 44, and 41.

A solution of 13.88 g (0.109 mol) of oxime **41a** and 16.35 g (0.151 mol) of Ac_2O in 25 ml of CH_2Cl_2 was refluxed for 3 hr and

(41) E. P. Blanchard, Jr., *J. Org. Chem.*, **28**, 1397 (1963).

(42) The melting points reported for the isomeric lactams are 90–91° and 91–92° for **46** [see ref 11 and (a) F. F. Blicke and N. J. Doorenbos, *J. Amer. Chem. Soc.*, **76**, 2317 (1954); (b) B. Philips, S. W. Tinsley, and P. S. Starcher, U. S. Patent 3,000,878; *Chem. Abstr.*, **56**, 1355 (1962)] and 97–98° for **47** (ref 11c).

then cooled and worked up (aqueous $NaHCO_3$ and CH_2Cl_2). Distillation of the residual liquid separated 17.06 g (93%) of **oxime acetate 41b** as a colorless liquid: bp 74–74.5° (0.16 mm); $n^{25}D$ 1.4768; ir (liquid film) 1765 (ester C=O) and 1635 cm^{-1} (C=N); nmr (CCl_4) δ 1.3–3.5 (9 H, m, aliphatic CH), 2.09 (3 H, s, CH_3CO), and 1.15 (3 H, d, J = 6.5 Hz, CCH_3); mass spectrum, molecular ion at m/e 169, abundant fragments at m/e 95, 81, 55, 43, 41, 39, and 27.

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.59; H, 8.93; N, 8.44.

A solution of 2.24 g (17.6 mmol) of oxime **41a** and 1.55 g (9.64 mmol) of 1,1,1,3,3,3-hexamethyldisilazane in 5 ml of CH_2Cl_2 was allowed to stand at 25–30° for 8 days and then concentrated and distilled to separate 3.184 g (91%) of **silyl ether 41c** as a colorless liquid: bp 78–79.5° (10 mm); $n^{25}D$ 1.4480. The product exhibited a single peak on glpc:[29] ir (liquid film) 1630 cm^{-1} (weak, C=N); nmr (CCl_4) δ 1.2–2.3 (9 H, m, aliphatic CH), 1.07 (3 H, d, J = 6.5 Hz, CCH_3), and 0.15 (9 H, s, $SiCH_3$); mass spectrum, molecular ion at m/e 199 (^{28}Si isotope), abundant fragments at m/e 184, 75, 73, 55, 45, 41, 29, and 27.

Anal. Calcd for $C_{10}H_{21}NOSi$: C, 60.24; H, 10.62; N, 7.03. Found: C, 60.06; H, 10.50; N, 6.88.

A similar reaction of 10.88 g (111 mmol) of cyclohexanone oxime with 9.374 g (58.1 mmol) of 1,1,1,3,3,3-hexamethyldisilazane in 75 ml of CH_2Cl for 83 hr yielded 14.81 g (77%) of the **trimethylsilyl ether of cyclohexanone oxime**, bp 73–75° (20 mm), $n^{25}D$ 1.4551, which contained on major component (>99%) by glpc.[43] A sample of the product was collected[43] for characterization: ir (CCl_4) 1630 cm^{-1} (C=N); nmr (CCl_4) δ 1.4–2.8 (10 H, m, aliphatic CH) and 0.15 (9 H, s, $SiCH_3$); mass spectrum, molecular ion at m/e 185 (^{28}Si isotope), abundant fragments at m/e 170, 96, 75, 45, 41, and 27.

Anal. Calcd for $C_9H_{19}NOSi$: C, 58.32; H, 10.33; N, 7.56. Found: C, 58.46; H, 10.36; N, 7.86.

Following a general procedure used previously for the isomerization of benzaldoxime,[13] a solution of 2.179 g (17.2 mmol) of oxime **41a** in 40 ml of anhydrous Et_2O was saturated with HCl gas at 25–30°. The crude hydrochloride salt which separated was washed with Et_2O and then added to a cold (0°), rapidly stirred solution of 1.85 g (17.4 mmol) of Na_2CO_3 in 150 ml of H_2O. The mixture (pH 9) was extracted with Et_2O and the extract was dried and concentrated. The ir and nmr absorption of the residual liquid (1.749 g or 80%) were similar to the spectra of the starting crystalline oxime **41a**. However, reaction of a 101-mg (0.795 mmol) sample of this crude oxime product with 180 μl of O,N-bis(trimethylsilyl)acetamide in 2.0 ml of hexane for 24 hr afforded a mixture of silyl ethers containing[29] both the previously described silyl ether **41c** and a component, believed to be the isomeric silyl ether **42c**, which was eluted slightly more rapidly. A cold (0°) solution of 1.277 g (10 mmol) of the mixture of oximes **41a** and **42a** in 4 ml of pyridine was treated with 2.127 g (20.8 mmol) of Ac_2O. After the resulting mixture had been allowed to stand at 0° for 22 hr, 4 ml of MeOH was added and the mixture was concentrated under reduced pressure to leave 1.643 g (97%) of a mixture of oxime acetates **41b** and **42b**. A portion of this product was distilled in a short-path still (0.1 mm and 60° bath). Although the ir spectra of these samples (distilled and undistilled) are similar to the spectrum of the previously described acetate **41b**, the nmr spectrum (C_6D_6) of the distilled mixture shows, in addition to an aliphatic CH multiplet (δ 1.0–3.4) and an acetyl singlet (δ 1.88), two doublets of approximately equal intensity at δ 1.11 (J = 6.5 Hz) and 0.91 (J = 7.2 Hz) attributable to the C-methyl doublets of **41b** and **42b**, respectively. In $CDCl_3$ solution these doublets are located at δ 1.12 and 1.14. Since complications from isomerization and thermal instability prevented us from isolating the pure oxime acetate **42b**, this mixture of oxime acetates **41b** and **42b** was employed in our subsequent studies.

Conversion of 2-Methylcyclohexanone Oxime Acetate (41b and 42b) into the Acetoxy Ketones 43 and 44.—After a solution of 13.22 g (78.1 mmol) of oxime acetate **41b** and 13.16 g (89.0 mmol) of trimethyloxonium fluoroborate in 30 ml of CH_2Cl_2 had been stirred for 3 hr, the alkylation was complete (ir analysis) and the mixture was added to 75 ml of cold (0°) Et_3N, and then subjected to the usual hydrolysis and isolation procedure. Distillation separated 5.510 g (41%) of a mixture of acetoxy ketones, bp 62–64° (0.12 mm), which contained[29] 46% ketone **44** (eluted first) and 54% ketone **43** (eluted second). Less than 1% of the tertiary acetoxy ketone **45** was present. Collected[29] samples of ketones **43** and **44** were identified with subsequently described samples by comparison of ir spectra and glpc retention times. In a comparable experiment where an internal standard (*n*-butylbenzene) was added to the crude product, the calculated[29] yields were 0.5% **45** (retention time 45.3 min), 17% **44** (52.9 min), and 31% **43** (61.2 min). The same experiment was repeated employing the previously described mixture of oxime acetates **41b** and **42b**. The calculated[29] yields of products were 17% ketone **44** and 34% ketone **43** with less than 1% tertiary acetate **45**.

To obtain authentic samples of acetoxy ketones **43–45**, a solution of 68.28 g (0.608 mol) of 2-methylcyclohexanone (**38**) and 139.5 g (0.315 mol) of $Pb(OAc)_4$ in 500 ml of PhH was refluxed for 12 hr at which time no Pb(IV) salt remained. The reaction mixture was partioned between H_2O and CH_2Cl_2 and the organic layer was washed with aqueous $NaHCO_3$, dried, and concentrated Fractional distillation of the residue (75 g of yellow liquid) separated 20.1 g of crude starting ketone **38**, bp <40° (5.2 mm), 13.45 g of fractions, bp 40–60.5° (5.2–0.2 mm), containing[29,43] starting material and acetoxy ketones **43–45**, 22.16 g of fractions, bp 60.5–64.2° (0.2 mm), containing[29,43] acetoxy ketones **43–45**, and 5.00 g of fractions, bp 64–105° (0.2 mm), containing[43] the three acetoxy ketones and higher boiling materials. The composition of the acetoxy ketone mixture in this reaction was 23% **45** (first eluted), 54% **44** (eluted second), and 23% **43** (eluted third). Further distillation (50-cm Teflon spinning-band column) afforded fractions enriched in each of the acetoxy ketones from which pure samples were collected.[43] The tertiary **acetoxy ketone 45**[44] has the following spectral propertes: ir (CCl_4) 1745 (ester C=O) and 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.2–2.8 (8 H, m, aliphatic CH), 2.09 (3 H, s, CH_3CO), and 1.42 (3 H, s, CCH_3); mass spectrum, molecular ion at m/e 170, abundant fragments at m/e 127, 81, 71, 58, and 43.

The second acetate eluted is believed to be the less stable *trans* **isomer 44**: ir (CCl_4) 1750 (ester C=O) and 1730 cm^{-1} (C=O); nmr (CCl_4) δ 5.05 (1 H, m, AcOCHCO), 1.0–3.0 (7 H, m, aliphatc CH), 2.07 (3 H, s, CH_3CO), and 1.12 (3 H, d, J = 7.0 Hz, CCH_3); mass spectrum, molecular ion at m/e 170, abundant fragments at m/e 128, 81, 55, 43, and 41.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.44; H, 8.31.

The third acetoxy ketone eluted is believed to be the more stable *cis* **isomer 43**: ir (CCl_4) 1755 (ester C=O) and 1735 cm^{-1} (C=O); nmr (CCl_4), δ 5.06 (1 H, m, AcOCHCO), 1.2–2.8 (7 H, m, aliphatic CH), 2.06 (3 H, s, CH_3CO), and 1.00 (3 H, d, J = 6.5 Hz, CCH_3); mass spectrum, molecular ion at m/e 170, abundant fragments at m/e 128, 127, 81, 55, 43, and 41.

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.66; H, 8.37.

The nmr spectra of the two secondary acetoxy ketones **43** and **44** were also determined in C_6D_6 solution. *cis* isomer **43** (presumably with both acetoxy and methyl groups in equatorial positions) has peaks at δ 1.94 (3 H, s, CH_3CO) and 0.93 (3 H, d, J = 6.2 Hz) whereas the corresponding peaks for *trans* isomer **44** (presumably a mixture of conformers in which either the AcO group or the Me group is axial) are found at δ 1.90 and 0.99 (J = 7.0 cps). Because of the small differences in chemical shifts and coupling constants observed for the two isomers, it seemed inadvisable to use the various empirical relationships[45] to assign stereochemistry to the two acetoxy ketones. Consequently, mixtures containing various proportions of acetoxy ketones **43–45** were heated to 150° in quinoline solution until the proportions of compounds **43** and **44** became constant. The approximate equilibrium concentrations of the two secondary

(43) A gas chromatography column packed with silicone fluid, no. 710, suspended on Chromosorb P was employed for this analysis.

(44) E. W. Warnhoff and W. S. Johnson [*J. Amer. Chem. Soc.*, **75**, 494 (1953)] reported by 105–107° (6 mm); J. Colonge and J. C. Dubin reported[32] bp 89° (4.5 mm).

(45) Usually an axial C-methyl group is found at higher field and, when α to a ketone, this group undergoes a larger upfield shift when the solvent is changed from CCl_4 to C_6D_6: (a) N. S. Bhacca, and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964; (b) M. Fetizon, J. Gore, P. Laszlo, and B. Waegell, *J. Org. Chem.*, **31**, 4047 (1966). (c) It has also been noted [T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962)] that the vicinal coupling constant is usually larger for an equatorial H–axial CH_3 arrangement than for an equatorial CH_3–axial H. This latter coupling constant correlation is consistent with our assignment. The chemical shift differences ($\Delta_{CCl_4}^{C_6D_6}$ values of 0.07 ppm for **43** and 0.13 ppm for **44**) are also in the predicted direction.

acetates were 75–80% **43** and 20–25% **44** leading to the assignment of the *cis* stereochemistry **43** (two equatorial substituents) to the more stable epimer.

Reaction of 2-Methylcyclohexanone (38) with O-Acetyl-N-methylhydroxylamine Hydrochloride (29).—A mixture of 306 mg (2.73 mmol) of ketone **38**, 257 mg (2.06 mmol) of hydroxylamine salt **29**, 1.15 g of Linde Molecular Sieves No. 5A, and 2.5 ml of CH_2Cl_2 was stirred at 25–30° for 44 hr. The resulting mixture was mixed with *n*-butylbenzene (internal standard), washed with H_2O, and analyzed.[29] The calculated yield of the acetoxy ketone mixture was 25% containing 56% **45**, 30% **44**, and 14% **43**. The same mixture of acetoxy ketones was obtained in a duplicate experiment. Collected[29] samples of the three acetoxy ketones were identified with previously described samples by comparison of ir spectra and glpc retention times.

Preparation of the Oxime Derivatives 39 and 40 of Ketone 37.—Reaction of 10.01 g (35.6 mmol) of ketone **37** with a mixture of $NaHCO_3$ and $HONH_3Cl$ in H_2O–MeOH yielded 10.07 g (95.7%) of a mixture of oximes **39a** and **40a** as tan needles, mp 100–110°. Application of the subsequently described nmr analysis indicated that this crude product contained 41% *syn-p*-methoxybenzyl isomer **40a** and 59% *syn-p*-nitrobenzyl isomer **39a**. Application of the previously described[2a] fractional crystallization with 1,2-dimethoxyethane–Et_2O (1:1 v/v) as a solvent separated 1.439 g of the less-soluble *syn-p*-nitrobenzyl isomer **39a** as pale yellow prisms, mp 138–144.5° (lit.[2a] mp 141.3–143.2°), estimated (nmr analysis) to contain more than 95% isomer **39a**. A series of fractional crystallizations separated 273 mg of a sample of the more-soluble oxime isomer **40a** as pale yellow needles, mp 130–133 (lit.[2a] mp 133–134.2°), estimated (nmr analysis) to contain 95% isomer **40a**. The nmr absorptions of the two oxime isomers were effectively resolved by use of CD_3COCD_3 as a solvent. In this medium the *syn-p*-nitrobenzyl isomer **39a** has absorption at δ 6.7–8.3 (8 H, m, aryl CH), 3.74 (5 H, superimposed signals for OCH_3 and *p*-nitrobenzyl CH_2), and 3.42 (2 H, s, *p*-methoxybenzyl CH_2) while the *syn-p*-methoxybenzyl isomer **40a** has absorption at δ 6.7–8.3 (8 H, m, aryl CH), with singlets at δ 3.74 (3 H, OCH_3), 3.63 (2 H, *p*-nitrobenzyl CH_2), and 3.55 (2 H, *p*-methoxybenzyl CH_2). These chemical shift values are consistent with the empirical correlation[20] which noted that α-methylene protons *cis* to an oxime hydroxy function are found at lower field than the corresponding *trans*-α-methylene protons (*e.g.*, the *p*-methoxybenzylic protons are at lower field for isomer **40a** than for isomer **39a**). Consequently, these nmr data are consistent with the configuration assigned previously[2a] to the oximes **39a** and **40a** as a result of Beckmann rearrangements.

A cold (0°) solution of 273 mg (0.91 mmol) of the more-soluble oxime isomer **40a** (mp 130–133°) in 2 ml of pyridine was treated with 205 mg (2.0 mmol) of Ac_2O and allowed to stand in the cold for 20 hr. After dilution with MeOH and concentration, the residual crude acetate **40b** (290 mg or 93%, mp 93–98°) was recrystallized from MeOH to separate 175 mg (56%) of **oxime acetate 40b** as pale yellow needles: mp 102–103°; ir ($CHCl_3$) 1765 (ester C=O) and 1630 cm^{-1} (C=N); uv (CH_3CN) 215 mμ (ε 15,400) and 273 (11,800); nmr (CD_3COCD_3) δ 6.7–8.3 (8 H, m, aryl CH) with three closely spaced singlets (total 7 H) at δ 3.76 (OCH_3), 3.72 (benzylic CH_2), and 3.70 (benzylic CH_2) as well as a singlet at δ 2.17 (3 H, CH_3CO).

Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.03; H, 5.39; N, 8.15.

Crystalline oxime acetate **40b** was more efficiently prepared by direct actylation of the crude mixture of oximes **39a** and **40a** either before or after removal of the less-soluble oxime **39a** by fractional crystallization.

Following the previously described procedure, 1.222 g (4.075 mmol) of the less-soluble oxime isomer **39a** (mp 138–144.5°) was acetylated to yield 1.495 g of he crude oxime acetate **39b** as a yellow oil. Since attempts to recrystallize this material were unsuccessful, a sample was chromatographed (SiO_2). The pure **oxime acetate 39b** was eluted with hexane–Et_2O as a pale yellow liquid: ir ($CHCl_3$) 1765 (ester C=O) and 1630 cm^{-1} (C=N); uv (CH_3CN) 274 mμ (ε 10,900); nmr (CD_3COCD_3) δ 6.7–8.3 (8 H, m, aryl CH), 3.85 (2 H, s, *p*-nitrobenzyl CH_2), 3.75 (3 H, s, OCH_3), 3.59 (2 H, s, *p*-methoxybenzyl CH_2), and 2.13 (3, H, s, CH_3CO).

Anal. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18. Found: C, 63.30; H, 5.38; N, 8.09.

Alkylation and Rearrangement of Oxime Acetates 39b and 40b.—A solution of 927 mg (6.17 mmol) of trimethyloxonium fluoroborate and 321 mg (0.938 mmol) of the *syn-p*-nitrobenzyl isomer **39b** in 3 ml of CH_3NO_2 was stirred at 25–30° for 2 hr and subjected to the usual hydrolysis and isolation procedure. Since we were unsuccessful in attempts to isolate the pure acetoxy ketones **48** and **49** from the crude reaction product, the following analytical procedure was followed. The crude product was chromatographed (SiO_2) and 96 mg of fractions containing acetoxy ketones **48** and **49** [ir ($CHCl_3$) 1750–1700 (broad, ester and ketone C=O) and 1235 cm^{-1} (ester COC)] were eluted with PhH and with PhH–Et_2O. Other fractions eluted from the column were identified as follows: (1) 18 mg of crude *p*-nitrophenylacetonitrile which melted at 113–114° after recrystallization from methanol and was identified with an authentic sample by a mixture melting point and comparison of ir spectra; (2) 35 mg of crude ketone **37** which melted at 91.5–94° after recrystallization and was identified by a mixture melting point and comparison of ir spectra. A solution of the acetoxy ketone fractions and 2 ml of 2 *M* aqueous HCl in 8 ml of MeOH was stirred at 25–30° for 91 hr and then diluted with H_2O and extracted with CH_2Cl_2. The resulting crude neutral product (85 mg of hydroxy ketones as a brown liquid) had ir absorption at 3450 (OH) and 1720 cm^{-1} (C=O) but lacked absorption in the 1200–1240-cm^{-1} region attributable to unchanged acetoxy ketone. Following the cleavage procedure previously described for 1-hydroxy-1,3-diphenyl-2-propanone, a solution of the crude hydroxy ketones was treated with 270 mg (0.59 mmol) of $Pb(OAc)_4$ in a mixture of 5 ml of anhydrous MeOH and 5 ml of anhydrous HOAc for 2.1 hr. The resulting crude neutral product was mixed with a known weight of biphenyl (internal standard) and analyzed by glpc.[29,30] The calculated[29,30] yields of cleavage products, in order of increasing retention times, were **51**, 5.1%; **50**, 4.3%, **52**, 5.1%; and **53**, 3.7%. From a second comparable experiment, the calculated yields were **51**, 4.8%; **50**, 5.9%; **52**, 5.6%; and **53**, 3.7%. A collected sample[29] of each product was identified with an authentic sample by comparison of ir spectra and glpc retention times.

Comparable reaction sequences were performed on 499-mg (1.46 mmol) and 507-mg (1.48 mmol) samples of the *syn-p*-methoxybenzyl isomer **40b**. The calculated[29,30] yields of products from the two experiments were **51**, 7.0%, 6.5%; **50**, 2.0%, 12%; **52**, 9.8%, 12%; and **53**, 6.0%, 4.0%. Collected[29] samples of these products were identified as previously described. In one experiment 27 mg of ketone **37**, mp 92–94°, was also isolated. As a blank experiment, a sample of ketone **37** was treated with $Pb(OAc)_4$ under the conditions employed to cleave the corresponing hydroxy ketones. None of the cleavage products **50–53** was detected[29,30] in the crude neutral product from this blank experiment.

Registry No.—**9**, 19689-91-9; **15**, 19690-01-8; **23**, 19689-92-0; **25**, 19689-93-1; **26**, 19689-94-2; **29**, 19689-95-3; **30**, 19689-96-4; **31**, 19689-97-5; **39b**, 19684-38-9; **40b**, 19684-33-4; **41b**, 19684-34-5; **41c**, 19684-35-6; **43**, 19684-36-7; **44**, 19684-37-8; **45**, 16963-12-5; 1-acetoxy-1-(4-methoxyphenyl)-3-(4-nitrophenyl)propane, 19689-99-7; trimethylsilyl ether of cyclohexanone oxime, 19690-00-7.

Conformational Equilibria in the 2-Amino-1,2-diphenylethanol System. II. Infrared Studies

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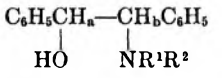
Conformational preferences in a series of 2-(N,N-dialkylamino)-1,2-diphenylethanols (**1a–d**) have been examined by means of high-dilution infrared spectroscopy. With a single exception (**1c**) the *dl-threo* amino alcohols reveal a single, intense absorption band in the 3-μ region, assigned to an intramolecular OH···N bond. In contrast, three absorption bands appear in the spectra of the *dl-erythro* amino alcohols, attributable, in order of decreasing frequency, to the presence of unassociated OH, intramolecular OH···π bonding and intramolecular OH···N bonding. These data are entirely consistent with the assignment of conformational preferences based on nmr, *i.e.*, the conformation of the *dl-threo* amino alcohols (**1c** excepted) may be adequately represented by a single rotamer, tA, and that of the *dl-erythro* amino alcohols by an equilibrium mixture of rotamers, eA and eB.

A conformational analysis of a series of diastereomeric 2-(N,N-dialkylamino)-1,2-diphenylethanols (**1a–d**), employing nmr as a diagnostic tool, has been discussed in a previous paper.[1] That analysis, based on the magnitude of the vicinal coupling constant J_{ab}, attributed an influential role to intramolecular hydrogen bonding with the basic amino group acting as proton acceptor (OH···N).

Infrared spectroscopy provides a powerful and proven tool for the study of hydrogen-bonding phenomena.[2] As such, the method is an alternate route to the examination of conformational preferences in systems in which hydrogen bonding operates.[3] The results of the infrared study reported herein complement the nmr study of the amino alcohols **1a–d**, in part, because of the



1a, $R^1R^2 = O(CH_2CH_2-)_2$
b, $R^1R^2 = (CH_2)_5$
c, $R^1R^2 = (CH_2)_4$
d, $R^1 = R^2 = CH_3$

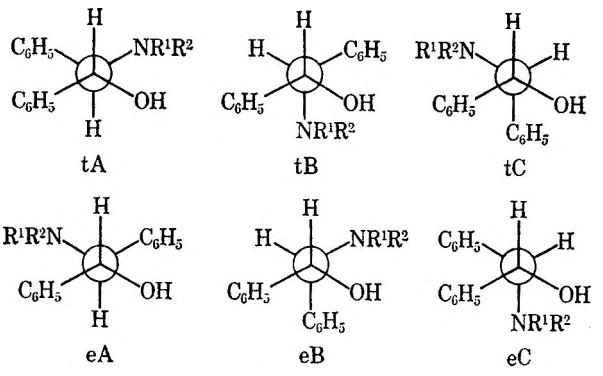
intrinsic differences in the nature of the information derived from the two sources. Briefly, because of the rapid rate of rotation about the central carbon–carbon bond and the difference in the frequency of electromagnetic radiation utilized, an "average" spectrum, weighted to reflect the relative populations of rotamers present at equilibrium, is obtained by nmr, while, in contrast, with infrared measurements it is possible to observe vibrational bands characteristic of each of the rotamers present at equilibrium.

The OH stretching frequencies listed in Table I were determined in a solvent of poor proton-acceptor qualities, carbon tetrachloride, and at high dilution (0.004 *M*) in order to minimize interference by bands characteristic of *intermolecular* hydrogen bonding between amino alcohol molecules. With one exception (**1c**), the spectra of the *threo*[4] amino alcohols **1a–d** reveal only a single, broad absorption band. This intense peak in the 3350–3380-cm^{-1} region is attributed to intramolecularly hydrogen-bonded OH in which the amine nitrogen acts as the proton acceptor (OH···N). Except for the presence of a very weak band ($\epsilon_{OH/OH\cdots N} = 0.05$) at 3620 cm^{-1} in the spectrum of the *threo*-pyrrolidino amino alcohol **1c**, *no* absorption characteristic of unassociated OH could be detected in the *threo* series.

Intramolecular hydrogen bonding to nitrogen (OH···N) would appear to be possible in two of the three rotamers[5] of the *threo* amino alcohols, the *anti* rotamer tA and the *gauche* rotamer tB (Chart I). If a *pure* staggered conformation (*i.e.*, an O–C–C–N dihedral angle of 60°) is assumed, and normal bond lengths and bond angles are employed,[6,7] a N–O distance of 2.85 Å is calculated[8] for rotamers tA and tB. This distance is comparable to the average N–O distance of 2.80 Å observed for the *intermolecular* OH···N bond in the crystalline state.[9] It should be noted, however, that: (a) none of the examples of OH··· N bonding studied in the crystalline state involved an aliphatic hydroxyl and amino group, and (b) the O–H···N angle in the intramolecularly hydrogen-bonded system under study (Dreiding molecular models suggest an O–H···N angle of about 115°) is considerably less than in the examples of intermolecular hydrogen bonding examined, where

CHART I

ROTAMERS IN THE *threo* AND *erythro* SERIES



(1) M. E. Munk, M. K. Meilahn, and P. Franklin, *J. Org. Chem.*, **33**, 3480 (1968).

(2) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960.

(3) For a review see M. Tichy, *Advan. Org. Chem.*, **5**, 115 (1965).

(4) The terms *threo* and *erythro* as used in this paper indicate *dl-threo* and *dl-erythro*, respectively.

(5) For clarification of the term "rotamer" as used in this paper, see footnote 7, ref 1.

(6) The following bond distances were employed: C–C, 1.54 Å; C–O, 1.43 Å; and C–N, 1.47 Å.[7] Bond angles C–C–O and C–C–N were assumed to be 109.5°.

(7) "Table of Interatomic Distances and Configuration in Molecules and Ions," Special Publication No. 11, The Chemical Society, London, 1958.

(8) The problem was reduced to one of calculating the distance between two points in space, whose spherical coordinates are known.

(9) (a) Reference 2, p 289. Values ranging from 2.62 to 2.93 Å are recorded. (b) W. C. Hamilton and J. A. Ibers, "Hydrogen Bonding in Solids," W. A. Benjamin, Inc., New York, N. Y., 1968, p 16, also report 2.8 Å as an average observed N–O distance.

TABLE I
INFRARED SPECTRAL PROPERTIES OF AMINO ALCOHOLS[a]

Compound	ν cm⁻¹[b] OH	OH···π	OH···N	Δν cm⁻¹ OH···π	OH···N	ΔνOH···N (*threo*)/ ΔνOH···N (*erythro*)	ε OH	OH···π	OH···N	εOH/ εOH···N
threo **1a**			3380		240[c]				34	0
						2.2				
erythro **1a**	3620	3590	3510	30	110		4.9	1.8	17	0.29
threo **1b**			3350		270[c]				35	0
						2.0				
erythro **1b**	3620	3595	3485	25	135		3.6	3.6	14	0.26
threo **1c**	3620		3360		260		2.0		36	0.05
						2.4				
erythro **1c**	3620	3575	3510	45	110		1.2	1.1	25	0.05
threo **1d**			3380		240[c,d]				38	0
						2.4				
erythro **1d**	3620	3590	3520	30	100[d]		2.4	1.2	19	0.13
trans **2**			3460						42	
$C_6H_5CH(OH)CH_2C_6H_5$ (**3**)	3620	3590		30			54	3.0		
$C_6H_5CH(OH)CH_3$ (**4**)	3620						45			

[a] All spectra were determined in carbon tetrachloride solution (0.004 *M*). [b] Probable errors: ±1.5 cm⁻¹ for unassociated OH; ±2.5 cm⁻¹ for bonded OH band. [c] ν_{OH} = 3620 cm⁻¹ is used in calculating $\Delta\nu_{OH\cdots N}$ for the *threo* isomer. [d] Pitha, *et al.*,[13] report $\Delta\nu_{OH\cdots N}$ values of 255 and 110 cm⁻¹, respectively, for the *threo* and *erythro* amino alcohols **1d**.

linearity or near linearity is likely. In connection with the latter point, there is no information presently available that relates the A–H···B angle and the A–B distance.[10]

The absence of unassociated OH absorption in the spectra of the *threo* amino alcohols **1a**, **b**, and **d** indicates that rotamer tC, whose geometry precludes intramolecular OH···N bonding, must be negligibly populated at equilibrium and that the monomeric species exists exclusively as the intramolecularly hydrogen-bonded form. This strong preference for the intramolecularly hydrogen-bonded form is also observed in related systems. *trans*-2-(1-Piperidino)cyclohexanol (**2**) shows no unassociated OH in its high-dilution infrared spectrum; therefore, the monomeric species must reside only in that chair conformation with the two vicinal substituents equatorial to one another and exist exclusively as the intramolecularly hydrogen-bonded form.

It is interesting to note that, whereas neither *cis*- nor *trans*-2-(N,N-dimethylamino)cyclohexanol show unassociated OH absorption in carbon tetrachloride,[11] *cis*- and *trans*-2-amino-[12] and 2-(N-methylamino)cyclohexanol[13] do. Drefahl and Hörhold[14] report the appearance of an unassociated OH band in the high-dilution spectra of *threo*-2-amino- and 2-(N-methylamino)-1,2-diphenylethanol in carbon tetrachloride and carbon disulfide, respectively, but the absence of the same absorption band in the spectrum of *threo*-2-dimethylamino-1,2-diphenylethanol.

Infrared evidence, therefore, would appear to limit the conformational equilibrium in the *threo* amino alcohols **1a**, **b**, and **d** to tA ⇄ tB, but would not define the position of that equilibrium. Nmr studies[1] in chloroform,[15] which indicate the presence of little, if any, of *gauche* rotamer tB or tC at equilibrium, are therefore compatible with and strengthened by this evidence. The strong preference for rotamer tA in the *threo* series has been discussed in steric terms.[1]

The infrared spectrum of the *threo*-pyrrolidino alcohol **1c** is unique to the *threo* series because of the appearance of weak unassociated OH absorption. This unexpected observation, which recalls the anomalies observed in the nmr spectra of pyrrolidino compounds,[1] requires the presence of a detectable amount of one or more of the three rotamers in *unassociated* form. The case for a negligibly populated rotamer tC has been made previously on steric grounds.[1] A comparison of Corey–Pauling–Koltun (CPK) models of rotamer tA of *threo* **1b**[16] and **1c**, in which the groups attached to the ethane backbone are aligned to permit intramolecular hydrogen bonding (OH···N) and minimize steric interaction, reveals greater crowding in the pyrrolidino compound **1c** between the amino group and that phenyl group attached to the same carbon atom, a consequence of the subtle steric requirements unique to the pyrrolidine ring.[17] Because of the favorable orientation of hydroxyl and amino groups for intramolecular hydrogen bonding (OH···N) these differences would not be expected to cause selectively an increase in the population of the unassociated OH form of rotamer tA (designated tA_{OH}) in the case of *threo* **1c**. As previously suggested,[1] however, this congestion in rotamer tA of *threo* **1c** can result in a slight shift of the heavily biased equilibrium tA ⇄ tB to the right. That this shift, *which apparently occurs to any measurable extent only in the case of the pyrrolidino alcohol* **1c**, probably accounts for the appearance of unassociated OH absorption in the spectrum of *threo* **1c** becomes clear from an inspection of CPK models of rotamer tB. With the amino group properly oriented for intramolecular hydrogen bonding, a strained system results due, in particular, to the steric interaction between the amino group and *both* phenyl groups (Figure 1). This crowding in rotamer tB between the amino and the phenyl groups is clearly more severe than in the *anti* rotamer tA and models suggest an alternate orientation of groups, *not conducive* to intramolecular hydrogen bonding (OH···N), which

(10) Chapter 6 of ref 9b.

(11) K. Adank and W. G. Stoll, *Helv. Chim. Acta*, **42**, 887 (1959).

(12) (a) J. Sicher, M. Horak, and M. Svoboda, *Collect. Czech. Chem. Commun.*, **24**, 950 (1959); (b) G. Drefahl and G. Heublein, *Chem. Ber.*, **94**, 915 (1961).

(13) J. Pitha, M. Horak, J. Kovar, and K. Blaha, *Collect. Czech. Chem. Commun.*, **25**, 2733 (1960).

(14) G. Drefahl and H. Hörhold, *Chem. Ber.*, **94**, 1641 (1961).

(15) A. Allerhand and P. von R. Schleyer, *J. Am. Chem. Soc.*, **85**, 371 (1963), suggest that chloroform and carbon tetrachloride may be used interchangeably in infrared studies of hydrogen bonding.

(16) The *threo*-piperidino alcohol **1b** serves as the standard of comparison.

(17) Models suggest the focal point of the crowding to be between pseudo-axial hydrogens at positions 2 and 5 of the pyrrolidino group and the carbon atoms of the phenyl group in *threo* **1c** and between the axial hydrogens at positions 2 and 6 of the piperidino group and the carbon atoms of the phenyl group in *threo* **1b**. The particular interaction closely resembles that observed in a comparison of rotamer eA of *erythro* **1d** and **1c** and is illustrated in Figure 1 of ref 1. Although intramolecular hydrogen bonding to nitrogen is precluded in eA, it is interesting to note the similarities in orientation of groups in rotamers tA and eA as suggested by models.

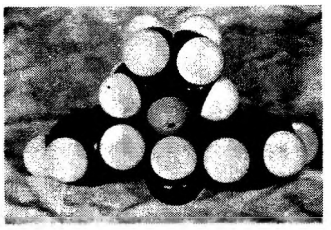


Figure 1.—CPK molecular model of *threo* amino alcohol **1c** as the intramolecularly hydrogen-bonded form of rotamer tB.

minimizes steric crowding. Thus, it may be the presence of rotamer tB in its *unassociated* OH form (tB_{OH}) at equilibrium that accounts for the appearance of weak unassociated OH stretching absorption in the spectrum of *threo* **1c**. It should be noted that the intramolecularly hydrogen-bonded (OH···N) form of rotamer tB (designated $tB_{OH\cdots N}$) is strained irrespective of the amino group present, although the strain appears to be greater with the piperidino than with the pyrrolidino group. In retrospect, this slight shift in the equilibrium tA $\rightleftarrows$ tB to the right in the case of *threo* **1c** may be reflected in the slightly lower value of the vicinal coupling constant J_{ab} (by 0.3–0.5 Hz in $CDCl_3$ solution) as compared to those for amino alcohols **1a**, **b** and **d**.[1]

In summary, under the conditions of examination, the conformation of *threo* amino alcohols **1a**, **b**, and **d** may be adequately represented by a single rotamer in its intramolecularly hydrogen-bonded form, $tA_{OH\cdots N}$; that of *threo* **1c** by the equilibrium $tA_{OH\cdots N} \rightleftarrows tB_{OH}$ in which $tA_{OH\cdots N}$ is by far the heavily populated species.

In contrast to the simple spectra observed for the *threo* amino alcohols, the corresponding *erythro* amino alcohols, without exception, display three absorption bands in the 3-μ region (Figure 2). The sharp band at highest frequency is assigned to unassociated OH stretching and appears in each case at 3620 cm^{-1}, a value identical with that observed for the unassociated OH band of 1,2-diphenylethanol (**3**). The band at next lowest frequency, appearing in the range 3575–3595 cm^{-1}, is attributed to an intramolecularly hydrogen bonded OH stretching vibration in which the π-electron cloud of the phenyl ring on the adjacent carbon atom acts as a proton acceptor. The low-frequency and most intense band, appearing in the 3485–3520-cm^{-1} region, is assigned to the OH stretching vibration of the intramolecular OH···N bond. Because of the breadth of the low-frequency band the other two absorption peaks appear as shoulders. For the purpose of measuring frequencies and calculating extinction coefficients in the *erythro* series, the absorption curves are resolved by means of a special-purpose analog computer, the Dupont Model 310 curve resolver.

The absorption band attributed to OH···π is assigned on the basis of the known weak intramolecular interaction of hydroxyl groups with suitably disposed π electrons of multiple-bond systems.[3] In this case 1,2-diphenylethanol (**3**) served as a model and its spectrum revealed a barely discernible shoulder on the main absorption band at 3620 cm^{-1} (unassociated OH) which could be identified as a weak band ($\epsilon_{OH}/\epsilon_{OH\cdots\pi}$ = 18) at 3590 cm^{-1} after resolution by the curve resolver. The $\Delta\nu_{OH\cdots\pi}$ value of 30 cm^{-1} is comparable to that observed for the *erythro* amino alcohols **1a–d**. The absence of such a shoulder in the infrared spectrum of

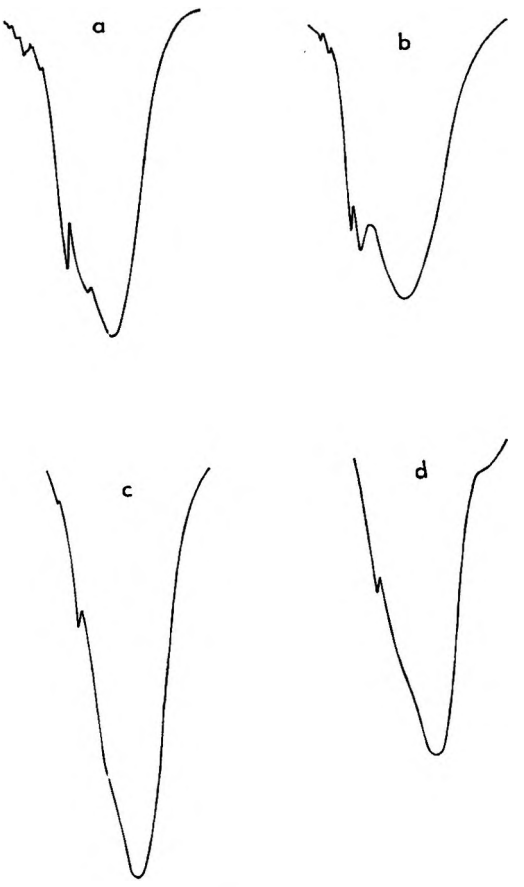


Figure 2.—Infrared absorption spectra of the *erythro* amino alcohols: (a) **1a**, (b) **1b**, (c) **1c**, and (d) **1d**.

1-phenylethanol (**4**) suggests that the π-electron interaction indeed involves the phenyl group on the *adjacent* (C-2) rather than on the *same* carbon atom (C-1).

In contrast to these findings Drefahl and Hörhold[14] failed to observe the appearance of either unassociated OH or π-bonded OH absorption in the high-dilution infrared spectrum (CCl_4) of the *erythro* amino alcohol **1d**, although absorption characteristic of both of these modes of stretching vibration are observed and assigned by these authors in the spectra of *erythro*-2-amino- (CCl_4) and 2-(N-methylamino)-1,2-diphenylethanol (CS_2); $\Delta\nu_{OH\cdots\pi}$ = 30 and 25 cm^{-1}, respectively. Kanzawa[18] also reports the appearance of a doublet in the 3600-cm^{-1} region ($\Delta\nu$ = 30 cm^{-1}) of the spectrum of *erythro*-2-(N-methylamino)-1,2-diphenylethanol, but rejects the operation of such intramolecular hydrogen bonding because of his failure to observe a similar doublet in the spectrum of 1,2-diphenylethanol, a finding in contrast to our own (see above).

The infrared data for the *erythro* amino alcohols **1a–d** can be interpreted in terms of conformational preferences if the reasonable assumption is made that rotamer eC is negligibly populated.[19] Intramolecular hydrogen bonding with nitrogen as the proton acceptor is possible then only in *gauche* rotamer eB and, therefore, the intense absorption in the 3485–3520-cm^{-1} region reflects the presence of that rotamer at equilibrium. In the *threo* series it was noted that rotamer tA, with N and O *gauche* to one another, exists exclusively as the intramolecularly hydrogen-bonded form $tA_{OH\cdots N}$. Since

(18) T. Kanzawa, *Bull. Chem. Soc. Japan*, **29**, 604 (1956).

(19) The reasonable assumption is founded on steric factors described in ref 1. In particular, see footnote 10 in that paper.

CPK models of rotamer eB suggest that that orientation of groups required for intramolecular hydrogen bonding to nitrogen minimizes steric crowding as well, it is probable that the same behavior characterizes eB, *i.e.*, rotamer eB exists exclusively as $eB_{OH\cdots N}$.[20] With this as a premise, the appearance of unassociated OH and $OH\cdots\pi$ absorption in the spectra of the *erytho* amino alcohols requires the presence of rotamer eA, a conclusion consistent with nmr data as well.[1] In summary, then, in the *erytho* series the infrared and nmr data are best accommodated by the presence of three species at equilibrium: eA_{OH}, $eA_{OH\cdots\pi}$, and $eB_{OH\cdots N}$.

Molar extinction coefficients and the ratio $\epsilon_{OH}/\epsilon_{OH\cdots N}$ are included in Table I, but only qualitative significance is intended since, in general, hydrogen-bonded OH bands have a higher molar absorptivity than free OH bands.[3] The values of the ratio $\epsilon_{OH}/\epsilon_{OH\cdots N}$ for the *erytho* series, therefore, are compatible with the relative populations of rotamers eA and eB reported on the basis of nmr studies.[1] Noteworthy is the significantly reduced value of $\epsilon_{OH}/\epsilon_{OH\cdots N}$ for the *erytho* amino alcohol **1c** compared to those for *erytho* **1a**, **b**, and **d**. This observation, suggesting that in the *erythro* series the equilibrium eA $\rightleftarrows$ eB lies *farthest* to the right in the case of the pyrrolidino alcohol **1c**, is consistent with the conclusion, deduced from nmr data, that the *least* steric crowding in rotamer eB exists in this compound. Thus, some independent evidence is provided in support of the proposed unique steric requirements of the pyrrolidino group[1] and its conformational implications in sterically encumbered systems.

The foregoing discussion limits intramolecular $OH\cdots N$ bonding to rotamer tA in the *threo* series and rotamer eB in the *erythro* series. It has been suggested that in each case the orientation of nitrogen required for such intramolecular bonding also minimizes steric crowding. In view of this, the striking and consistent differences in $\Delta\nu_{OH\cdots N}$ for the *threo* and *erythro* amino alchols **1a–d** require examination in terms of the proposed conformational analysis since, as pictured in Chart I, the amino and hydroxyl groups are similarly disposed in space in *both* rotamers and, therefore, similar heats of formation (ΔH) and, consequently, similar $\Delta\nu_{OH\cdots N}$ values might be expected in both series.[21] These observed differences lead us to suggest a more detailed description of rotamers tA and eB.

The chemical literature reveals numerous examples of acyclic diastereomeric 1,2-diols and 1,2-amino alcohols in which the $\Delta\nu$ value of the *threo* (or *dl*) compound exceeds that of the corresponding *erythro* (or *meso*) compound.[3] The usually offered explanation,[3] *i.e.*, steric crowding between *gauche* R groups (phenyl groups in the present study) increases the R–C–C–R dihedral angle (*e.g.*, see rotamer tA) and drives A and B closer together in the *threo* (or *dl*) series permitting formation of a stronger $A\text{–}H\cdots B$ bond, is undoubtedly applicable here as well. It is likely that in the system under study an N–O distance somewhat less than the 2.85 Å characteristic of the "pure-staggered" form is optimal.[9] In rotamer tA a $C_6H_5\text{–}C\text{–}C\text{–}C_6H_5$ angle greater than 60° leads to a decrease in *gauche*-phenyl interaction as well as a decrease in the N–O distance. The result should be an increase in the heat of formation of the $OH\cdots N$ bond, and consequently, the $\Delta\nu_{OH\cdots N}$ value, in the *threo* series. In contrast, in the *erythro* series a $C_6H_5\text{–}C\text{–}C\text{–}C_6H_5$ angle greater than 60° in rotamer eB leads to an N–O distance greater than 2.85 Å and a concomitant decrease in the heat of formation of the $OH\cdots N$ bond.

That additional factors may be operative in the 2-dialkylamino-1,2-diphenylethanol system is suggested by the surprisingly high $\Delta\nu_{OH\cdots N(threo)}/\Delta\nu_{OH\cdots N(erythro)}$ ratio, 2.0–2.4, as compared to the values 1.2–1.3 reported for diastereomeric acyclic 1,2-diols and other 1,2 amino alcohols.[3] Based on the premise that a decrease in N–O distance from the 2.85 Å of the undistorted, pure-staggered form leads to a strengthening of the $OH\cdots N$ bond, CPK models of rotamer tA and eB were again compared. These models suggest that the previously noted congestion in rotamer tA between the amino group and phenyl on the same carbon atom could result in a decrease of the C–C–N bond angle and, consequently, a decrease in N–O distance. The operation of a similar deformation effect, the Thorpe–Ingold effect, has been suggested to account for the variations observed in $\Delta\nu_{OH\cdots O}$ for a series of 2-substituted propane-1,3-diols.[22] A comparable repulsive interaction leading to deformation of the C–C–N angle does not appear to exist in models of rotamer eB. In effect, then, in the *threo* series a sterically induced decrease in both the O–C–C–N dihedral angle and C–C–N bond angle may reinforce one another and contribute to the larger-than-usual $\Delta\nu_{OH\cdots N}$ values in this sterically encumbered system. This discussion is not intended to imply a thorough understanding of the factors controlling the magnitude of the ratio of $\Delta\nu_{OH\cdots N}$ values, rather, to serve as a point of departure for additional study.

In summary, in the series of 2-dialkylamino-1,2-diphenylethanols examined, infrared evidence confirms the existence of intramolecular hydrogen bonding ($O\text{–}H\cdots N$) and lends support to its importance as a factor in determining conformation. This is most clearly seen in the *erythro* series, where the significant population of *gauche* rotamer eB at equilibrium is the result of a balance between steric control and intramolecular hydrogen bonding.

Experimental Section

Preparation of Compounds.—The *threo* and *erythro* amino alcohols **1a–d** and *trans* **2** were prepared according to the method of Munk and Kim[23] and are described by Munk, Meilahn, and Franklin.[1] Product homogeneity was demonstrated by gas–liquid partition chromatography (6-ft stainless steel column packed with 5% XE-60 on an Anakrom ABS support) prior to high-dilution infrared runs.

1,2-Diphenylethanol (**3**) was prepared by the lithium aluminum hydride reduction of desoxybenzoin, mp 66–67° (Skellysolve B[24]). A commercial sample of 1-phenylethanol (**4**) was carefully distilled prior to the determination of its infrared spectrum.

High-Dilution Infrared Technique.—The infrared spectra of compounds **1–4** were determined at a concentration of 0.004 *M* in carbon tetrachloride (analytical reagent, Mallinckrodt Chem-

(20) It can be noted that CPK models of rotamers $tA_{OH\cdots N}$, $eB_{OH\cdots N}$, and $tB_{OH\cdots N}$ suggest that rotamer stability decreases in that order. This order, based on an evaluation of the steric environment (crowding) about the amino group, appears to hold for all the amino alcohols examined in this study and parallels the order of rotamer stability reported earlier.[1]

(21) This is in accord with the relationship of R. M. Badger and S. H. Bauer, (ref 2, pp 82–83), since we deal here with a limited series of closely related compounds. See R. West, D. L. Powell, L. S. Whatley, M. K. T. Lee, and P. von R. Schleyer, *J. Am. Chem. Soc.*, **84**, 3221 (1962).

(22) P. von R. Schleyer, *ibid.*, **83**, 1386 (1961).

(23) M. E. Munk and Y. K. Kim, *J. Org. Chem.*, **30**, 3705 (1965).

(24) A petroleum ether fraction supplied by Skelly Oil Co.

ical Works) that had been dried by azeotropic distillation. Matched silica cells (5 cm) were employed and the spectra were recorded on a Beckman Model IR-12 spectrometer in the region 3100–3700 cm^{-1}. The single beam–double beam ratio was adjusted to 1 at a base line of 90% transmittance. The base line was determined with both cells containing the solvent at a scanning speed of 70 cm^{-1}/min. Several milliliters of solvent were then removed by syringe from the sample cell, the alcohol was quickly transferred to the cell, and the solvent was replaced. The cell was stoppered and gently shaken to achieve a homogeneous solution. The spectrum was then recorded at a scanning speed of 70 cm^{-1}/min. All samples were run at room temperature, *i.e.*, 23°. Using identical instrument parameters good reproducibility of spectra was observed.

In the *threo* amino alcohols **1a–d** the peak position of the broad OH···N band could be estimated to an accuracy of about ±2.5 cm^{-1} directly from the spectra. Peak positions of the multicomponent curves (Figure 2) of the *erythro* amino alcohols **1a–d** and 1,2-diphenylethanol (**3**) were assigned after resolution by a special-purpose analog computer, the Du Pont 310 curve resolver. In generating each component of the curve, shapes corresponding to Gaussian distribution were assumed. The positions of the resolved, relatively sharp unassociated OH and OH···π peaks could be estimated to ±1.5 cm^{-1}; the broad OH···N peak was estimated to an accuracy of ±2.5 cm^{-1}. Extinction coefficients were measured by employing peak height. The resolved curve was used to measure peak heights in the case of multicomponent absorption curves.

Registry No.—**1a** (*threo*), 19640-34-7; **1a** (*erythro*), 19640-35-8; **1b** (*threo*), 19640-36-9; **1b** (*erythro*), 19640-37-0; **1c** (*threo*), 19640-38-1; **1c** (*erythro*), 19640-39-2; **1d** (*threo*), 2576-07-0; **1d** (*erythro*), 19640-41-6; **2** (*trans*), 7581-94-4; **3**, 614-29-9; **4**, 98-85-1.

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Alumina-Catalyzed Dehydration of Methylhexadienols. A Reinvestigation[1]

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Catalytic dehydration of substituted hexadienols usually produces a mixture of substituted 1,3,5-hexatrienes and the corresponding substituted 1,3-cyclohexadienes. Alumina dehydration of 1,5-heptadien-4-ol or 3-methyl-1,5-hexadien-3-ol at temperatures ranging from 250 to 350° yielded the expected methyltrienes, but the cyclohexadiene fraction consisted of double-bond isomers whose distribution proved to be temperature dependent. Thermolysis of authentic 1,3,5-heptatriene or 3-methyl-1,3,5-hexatriene over alumina or glass helices yielded similar results. The 1,3-cyclohexadienes formed at 250° can be predicted on the basis of electrocyclic ring closure of an intermediate triene having a *cis* configuration about the central double bond. At 350°, 1,3-cyclohexadiene mixtures, resulting from intramolecular 1,5-hydrogen shifts in the Woodward–Hoffmann product, predominate.

Until very recently, the preparation of substituted 1,3,5-hexatrienes has involved either a vapor phase catalytic dehydration over alumina or an acid-catalyzed dehydration of an appropriately substituted hexadienol. The products isolated from these procedures, in most cases, have been of doubtful purity. Pure substituted 1,3,5-hexatrienes have been prepared by means of a Hofmann elimination.[2-4] It has been established that the major by-product of catalyzed hexadienol dehydration is a corresponding cyclohexadiene. The formation of these cyclohexadienes has been described by Woods and coworkers,[5,6] who considered thermal trienic ring closure an internal Diels–Alder reaction. However, Woodward and Hoffmann[7] now describe it as a disrotatory electrocyclic transformation.

Woods and Fleishacker[5] attempted the preparation of the three possible methyl-1,3,5-hexatrienes by dehydration of appropriately substituted hexadienols over alumina, however, only 1,3,5-heptatriene was obtained in a relatively pure state. The 2-methyl- and 3-methyl-1,3,5-hexatrienes were apparently contaminated with appreciable quantities of methylcyclohexadienes. These workers also reported that either dehydration of the methylhexadienol over alumina at 500° or passage of methyl-1,3,5-hexatriene over the catalyst under the same conditions yielded methylcyclohexadienes of indeterminate double-bond position. We have recently shown[8] that under the experimental conditions employed by Woods and Fleischacker, cyclization followed by dehydrogenation to toluene is also an important reaction. Hence, it is probable that products formed at these temperatures were contaminated with toluene.

Lewis and Steiner[9] have studied the cyclization of 1,3,5-hexatriene and found that the purely thermal cyclization of the *cis* isomer was practically quantitative at 120–190°; the *trans* isomer was unaffected. We decided, therefore, to reinvestigate both the catalytic dehydration of methylhexadienols and the thermal cyclization of the pure methyl-1,3,5-hexatrienes at temperatures lower than those employed by Woods, *et al.*, in order to suppress the methylcyclohexadiene to toluene reaction. We also hoped to elucidate the structures of the methyl cyclohexadienes formed in both of the above reactions.

Both 1,5-heptadien-4-ol (**1**) and 3-methyl-1,5-hexadien-3-ol (**2**) were dehydrated in the vapor phase over activated alumina at 250° and at 350°. Table I summarizes the products obtained from these dehydrations.

Application of earlier[5-9] observations on dienol dehydration to the alumina-catalyzed dehydration of either **1** or **2** would lead one to predict the reaction sequences given in Scheme I. Although most previous

(1) (a) Portions of this paper were presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968. (b) The authors would like to express their appreciation to the National Science Foundation for partial support of this research under an Undergraduate Research Participation Grant.

(2) C. W. Spangler and G. F. Woods, *J. Org. Chem.*, **28**, 2245 (1963).

(3) C. W. Spangler and G. F. Woods, *ibid.*, **30**, 2218 (1965).

(4) J. C. H. Hwa, P. L. de Benneville, and H. J. Sims, *J. Amer. Chem. Soc.*, **82**, 2537 (1960).

(5) H. Fleischacker and G. F. Woods, *ibid.*, **78**, 3436 (1956).

(6) G. F. Woods and A. Viola, *ibid.*, **78**, 4380 (1956).

(7) R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965).

(8) C. W. Spangler, *J. Org. Chem.*, **31**, 346 (1966).

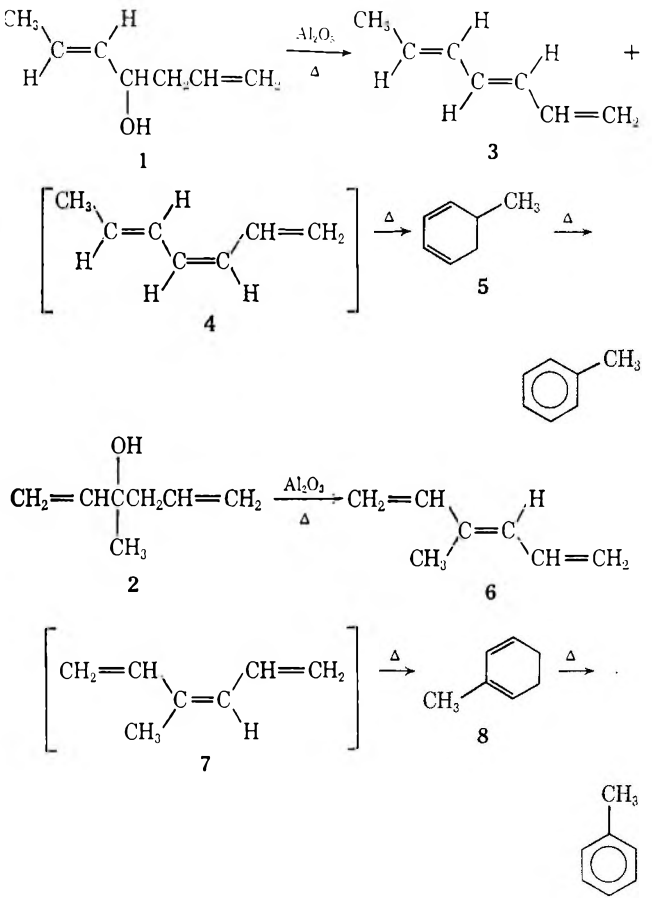
(9) K. E. Lewis and H. Steiner, *J. Chem. Soc.*, 3080 (1964).

TABLE I
METHYLHEXADIENOL–ALUMINA DEHYDRATION PRODUCTS

Dienol	Temp, °C	% of total product[a] 1,3,5-Triene 1-Me	1,3,5-Triene 3-Me	1,3-Cyclohexadiene 1-Me	1,3-Cyclohexadiene 2-Me	1,3-Cyclohexadiene 5-Me	Toluene
1	250	62[b]		Trace	Trace	35	Trace
1	350	31[c]		18	11	29	Trace
2	250		26[d]	3	25	31	3
2	350		22[e]	24	20	11	4

[a] Several minor products (*ca.* 1–2% each) make up the balance of products. 3-Methylenecyclohexene was present in each dehydration product (1–4%). [b] 78% *trans, trans*, 22% *cis, trans*. [c] 68% *trans, trans*, 32% *cis, trans*. [d] *cis–trans* peaks not totally resolved. [e] *trans* isomer at least 90% of mixture.

SCHEME I

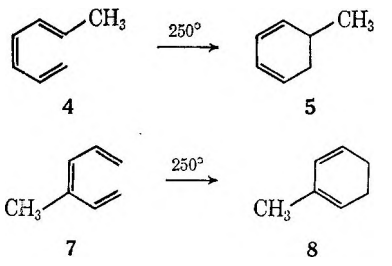


workers have failed to detect the labile trienes having a *cis* configuration about the central double bond, they have found considerable quantities of the corresponding 1,3-cyclohexadienes. If the above reaction scheme is correct, then the quantity of cyclized product found in dienol dehydrations may be utilized to indicate the ratio of *cis* to *trans* product in the original dehydration step. However, there have been no definitive experiments to determine if *cis–trans* triene mixtures actually follow the on-column cyclization sequence postulated in dienol dehydration.

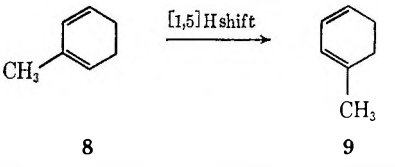
Thermolyses of pure 1,3,5-heptatriene[3] (56% **3**, 44% **4**) or of 3-methyl-1,3,5-hexatriene[3] (55% **6**, 45% **7**) in a dehydration column packed with either glass helices or with activated alumina were carried out under reaction conditions essentially identical with those employed for the dehydration of either **1** or **2**. Table II summarizes the results of these comparative cyclizations.

It can immediately be seen that thermolyses carried out at 250° tend to support the proposed dehydration scheme. The methyl-1,3-cyclohexadiene obtained from both **4** and **7** has the double bond positional structure expected from simple electrocyclic ring closure (**5** and **8**, respectively) (Scheme II). However, other processes

SCHEME II

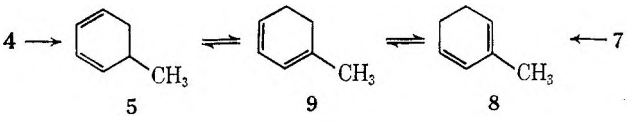


apparently can occur simultaneously when alumina replaces Pyrex as a thermolysis solid support. Thus 1-methyl-1,3-cyclohexadiene (**9**) and 3-methylenecyclohexene (**10**) appear in the 250° alumina thermolysis product of 3-methyl-1,3,5-hexatriene. The formation of **10** has been noted previously in similar systems by Pines, *et al.*,[10,11] and should not be surprising. However, **9** cannot result from a simple ring-closing process of **7**. The most probable source of this abnormal cyclization product is **8**, from which **9** can result by a [1,5] sigmatropic shift of hydrogen. Another alumina



process which must exist in order to account for the sum total of cyclization products is *trans* → *cis* isomer interconversion. That this is not a thermal process at 250° is evident from a material balance; the quantity of cyclization product formed is directly related to the initial central double bond *cis*-isomeric content. This conversion is appreciable at 250° over alumina: **3** → **4** → products (28.6%),[12] and **6** → **7** → products (32.8%).[12]

At 350°, thermolysis over Pyrex helices more closely resembles the alumina process than at 250°. In both cases, the cyclization products are complex mixtures of the three possible methyl-1,3-cyclohexadienes and/or 3-methylenecyclohexene and toluene. The residual yields of the corresponding 1,3,5-trienes are also considerably reduced. Thus cyclization followed by [1,5]



hydrogen shifts predominates. Similarly, at 350°, *trans* → *cis* conversion followed by cyclization becomes important in the purely thermal reaction over helices. Toluene formation is also evident at 350°, although it is a minor process compared to its importance at higher temperatures.[8]

Catalytic dienol dehydration processes, and the resultant complex product mixtures, thus can be readily interpreted on the basis of the above studies. Dehydra-

(10) H. Pines and R. H. Kozlowski, *J. Amer. Chem. Soc.*, **78**, 3776 (1955).
(11) H. Pines and C. Chen, *ibid.*, **81**, 928 (1958).
(12) Percentages indicate quantity of original central *trans* isomer following this process *via a vis* 0% for the purely thermal process over helices.

TABLE II
THERMOLYSIS METHYL-1,3,5-HEXATRIENES

1,3,5-Triene	Temp, °C	Support	% of total[c] 3	4	6	7	5	8	9[a]	10[b]
1-Me (56% **3**, 44% **4**)	250	Helices	56	22			22			
	250	Al_2O_3	40	18			42		Trace	
	350	Helices	45	10			15	8	22	
	350	Al_2O_3[d]	8	4			21	25	29	8
3-Me (55% **6**, 45% **7**)	250	Helices			55	Tr	Tr	45	Tr	
	250	Al_2O_3			37	Tr	Tr	40	13	10
	350	Helices			43	Tr	1	44	12	
	350	Al_2O_3[e]			20	Tr	6	26	32	9

[a] **9**, 1-methyl-1,3-cyclohexadiene. [b] **10**, 3-methylenecyclohexene. [c] Several minor products (*ca.* 1–2% each) were present in those thermolysis products totalling less than 100%. [d] Toluene, 5% of product. [e] Toluene, 7% of product.

tions in which the central trienic double bond is generated yield an initial mixture of geometric isomers. This mixture can contain appreciable quantities of the less stable *cis* isomers. At the reaction temperatures of most catalytic dehydrations, however, electrocyclic ring closure of the *cis* isomer is a highly favored reaction, and usually little, if any, *cis* isomer survives.[13] Unfortunately, the total quantity of cyclized product is not a reliable measure of the initial *cis/trans* product ratio, since alumina can catalyze *trans* → *cis* conversion, even at 250°. In most cases the predominating, if not sole, cyclization product at 250° will be a 1,3-cyclohexadiene arising from electrocyclic ring closure of the *cis*-triene. However, at elevated temperatures (350° or higher), other processes predominate: (1) substituted 1,3-cyclohexadienes undergo thermal [1,5] sigmatropic rearrangement resulting in a mixture of positional isomers[14]; (2) extensive *trans* → *cis* → cyclization takes place, thus reducing the yield of triene considerably; (3) dehydrogenation of intermediate cyclohexadienes yields aromatics, apparently catalyzed by alumina rather than by thermal means. Although the mechanism by which some of these products, and the nature of some minor processes, are still obscure, we feel that these studies extend our understanding of the catalytic dehydration of unsaturated alcohols considerably.

Experimental Section[15]

Dehydration of 1,5-Heptadien-4-ol (1). **A.**—Through a 22-mm Pyrex tube packed to a depth of 12 in. with activated alumina (8–14 mesh), and externally heated at 250° with a Lindberg Hevi-Duty split-tube electric furnace, was dropped 1,5-heptadien-4-ol (21.3 g, 0.19 mol) at the rate of 0.5 ml/min. The alumina had been dried previously by heating the column at 300° under vacuum for 1 hr. A pressure of 20–25 mm was maintained in the system to facilitate rapid removal of the product from the column.[16] The product was trapped in a flask immersed in a Dry Ice–acetone bath, and subsequently warmed to room temperature and separated from a small quantity of water by filtration through anhydrous magnesium sulfate. After filtration, the clear yellow liquid was distilled at reduced pressure and the volatile fraction collected. No attempt was made to maximize the yield (75%) and a substantial quantity of liquid was allowed to remain in the distillation flask due to the possibility of cyclohexadiene peroxide formation reported by Woods and Fleischacker.[5] Glpc analysis showed the presence of three products. The peak emanating from the chromatograph representing the supposed methylcyclohexadiene was trapped in a V tube immersed in a Dry Ice bath. Reinjection of this sample under conditions known to allow the separation of all isomeric methylcyclohexadienes showed that it was free of triene and was 98+% pure. For this product, $n^{25}D$ 1.4628, λ_{max} 259 mμ (ϵ_{max} 3700) was compared to that reported by Woods, *et al.*[5] [$n^{28}D$ 1.474 and λ_{max} 259 (ϵ_{max} 3300)]. The nmr spectrum revealed a doublet at τ 8.8 (three methyl protons, J = 5.5 Hz), multiplet 7.3–8.0 (three allylic protons), multiplet 3.8–4.3 (four vinyl protons). This compares favorably with 1,3-cyclohexadiene, τ 7.8–7.9 (four allylic protons) and 3.9–4.2 (four vinyl protons). The infrared spectrum was consistent with the assigned structure. On the basis of the above we assign the structure as 5-methyl-1,3-cyclohexadiene (**5**).

B.—1,5-Heptadien-4-ol (20.0 g, 0.18 mol) was dehydrated, as described above, at 350°. The crude product was isolated and purified (85% yield). Glpc analysis revealed that at least 13 components were present in the product mixture. Six of these minor constituents (6.4% of total) were not identified. The C_7H_{10} isomers were separated from the gc effluent as described above and analyzed by uv, ir, and nmr spectrometry. In general, a rapid qualitative analysis could be made based on uv maxima (λ_{max} mμ (isooctane) is given in parentheses): **5** (259), **8** (261), **9** (264), **10** (232). The ir and nmr spectra of all C_7H_{10} isomers were consistent with this assignment.

Dehydration of 3-Methyl-1,5-hexadien-3-ol (2). **A.**—3-Methyl-1,5-hexadien-3-ol (**2**, 8.0 g, 0.071 mol) was dehydrated, as described above, at 250° yielding a crude product mixture (4.8 g, 72%) which upon glpc analysis was shown to consist of at least 12 components. Five of these minor constituents (8–9% of total) were not identified.

B.—3-Methyl-1,5-hexadien-3-ol (**2**, 5.0 g, 0.045 mol) was dehydrated, as described above, at 350° yielding a crude product mixture (3.0 g, 71%) which upon glpc analysis was shown to consist of at least 12 components. Five of these minor constituents (15% of total) were not identified.

Cyclization of 1,3,5-Heptatriene (3, 4). **A.**—A mixture of 56% *trans,trans* **3** and 44% *cis,trans*-1,3,5-heptatriene (**4**, 9.0 g) was added dropwise through a 22-mm Pyrex tube packed to a depth of 12 in. with $^1/_{16}$ in. Pyrex helices and externally heated at 250° as in the above dehydration studies. The thermolysis product was isolated in a manner similar to the above dehydrations, finally yielding a product composed of 56% *trans,trans*-, 22% *cis,trans*-1,3,5-heptatriene and 22% 5-methyl-1,3-cyclohexadiene (**5**), as determined by glpc (63% recovery).

B.—A similar thermolysis at 350° yielded 45% *trans,trans*-, 10% *cis,trans*-1,3,5-heptatriene 15% **5**, 8% **8**, and 22% **10** (72% recovery).

C.—A similar thermolysis at 250°, except that activated alumina (8–14 mesh) was utilized instead of Pyrex helices, yielded 40% *trans,trans*- 18% *cis,trans*-1,3,5-heptatriene and 42% **5** (65% recovery).

D.—A thermolysis similar to **C** at 350° yielded 8% *trans,trans*-, 4% *cis,trans*-1,3,5-heptatriene, 21% **5**, 25% **8**, and 29% **9** as well as several minor products (60% recovery).

Cyclization of 3-Methyl-1,3,5-hexatriene (6, 7). **A.**—A mixture of 55% *trans*- and 45% *cis*-3-methyl-1,3,5-hexatriene (10.0 g) was added to the above described thermolysis column

(13) A suggestion by a referee which we reject is that the *cis–trans* ratio triene observed at any dehydration temperature, T, might well represent the equilibrium ratio, K. As can be seen from our data, however, the experimental ratio varies considerably from dehydration to thermolysis.

(14) For an excellent review of thermal [1,5] hydrogen shifts, see the following, and references therein: (a) D. S. Glass, R. S. Boikess, and S. Winstein, *Tetrahedron Lett.*, 999 (1966); (b) K. W. Egger, *J. Amer. Chem. Soc.*, **89**, 3688 (1967).

(15) Gas–liquid partition chromatography was performed with an Aerograph Model 202-1B with dual 15-ft, 15% β,β′-oxydipropionitrile-on-Chromosorb W columns. This instrument was equipped with a Disc integrator for peak area measurement. Ultraviolet spectra were obtained with a Perkin-Elmer Model 202 spectrophotometer (Spectrograde isooctane), infrared spectra with a Beckman IR-8. Nmr spectra were obtained with a Varian A-60A spectrometer using TMS (τ 10) as an internal standard and $CDCl_3$ solvent. Activated alumina utilized in these experiments was Matheson Coleman and Bell grade (8–14 mesh) and was not treated further.

(16) Contact time of the alcohol vapor with the alumina catalyst averages between 45 and 60 sec.

packed with helices and maintained at 250°. The products were isolated in a similar manner, yielding 55% *trans*-3-methyl-1,3,5-hexatriene and 45% 2-methyl-1,3-cyclohexadiene (**8**, 74% recovery).

B.—A similar thermolysis at 350° yielded 43% *trans*-3-methyl-1,3,5-hexatriene, 1% **5**, 44% **8**, and 12% **9** (78% recovery).

C.—A similar thermolysis at 250°, except that activated alumina (8–14 mesh) was utilized instead of Pyrex helices, yielded 37% *trans*-3-methyl-1,3,5-hexatriene, 40% **8**, and 13% **9** as well as several minor products (65% recovery).

D.—A thermolysis similar to **C** at 350° yielded 20% *trans*-3-methyl-1,3,5-hexatriene, 6% **5**, 26% **8**, and 32% **9** as well as several minor products (72% recovery).

Registry No.—**5**, 19656-98-5; **8**, 1489-57-2; **9**, 1489-56-1; **10**, 1888-90-0.

The Chemistry of 10α-Estr-4-en-17β-ol-3-one and Selected Transformation Products[1]

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Received November 1, 1968

Hydrogenation of estra-4,9(11)-dien-17β-ol-3-one (**1**) gave 10α-estr-4-en-17β-ol-3-one (**2**), the parent member of a new series of steroids. Spectral studies indicate that ring B in this series has a boat conformation. This strained system is readily isomerized to 19-nortestosterone in acids and in base. Reduction with lithium aluminum tri-*t*-butoxyhydride gave the corresponding equatorial 3α-alcohol **7**, which was converted into the 3-deoxy-Δ^4 and -$\Delta^{5(6)}$ olefinic analogs by hydrogenolysis with lithium in ethylamine. The C-4 double bond appears to shift to the corresponding C-5(6) olefin in the presence of strong base. Reduction of **2** with lithium–ammonia solutions gave 10α,5β-estra-17β-ol-3-one (**10**).

Alteration of one or more of the asymmetric centers in the steroid nucleus has led to some interesting changes in its chemical and biological properties.[2] In the present study we would like to describe the synthesis and chemistry of 10α-estr-4-en-17β-ol-3-one (**2**) and of some of its derivatives.

The introduction of the 10α stereochemistry in the estrene nucleus was readily accomplished by selective catalytic hydrogenation of the 9(10) double bond of estra-4,9(10)-dien-17β-ol-3-one (**1**),[3] using as catalyst either palladium on barium sulfate or 2% palladium on strontium carbonate in benzene.[4] The latter resulted in a high degree of selectivity, giving directly in 60% yield a dihydro product which was identified as 10α-estr-4-en-17β-ol-3-one (**2**). In general, all other catalysts and reaction conditions studied gave significant quantities of mixed tetrahydro and aromatized steroids.

Spectral properties of **2** displayed features characteristic of a 19-nortestosterone derivative.[5] Inspection of ORD and CD spectra using dioxane as solvent showed a small negative Cotton effect in the π–π^* region, a result similar to that reported for 10α-testosterone.[6,7] Surprisingly, a small positive Cotton effect was obtained in this region with methanol.[8] The sign of the Cotton effect in the n–π^* region is negative in both solvents. This change in sign in the low-wavelength region can be attributed to a solvation effect. Alternately, and perhaps more likely, a shift in the conformer populations may occur upon changing polarity. Neither 19-nortestosterone nor its 9β,10α-isomer exhibit this behavior. Examination of Dreiding models of **2** revealed that the A ring is relatively flat and can readily assume a positive or a negative chirality. The RD results obtained in dioxane, when analyzed using the chirality rule,[7] are best accommodated by assignment of 10α stereochemistry to the dihydro product **2**. The most plausible conformation consistent with these data is shown in Figure 1. The nmr spectrum of **2** reflects a greater degree of shielding of the C-18 methyl groups by its greater proximity to the C–C bonds in rings A and B resulting in a net diamagnetic shielding, relative to its 10β isomer **5**.[9] The chemical shifts of the C-18 methyl groups of several of the 10α-estrenes reported in this study are shown in Table I, together with those of some corresponding 10β analogs.

The steric strain resulting from the ring-B boat conformation can be readily relieved by enolization and reprotonation at C-10β to give 19-nortestosterone (**5**) after acid or base treatment.[10,11] The configuration of the C-9 proton was therefore confirmed by the isolation of **5** and confirmed further by the hydrogenation of **2** to give the known 10α ketone **6**.[2g,h]

The monoacetate **3**, which could also be obtained by hydrogenation of the diene acetate **4**, was reduced with

(1) For a preliminary report regarding part of the present work see E. Farkas, J. M. Owen, M. Debono, R. M. Molloy, and M. M. Marsh, *Tetrahedron Letters*, 1023 (1966).

(2) For some recent examples of syntheses of steroids bearing unnatural stereochemistry at one or more asymmetric centers, see (a) P. Westerhof and E. H. Reerink, *Rec. Trav. Chim. Pays-Bas*, **79**, 771 (1960); (b) R. Wenger, H. Dutler, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **45**, 2420 (1962), and **46**, 1096 (1963); (c) L. Velluz, G. Nominé; R. Bucourt, A. Pierdet, and J. Tessier, *Compt. Rend.*, **252**, 3903 (1961); (d) J. A. Edwards, P. Crabbé, and A. Bowers, *J. Amer. Chem. Soc.*, **85**, 3313 (1963); (e) P. Westerhof, *Rec. Trav. Chim. Pays-Bas*, **83**, 1069 (1964); (f) F. Sondheimer, R. Mechoulam, and M. Sprecher, *Tetrahedron*, **20**, 2473 (1964); (g) R. T. Rapala and E. Farkas, *J. Org. Chem.*, **23**, 1404 (1958); (h) R. E. Counsell, *Tetrahedron*, **15**, 202 (1961).

(3) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Amer. Chem. Soc.*, **82**, 2402 (1960).

(4) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *ibid.*, **74**, 4223 (1952).

(5) (a) A. J. Birch, *J. Chem. Soc.*, 367 (1950); (b) A. L. Wilds and N. A. Nelson, *J. Amer. Chem. Soc.*, **75**, 5366 (1953).

(6) See ref 2b.

(7) W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961).

(8) A. Moscowitz, K. M. Wellman, and C. Djerassi, *Proc. Natl. Acad. Sci. U. S.*, **50**, 799 (1963).

(9) Shielding of hydrogen nuclei in rigid systems is believed to be due to diamagnetic anisotropic contributions associated with neighboring C–C bonds; see L. M. Jackman and R. H. Wiley, *J. Chem. Soc.*, 2881 (1960). For other leading references see J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. II, Permagon Press, New York, N. Y., 1966.

(10) This transformation has precedence in the base-catalyzed epimerization of the C-6 methyl group in the 6β-methyl-Δ^4-3-one system; see ref 11.

(11) A. Bowers and H. J. Ringold, *J. Amer. Chem. Soc.*, **80**, 3091 (1958); H. J. Ringold, E. Batres, and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957).

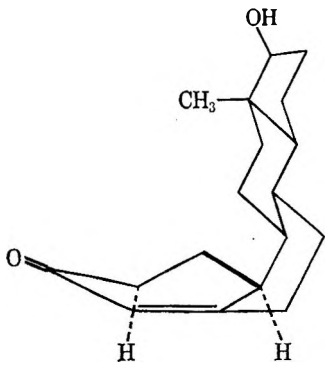


Figure 1.—Schematic representation of the conformation of 2.

TABLE I

Nmr Data for Some 19-Nor Steroids

Steroid	Chemical shift, ppm[a] C-18	C-4	C-6
1	0.90	5.67	
2	0.70	5.90	
3	0.77	5.87	
5	0.83	5.88	
10	0.80	5.38	
11	0.70	5.39	
11 (Δ^5 isomer)	0.75		5.65[b]
12	0.83	5.42	
13	0.84		5.68[b]
13 (Δ^4 isomer)	0.83	5.40	
10β-Estr-4-en-17β-ol	0.78	5.40	
10β-Estr-4-en-17-one	0.89	5.44	
10β-Estr-4-en-17α-ethynyl-17β-ol	0.87	5.43	
10β-Estr-5(6)-ene-3α,17β-diol diacetate	0.80		5.55[b]

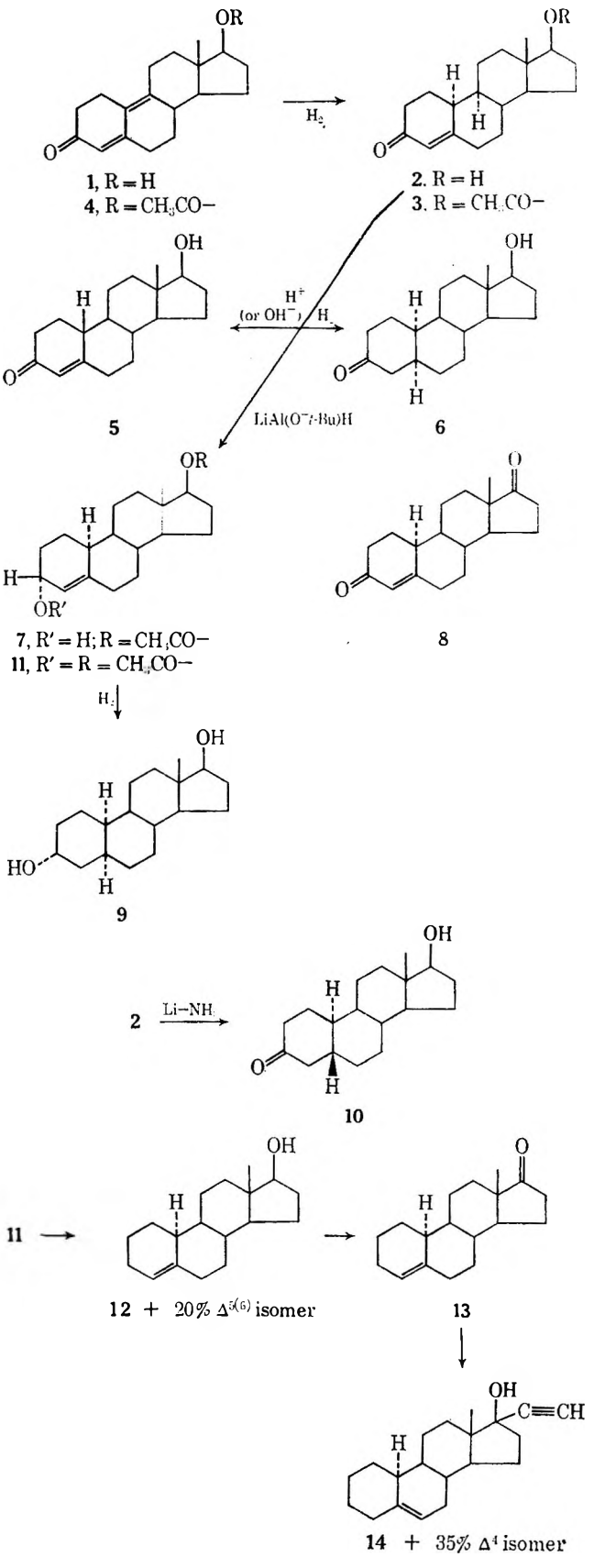
[a] Data for solution in $CDCl_3$. [b] The $\Delta^{5,6}$ olefins reported here exhibited allylic coupling of 3–6 Hz. No such coupling was observed for the corresponding Δ^4 isomer.

lithium tri-*t*-butoxyaluminum hydride to give the corresponding C-3 alcohol **7** in high yield[1] (Scheme I). Oxidation of **7** with activated manganese dioxide readily gave back **3** to confirm that the reduction and oxidation did not alter the 10α stereochemistry. Furthermore, **2** was found to undergo Sarett oxidation to the 3,17-dione **8** without altering the C-10 configuration.[12]

Wheeler and Mateos[13] reported that lithium tri-*t*-butoxyaluminum hydride reduced cholest-4-en-3-one quantitatively to the equatorial 3β-alcohol. Similarly, the reduction of **3**, which exists in a rigid conformation (see Figure 1), leads to the alcohol **7** whose C-3 hydroxyl group is both 3α and equatorial.[14] This assignment was confirmed by the conversion of **7** to 5α,10α-estra-3α,17β-diol (**9**) by hydrogenation and subsequent hydrolysis. The isolation of **7** verifies the plausibility of the conformation deduced from the ORD–CD data.

Chemical reduction of **2**, using a solution of lithium in liquid ammonia, resulted in the isolation of 5β,10α-estran-17β-ol-3-one (**10**) (60%) as the major product.[1,9] The fact that this material was different from the known

SCHEME I



10β,5α-[15] and the 10β,5β-estran-17β-ol-3-one[16] suggests that no epimerization at C-10 occurred before or during reduction. The 5β stereochemistry of the product is

(12) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(13) (a) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962); (b) O. H. Wheeler and J. L. Mateos, *Chem. Ind.* (London), 395 (1957).

(14) S. G. Levine, N. H. Eudy, and E. C. Farthing, *Tetrahedron Letters*, 1517 (1963).

(15) A. Bowers, H. J. Ringold, and E. Denot, *J. Amer. Chem. Soc.*, **80**, 6115 (1958), and references cited therein.

(16) R. T. Rapala and E. Farkas, *ibid.*, **80**, 1008 (1958).

consistent with the current theory of metal–ammonia reduction indicating β protonation of the stereoelectronically favored transition state (ring B half-chair).[17] The strong negative Cotton effect for **10** in the RD spectrum was communicated previously.[1] Additional support for this stereochemistry can be obtained from the nmr spectrum where the C-18 methyl protons of **10** occur at 42 cps, while the corresponding signal for the all-*trans* 5α,10β-estran-17β-ol-3-one occurs at 47 cps.

Hydrogenolysis of the allylic diacetate **11** with a solution of lithium in anhydrous ethylamine resulted in the isolation of a mixture of olefins (**12**).[18] The nmr spectrum of this mixture showed two distinct signals for olefinic protons at δ 5.42 and 5.65 ppm in a 3:2 ratio. In an analogous reaction sequence using the 10β isomer, only a single olefin, 10β-estr-4-en-17β-ol, was obtained; it showed a single nmr signal at δ 5.46 ppm.[19] Oxidation of mixture **12**, followed by careful purification, resulted in the isolation of one of the olefinic components as the 17-ketone **13**. Its nmr spectrum showed a single olefinic signal at δ 5.42 ppm, verifying that this signal was due to a single trisubstituted olefinic proton. The second component with the higher field nmr signal for its olefinic proton could not be purified.

In a variety of steroids the $\Delta^{5(6)}$ olefinic proton has a higher chemical shift than that of the corresponding Δ^4 isomer.[20] The δ 5.65 ppm signal shown by **12**, therefore, is assigned to the $\Delta^{5(6)}$ isomer, while the lower field signal at δ 5.42 ppm is attributed to the Δ^4 olefin. The chemical shifts of the angular methyl groups in **12** and **13**, when compared with similar compounds in the 10β series, are consistent with the assignment of the 10α-estrene structure to these compounds. Ethynylation of **13** to **14** with lithium acetylide–ethylenediamine complex[21] caused a reappearance of the mixture of olefinic isomers (nmr signals at δ 5.46 and 5.65 ppm). In this case the $\Delta^{5(6)}$ isomer predominated (65%) as estimated by integration of these nmr signals. The longer reaction time for ethynylation (6 hr) seems to favor the $\Delta^{5(6)}$ isomer, as compared to the lithium–ethylamine hydrogenolysis reaction which results in the formation of more of the Δ^4 olefins. The longer time could be expected to increase the thermodynamically favored product.

Careful purification of the ethynylation product gave nearly pure $\Delta^{5(6)}$ olefin (**14**). Its nmr spectrum showed the presence of a single trisubstituted olefinic proton at δ 5.62 ppm. These results demonstrate that in the 10α series the Δ^4 olefin can be converted to the $\Delta^{5(6)}$ isomer by organometallic bases.[22] No such transformation of Δ^4 to the $\Delta^{5(6)}$ olefin is observed in the 10β case, indicating that this conversion is probably a function of stereochemical differences. These differences are probably related to the steric strain inherent in the 10α-estrene system resulting from the ring-B boat conformation. This steric strain can be reduced by a shift of the Δ^4 olefinic bond to the $\Delta^{5(6)}$ position, thereby converting ring B to a half-chair conformation which is more planar and less strained.[23] The mechanism of this shift can be rationalized by postulating the formation of an allylic carbanion which can result from abstraction of a C-6 proton by an organometallic base. The double bond can then shift to the more sterically favored $\Delta^{5(6)}$ position, contributing considerably to relief of steric strain which is the probable driving force for this transformation.[18]

Experimental Section[24]

Estra-4,9(10)-dien-17β-ol-3-one (**1**).—A solution of 10 g (0.037 mole) of estr-5(10)-en-17β-ol-3-one[3] in 288 ml of dry pyridine was cooled to 0°, and 11.5 g (0.036 mole) of pyridinium bromide perbromide was added in portions with vigorous stirring. The temperature was maintained at 0° for an additional 1 hr and at room temperature for 3 hr. The brown reaction mixture was poured into 700 ml of saturated NaCl solution, extracted with CH_2Cl_2 (three times), washed with 5% HCl (eight times) and then with saturated NaCl, and dried (Na_2SO_4). Evaporation of the solvent under vacuum gave a tan crystalline product which was recrystallized three times from acetone to give 7.23 g (72%) of **1**, mp 182–184°, uv max (EtOH) 304 mμ (ε 20,400). *Anal.* Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.28; H, 9.01.

10α-Estr-4-en-17β-ol-3-one (**2**).—A solution of **1** (5.0 g) was hydrogenated in 318 ml of benzene containing 1.5 g of 2% Pd–$SrCO_3$ at atmospheric pressure.[4] The theoretical amount of H_2 (525 ml) was absorbed in 3 hr. Removal of the catalyst and evaporation of the solvent gave 2.13 g of fine needles (Et_2O): mp 163–165°; CD (*c* 0.00025, dioxane), $\Delta\epsilon_{380}$ ±0, $\Delta\epsilon_{361}$ −1.78, $\Delta\epsilon_{343}$ −3.46, $\Delta\epsilon_{332}$ −3.46, $\Delta\epsilon_{321}$ −2.3, $\Delta\epsilon_{310}$ −1.1, $\Delta\epsilon_{280}$ ±0, $\Delta\epsilon_{258}$ +0.25, $\Delta\epsilon_{252}$ ±0, $\Delta\epsilon_{242}$ −0.60; CD (c 0.00042, MeOH), $\Delta\epsilon_{375}$ ±0, $\Delta\epsilon_{223}$ −2.29, $\Delta\epsilon_{278}$ ±0, $\Delta\epsilon_{245}$ +1.8; uv max (EtOH) 243 mμ (ε 15,350); nmr ($CDCl_3$) δ 0.70 (s, 3 H, 18-Me), 5.90 ppm (s, 1 H, C-4, olefinic); ir ($CHCl_3$) 1680 cm^{-1}. *Anal.* Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.97; H, 9.33.

A solution of **2** (0.4 g) in pyridine (4 ml) and Ac_2O (2 ml) was allowed to stand overnight at room temperature. A crystalline acetate, **3**, was obtained upon removal of solvent and recrystallization from ether–petroleum ether (30–60°), mp 143–144°. This was identical with the acetate obtained by hydrogenation of the acetate of **1**.

Estr-4,9(10)-dien-17β-ol-3-one 17-Acetate (**4**).—A solution of 5.0 g of **1** was dissolved in 20 ml of pyridine containing 10 ml of Ac_2O. After standing at room temperature overnight, solvents were removed and residual oil crystallized from ether–petroleum ether, giving 5.83 g (94%) of **4**: mp 107.5–108°; uv max (EtOH) 303 mμ (ε 20,500); $[\alpha]^{25}D$ −290.2° (*c* 1, $CHCl_3$). *Anal.* Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.24. Found: C, 76.15; H, 8.47.

10α-Estr-4-en-17β-ol-3-one 17-Acetate (**3**).—A solution of 2.0 g (0.0063 mole) of **1** was dissolved in thiophene-free C_6H_6 (80 ml) and hydrogenated at atmospheric pressure (24°) using 0.235 g of prereduced 2% Pd–$SrCO_3$ catalyst. After 1.2 equiv of hydrogen were taken up (1.75 hr), the reaction was stopped. The catalyst was removed by filtration, and the solvent was evaporated under reduced pressure. Uv spectrum of this crude product had uv max (EtOH) 242 mμ (ε 10,350). Crystallization from 4:1 petroleum ether–ethyl ether gave 0.728 g of a crystalline solid, mp 143–144°, uv max (EtOH) 242 mμ (ε 15,200), $[\alpha]^{25}D$ − 211.3° (*c* 1.05, $CHCl_3$). *Anal.* Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.71; H, 8.85.

(17) (a) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **86**, 1761 (1964); (b) M. J. T. Robinson, *Tetrahedron*, **21**, 2475 (1965).

(18) A. S. Hallsworth, H. B. Hensbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).

(19) M. S. de Winter, C. M. Siegmann, and S. A. Szpilfogel, *Chem. Ind.* (London), 905 (1959).

(20) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 88.

(21) O. F. Beumel, Jr., and R. F. Harris, *J. Org. Chem.*, **29**, 1872 (1964).

(22) The nmr signals of $\Delta^{5(6)}$olefinic protons in the 10β-estrene and the androstene series were observed to possess a 3–4-Hz allylic coupling which was not so pronounced in the corresponding signal for the Δ^4 isomer.

(23) The $\Delta^{5(6)}$ isomers in **8**, **9**, and **10** have angular methyl signals 2–3 Hz upfield from those of the Δ^4 isomer which qualitatively confirms that the $\Delta^{5(6)}$ double bond serves to flatten out the nucleus in the 10α series (see ref 9).

(24) Melting points are uncorrected. Uv spectra were recorded on a Cary 15 spectrophotometer. Ir spectra were determined on a Perkin-Elmer 21 instrument in $CHCl_3$. Nmr spectra were obtained on a Varian HR-60 with TMS as internal standard. The CD and ORD curves were recorded on a Cary 50 recording spectropolarimeter.

Epimerization of 2 to 19-Nortestosterone. A. Basic Conditions.—A solution of 0.1 g of **2** in 10 ml of MeOH was treated with 0.85 ml of a sodium methoxide solution (0.1 g of sodium/10 ml of MeOH) under nitrogen atmosphere and refluxed overnight. Most of the solvent was removed under vacuum, and excess water was added. The reaction mixture was extracted several times with ether, washed with 10% $NaHCO_3$ and NaCl solutions, and dried ($MgSO_4$). The residue, after removal of solvent, was chromatographed on 10 g of Florisil using Et_2O. Fractions 3–6 (55-ml fractions) were combined and crystallized from ether to give 0.045 g of a crystalline compound, mp 110–112°, which gave no depression on admixture with authentic 19-nortestosterone.[5]

B. Acidic Conditions.—To a solution of 0.03 g of **2** in 5 ml of $CHCl_3$ was added 1 ml of a saturated solution of HCl gas in $CHCl_3$. After refluxing overnight, the solution was poured into excess water and extracted with CH_2Cl_2. The organic layer was washed with 10% $NaHCO_3$ solution and NaCl solution successively, and then dried ($MgSO_4$). Evaporation of the solvent under vacuum gave 0.008 g of an oil which was crystallized from Et_2O. The properties of this material were identical with those of 19-nortestosterone.[5]

Hydrogenation of 2 to 5α,10α-Estran-17β-ol-3-one (6).—A solution of 0.082 g of **2** in EtOH (30 ml) was hydrogenated at atmospheric pressure, using 0.082 g of 5% Pd–$BaSO_4$. One equivalent of hydrogen was taken up in 30 min, the catalyst was filtered off, and the solvent was removed under vacuum. The residue crystallized from Me_2CO–Skelly B to give 0.11 g of **5**, mp 150–151°, whose X-ray pattern was identical with that of authentic 5α,10α-estran-17β-ol-3-one.[2g,h]

10α-Estr-4-ene-3,17-dione (8).—To a cold mixture of pyridine (3 ml) and chromic anhydride (0.4 g) was added a cold solution of 0.4 g of **7** in 5 ml of pyridine.[12] This mixture was kept at ice-bath temperatures for 15 min and allowed to warm to room temperature overnight. The dark mixture was diluted with water and extracted thoroughly several times with ether. The combined ether extract was washed with 5% HCl and then with saturated NaCl solutions. Evaporation of solvent gave a residue which was crystallized from Et_2O, and then from Et_2O–Skelly F to give 0.29 g of **8**, mp 162–164°. *Anal.* Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.06; H, 8.88.

10α-Estr-4-ene-3α,17β-diol 17-Acetate (7).—A solution of 0.50 g (0.0016 mole) of **3** in 22 ml of freshly distilled THF was added slowly to a solution of 0.60 g (0.0023 mole) of lithium tri-*t*-butoxyaluminum hydride in 20 ml of THF and refluxed for 2 hr.[13] The reaction mixture was cooled, poured into water (30 ml), and extracted with six 200-ml portions of CH_2Cl_2. After drying ($MgSO_4$) the organic layer was evaporated to dryness under reduced pressure to give 0.479 g of white solid which crystallized from Me_2CO to give 0.30 g of **7**: mp 151.5–153°, $[\alpha]^{25}D$ − 136.5° (*c* 1.05, $CHCl_3$). *Anal.* Calcd for $C_{20}H_{30}O_3$: C, 75.44; H, 9.49. Found: C, 75.47; H, 9.58.

5α,10α-Estrane-3α,17β-diol (9).—A solution of 0.1 g of **7** in 15 ml of EtOH containing 0.042 g of 5% Pd–C was hydrogenated at atmospheric pressure until 1 equiv of hydrogen was absorbed. The catalyst was removed by filtration, and the solvent evaporated under reduced pressure. The residue crystallized from Et_2O–Skelly F with a yield of 0.055 g of the acetate, mp 122–124°; this was dissolved in 5 ml of MeOH containing 0.04 g of powdered KOH and refluxed for 1 hr. Most of the solvent was removed and excess water was added; this was extracted thoroughly with CH_2Cl_2. The combined extract was washed with NaCl, dried ($MgSO_4$), and evaporated to dryness. The residue crystallized from Me_2CO–Skelly B to give white needles, mp 222–224° (lit.[22] mp 223–225°), and was identical with an authentic sample by mixture melting point.

5β,10α-Estran-17β-ol-3-one (10).—A solution of 1.0 g of **2** in 120 ml of dry THF was reduced according to the procedure outlined by Bowers using lithium metal (2.0 g) dissolved in liquid NH_3 (500 ml) with vigorous stirring.[15] After 20 min solid NH_4Cl was added to destroy the excess reagent, and the excess NH_3 allowed to evaporate. The residue was treated with excess water and extracted with Et_2O. Combined ether extracts were washed with NaCl solution, dried ($MgSO_4$), and evaporated to dryness.

The residue was dissolved in 3:1 C_6H_6–Skelly F and chromatographed on 100 g of grade III alumina. The reaction eluted with C_6H_6 showed only one spot on tlc and was crystallized from ethyl ether to give 0.31 g of **9** as colorless needles: mp 138–139°; ORD (*c* 0.00032, dioxane), $[\phi]_{275}$ + 1190°, $[\phi]_{298}$ ± 0, $[\phi]_{319}$ − 3487°. *Anal.* Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.09; H, 10.07.

10α-Estr-4-ene-3α,17β-diol Diacetate (11).—A solution of 0.15 g (0.45 mmole) of **7** in 1.2 ml of pyridine containing 0.6 ml of Ac_2O was allowed to stand at room temperature for 16 hr. After evaporation to dryness a yellow oil was obtained which was crystallized from petroleum ether to give 0.148 g (91%) of **11**, mp 98.5–100.5°, $[\alpha]D$ − 89.78° (*c* 1.04, $CHCl_3$). *Anal.* Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.94. Found: C, 73.26; H, 8.94.

10α-Estr-4-en-17β-ol (12).—A blue solution of lithium metal (11.5 g) in anhydrous $EtNH_2$ (60 ml) was carefully prepared.[18] A solution of 1.6 g of **11** in $EtNH_2$ (10 ml) was added at a rapid rate. After 10 min the reaction was quenched with careful addition of solid NH_4Cl until the blue color disappeared. The reaction mixture was concentrated to one-third volume, diluted with water, and extracted with four portions (100 ml) of CH_2Cl_2. The dried ($MgSO_4$) extract evaporated to dryness, and the resulting oil was chromatographed on 2.5 g of Florisil with 1:1 C_6H_6–petroleum ether to obtain 0.672 g of white platelets: mp 100–105° (petroluem ether); nmr, see Table I; $[\alpha]^{25}D$ − 96.14° (*c* 1.01, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.04; H, 10.97.

Further elution of the column gave mixtures of more polar materials which were not further investigated.

10α-Estr-4-en-17-one (13).—A solution of 0.21 g of **12** was oxidized by the Sarrett procedure using 0.21 g of CrO_3 (anhydrous).[12] The usual work-up gave an oil which eventually crystallized. This crude product was fractionally crystallized at Dry Ice–Me_2CO temperature from petroleum ether: mp 109–110.5°; nmr, see Table I; ir ($CHCl_3$) 1750 cm^{-1}. *Anal.* Calcd for $C_{18}H_{26}O$: C, 83.66; H, 10.14. Found: C, 83.56; H, 10.17.

Chromatography of mother liquors over 9.0 g of Florisil with C_6H_6–petroleum ether mixtures gave an additional 36 mg of material melting at 109–111°. Total yield was 74 mg (38.5%).

10α-Estr-5-en-17α-ethynyl-17β-ol (14).—A solution of 620 mg of **13** in THF (7 ml) was added to a stirred suspension of 368 mg of lithium acetylide (ethylenediamine complex) and 20 ml of THF at 10° while acetylene was bubbled into the reaction mixture.[21] After addition was complete, the cooling bath was removed, and the reaction was allowed to continue for 6 hr. The reaction was quenched by dropwise and cautious addition of 10 ml of concentrated NH_4Cl solution. The reaction mixture was extracted three times with CH_2Cl_2 (300 ml), and the extract was washed with water and dried ($NaSO_4$) overnight. Concentration of these extracts gave an oil (525 mg) which was chromatographed over Florisil (5.0 g). Pentane eluted 426 mg of an oil which was purified with great difficulty and which had a tendency to be hygroscopic and air sensitive when crystallized several times (71.5 mg); mp 141–142° (ether); nmr ($CDCl_3$) δ 5.69 [m, 0.8 H, C-5(6) olefin], 5.39 (m, 0.2 H, C-4(5) olefin]. *Anal.* Calcd for $C_{20}H_{28}O \cdot 0.33H_2O$: C, 82.83; H, 10.08. Found: C, 83.00; H, 10.21.

Registry No.—**1**, 6218-29-7; **2**, 5670-56-4; **3**, 6017-86-3; **4**, 19684-98-1; **7**, 19685-01-9; **8**, 5696-23-1; **10**, 19685-03-1; **11**, 19685-04-2; **12**, 19685-05-3; **13**, 19685-06-4; **14**, 19685-07-5.

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Ring B Functionalization of the 10α-Estra-4-en-17β-hydroxy-3-one System

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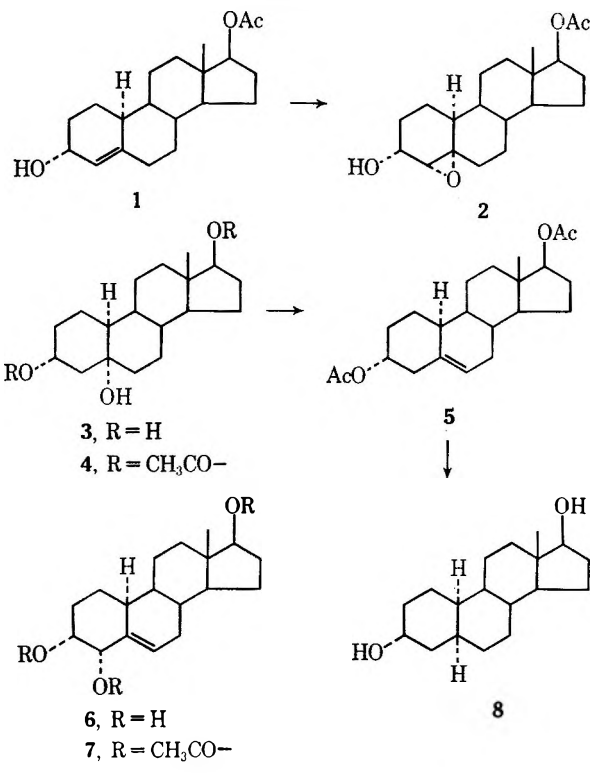
The syntheses and chemistry of ring-B functionalized members of the 10α-estrane series were studied. 10α-Estr-5(6)-en-3α,17β-dihydroxy diacetate (**5**) was synthesized from 10α-estr-4α,5α-oxido-3α,17β-diol 17-acetate **2** by lithium aluminum hydride reduction and subsequent dehydration of the resulting C-5 tertiary hydroxy group in **4**. The lithium aluminum hydride reduction of **2** also gave 3α,4α,17β-trihydroxy-10α-estr-5(6)-ene (**6**). The olefinic bond in **5** was used to introduce the $\Delta^{5(6)}$-7-one, 5α,6α-oxido, and 6-chloro-5-hydroxy groupings into the 10α-estrane system.

In the course of studies directed toward the preparation of steroids with modified (unnatural) stereochemistry, we have reported the properties of a new class of 19-nor steroids, the 10α-estrenes.[1] The present report is concerned with the synthesis and properties of some ring-B functionalized members of this series.

Functionalization of ring B in a variety of steroids has been accomplished using the $\Delta^{5(6)}$ double bond,[2] which can be introduced through dehydration of the corresponding C-5 hydroxy steroid. The synthesis of 10α-estr-5(6)-ene-3α,17β-diol was accomplished in a manner similar to that shown in Scheme I.

Scheme I



10α-Estr-4-ene-3α,17β-diol 17-acetate (**1**) was epoxidized with *m*-chloroperbenzoic acid to give the 4α,5α-epoxy alcohol (**2**).[1] The configuration of the oxirane ring was assigned on the basis of conformational considerations and its nmr spectrum. The unique conformation of the 10α-estrene system results in steric hindrance of the ring A β face due to the presence of the ring B boat.[1a] Reactions such as epoxidation and hydrogenation, therefore, are expected to occur preferentially on the less hindered α face.[3] In the nmr spectrum the signal for the proton at C-4 is a broadened doublet at δ 3.05 ppm (J = 2 Hz). Molecular models of **2** show that the dihedral angle between the 3β,4β protons is approximately 60°, leading to the predicted coupling constant of 2 Hz.[4] The corresponding dihedral angle for the 4β,5β-epoxide is 94° and would be expected to result in little or no coupling between the 4α,3β protons. The observed results, therefore, favor the 4α,5α configuration for the oxirane ring.

Reduction of the epoxy alcohol **2** with lithium aluminum hydride gave two triols. The predominant, more polar product **3** has two hydroxyl groups which were readily acetylated to give a diacetate to which structure **4** was assigned. Treatment of **4** with phosphorus oxychloride gave the desired C-5(6) olefin **5**. The nmr spectrum of **5** showed a single olefinic proton at δ 5.47 as a broadened doublet (J = 5–6 Hz), which represents a 0.1-ppm downfield shift from the corresponding signal of **4**.[1] Therefore, the double bond was assigned to the $\Delta^{5(6)}$ position.[5] Hydrogenation of **5** gave 5α,10α-estra-3α,17β-diol (**8**) which serves to establish that the 10α stereochemistry was retained during this reaction sequence.

The second triol **6** was shown by nmr spectrum to possess a new secondary alcohol function and a trisubstituted double bond. These observations were further verified by acetylation of **6** to a triacetate (**7**); the nmr spectrum of **7** retained the signal for the olefinic proton. The vicinal relationship of the newly introduced hydroxyl group to the hydroxyl group at C-3 was demonstrated by the facile periodic acid oxidation of **6** to an aldehyde.[6] Since Campion and Morrison observed that 3-methoxycholestanol 4α,5α-epoxide forms 3-methoxy-4α-hydroxycholesterol,[7] it is reasoned that the C-4 hydroxyl group of **6** also retains the 4α configuration. The exact mechanism for the formation of **6** remains obscure, although the intervention of aluminum salts as Lewis catalysts can not be discounted.

The chemical consequences of introducing a C-5(6) double bond into the 10α-estrane system were studied (see Scheme II). Epoxidation of **5** gave **9** in good yield. The configuration of epoxide **9** was deduced to be 5α,6α, using the nmr method described by Cross.[4]

(1) See M. Debono, E. Farkas, R. M. Molloy, and J. M. Owen, *J. Org. Chem.*, submitted for publication. Preliminary communication of the work appeared in E. Farkas, J. M. Owen, M. Debono, R. M. Molloy, and M. M. Marsh, *Tetrahedron Lett.*, 1023 (1966).

(2) (a) Pl. A. Plattner, H. Heusser, and M. Feurer, *Helv. Chim. Acta*, **32**, 587 (1949); (b) L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 4377 (1953); (c) A. J. Fudge, C. W. Shoppee, and G. H. R. Summers, *J. Chem. Soc.*, 958 (1954).

(3) H. B. Henbest and R. A. L. Wilson *ibid.*, 1958 (1957).

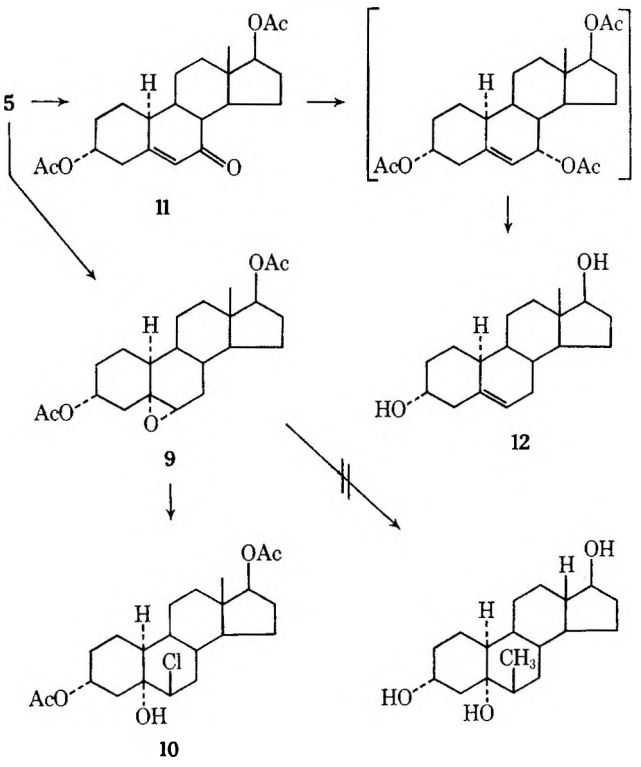
(4) A. D. Cross, *J. Amer. Chem. Soc.*, **84**, 3206 (1962).

(5) (a) J. N. Shoolery and M. T. Rogers, *ibid.*, **80**, 5121 (1958); (b) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 87.

(6) E. L. Jackson, *Org. Reactions*, **2**, 341 (1944).

(7) T. H. Campion and G. A. Morrison, *Tetrahedron Lett.*, 1 (1968).

SCHEME II



The coupling between the 6–7β protons is 4 Hz at δ 3.0 ppm, which is in good agreement with the predicted values (3.7–4.8 Hz). This reaction appeared to occur with high preference for formation of the α-epoxide; no significant amount of the β-oxide could be detected. The epoxide function of **9** proved to be resistant to attack by Grignard and organolithium reagents during attempts to synthesize the corresponding 6-methyl analog.[8] No explanation can be readily advanced at this time to account for the unreactivity of the oxirane ring toward these reagents. The possibility exists that the conformation of **9** produces interference with axial approach of the 6 position by the Grignard reagent from the β side, thereby interfering with the *trans*-diaxial cleavage of the epoxide ring.[9]

Addition of hydrogen chloride to **9** gave a chlorohydrin (**10**) in quantitative yield.[10] Treatment of **9** with boron trifluoride etherate resulted in no isomerization to 6-keto steroids under conditions known to cause this transformation in other series.[11]

Functionalization of C-7 was, however, readily accomplished by oxidation of **5** with *t*-butyl chromate, according to conditions outlined by Heusler to give the corresponding $\Delta^{5(6)}$-7-keto steroid **11**.[12] In order to confirm the retention of the 10α stereochemistry, **11** was reduced with $LiAlH_4$ to a mixture of triols; these were acetylated and reduced with a lithium solution in anhydrous ethylamine to remove the sole allylic acetate.[13] This process resulted in the regeneration of the $\Delta^{5(6)}$ system **12**. A photooxygenation path to **11**, using conditions described by Nickon,[14] failed and resulted in quantitative recovery of starting material.

(8) (a) For leading references to the addition of Grignard reagents to epoxides see J. G. Phillips and U. D. Parker, "Steroid Reactions," C. Djerassi Ed., Holden-Day, Inc., San Francisco, Calif., 1963, p 631; (b) R. Villotti C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 4566 (1959); (c) L. F. Feiser and J. Rigaudy, *ibid.*, **73**, 4660 (1951).

(9) For leading references see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 296.

(10) R. A. Baxter and F. S. Spring, *J. Chem. Soc.*, 613 (1943).

(11) H. B. Henbest and T. I. Wrigley, *ibid.*, 4596 (1957).

(12) (a) K. Heusler and A. Wettstein, *Helv. Chim. Acta*, **35**, 284 (1952); (b) K. Block, *ibid.*, **36**, 1611 (1953).

(13) A. S. Hallaworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, 1969 (1957).

(14) A. Nickon, N. Schwartz, J. B. DiGiorgio, and D. A. Widdowson, *J. Org. Chem.*, **30**, 1711 (1965).

(15) All melting points are uncorrected. Nmr data were obtained from a Varian HR-60 instrument; uv determinations were performed on a Cary-15 spectrophotometer; ir measurements were made on a Beckman IR-7 instrument.

Experimental Section[15]

Epoxidation of 1.—To a solution of **1** (5.52 g) in $CHCl_3$ (150 ml) which was cooled to 0° in an Me_2CO–ice bath, a solution of *m*-chloroperbenzoic acid (3.96 g) in $CHCl_3$ (125 ml) was added dropwise. The resultant solution was allowed to stand at 0° for 16 hr. After the addition of an equal volume of H_2O, the mixture was extracted with three portions of $CHCl_3$. The organic extracts were washed with $Na_2S_2O_3$ solution, 10% $NaHCO_3$ solution, H_2O, and dried overnight ($MgSO_4$). The solvent was evaporated to give **2** as a white powder (2.19 g); this was crystallized from Me_2CO: mp 177–178°; nmr ($CDCl_3$) δ 0.74 (s, 3 H, 18-CH_3), 2.02 (s, 3 H, acetate), 3.02 (d, 1 H, J = 2 Hz, 4β-H), 2.92 (m, 1 H, $W_{1/2}$ = 15 Hz, 3β-H), 4.65 (t, 1 H, J = 7 Hz, 17-H). *Anal.* Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.73; H, 9.15.

$LiAlH_4$ Reduction of 2.—A solution containing 8.24 g of **2** in 400 ml of THF was added dropwise to a cooled and stirred suspension of 3.2 g of $LiAlH_4$ in 900 ml of THF. The reaction was judged to be essentially complete by tlc after 14 hr. The excess $LiAlH_4$ was destroyed by successive additions of EtOAc, aqueous EtOH, and finally H_2O. The ether layer was washed with H_2O, dried ($MgSO_4$), and evaporated to dryness. The residual oil was chromatographed over 300 g of Davison silica gel (60–200 mesh), using benzene–EtOAc mixtures. Elution with solvent up to 50% EtOH in benzene gave unidentified oily products. A crystalline product (**6**) (2.19 g) was eluted with 20% EtOAc–benzene and 30% EtOAc–benzene: mp 181–182°; nmr ($CDCl_3$) δ 0.71 (s, 3 H, 17-CH_3), 3.55 (m, 2 H, 3- and 17-H), 4.08 (d, 1 H, J = 3 Hz, 4βH), 5.60 (d, broad, 1 H, J = 5 Hz, 6-H). *Anal.* Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.77; H, 9.62.

A sample of **6** (100 mg) was oxidized rapidly by a molar quantity of periodic acid to an oily aldehyde which resisted purification. Ir (1685 cm^{-1}) and nmr data [δ 9.4 (s, 1 H, HCOC=), 6.7 ppm (m, 1 H, OC=CH–)] indicate the presence of the α,β-unsaturated aldehyde group expected from structure **6**.

Further elution with 20% Me_2CO in EtOAc gave 3.39 g of crystalline product **3**, mp 214–216° (Me_2CO). *Anal.* Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.41; H, 10.35.

Acetylation of 3.—A solution of **3** (100 mg) in pyridine (3 ml) containing acetic anhydride (1.5 ml) was allowed to stand at room temperature overnight. After evaporation of solvents crystalline diacetate **4** (106 mg) was obtained: mp 178–179° (Et_2O); nmr ($CDCl_3$) δ 0.78 (s, 3 H, 18-CH_3), 2.02 (s, 6 H, CH_3COO–), 4.6 (m, 2 H, 3- and 17-H). *Anal.* Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 70.00; H, 9.28.

Acetylation of 6.—Acetylation of **6** (100 mg) was accomplished by the above procedure. Colorless crystalline triacetate **7** (49 mg) was obtained: mp 151–152° (Et_2O); nmr ($CDCl_3$) δ 0.80 (s, 3 H, 18-CH_3), 2.0, 2.04, 2.10 (s, 3 H each acetate), 4.05 (m, 2 H, 3- and 17-H), 5.5 (d, 1 H, J = 2.5 Hz, 4α-H), 5.80 (d, broad, 1 H, J = 6 Hz, 6-H). *Anal.* Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.64; H, 8.15.

10α-Estra-5(6)-ene-3α,17β-diol Diacetate (5).—Compound **4** (2.9 g) was dissolved in pyridine (50 ml) to which was slowly added $POCl_3$ (15 ml) with external cooling. This mixture was allowed to stand for 64 hr at 10° and the poured slowly into 150 ml of ice water. The reaction product was isolated by extraction with three portions of Et_2O which were combined and washed successively with H_2O, saturated $NaHCO_3$ solution, and H_2O. After drying ($MgSO_4$) and evaporation of solvent, 2.2 g of **5** was obtained as a colorless crystalline product: mp 135–136° (Et_2O); nmr ($CDCl_3$) δ 0.79 (s, 3 H, 18-CH_3), 2.0 (s, 6 H, 2-acetates), 4.62 (m, 2 H, 3β- and 17α-H), 5.47 (d, 1 H, J = 6 Hz, 6-H).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.26; H, 9.01.

Epoxidation of 5.—The epoxidation procedure utilized above was employed to convert 500 mg of **5** into epoxide **9** (392 mg): mp 138.5–139.5° (Et_2O); nmr ($CDCl_3$) δ 0.77 (s, 3 H, 18-H, 18-CH_3), 2.02 (s, 6 H, CH_3COO–), 3.0 (d, 1 H, J = 4 Hz, 6β-H), 4.68 (m, 2 H, 3β-, 17α-H). *Anal.* Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.24; H, 8.47.

Hydrogenation of 5.—A sample of **5** (50 mg) was hydrogenated for 18 hr at atmospheric pressure using 75 mg of PtO_2 in 15 ml CH_3OH containing 3 drops of 48% HBr solution. The usual work-up gave 31 mg of fine, amorphous solid **8**, mp 219–222° (Me_2CO–petroleum ether (bp 30–60°)); melting point and X-ray differaction pattern were identical with those of authentic 5α,10α-estrane-3α,17β-diol. No depression was observed in the mixture melting point determination.

HCl Addition to 9.—Hydrogen chloride gas was bubbled into a solution containing 100 mg of **9** in 8 ml of $CHCl_3$ for 30 min.[10] Evaporation of solvent gave a residue which was recrystallized twice from Et_2O to give chlorohydrin **10** (67 mg), mp 197–198°. *Anal.* Calcd for $C_{22}H_{33}O_5Cl$: C, 63.98; H, 8.05. Found: C, 63.97; H, 7.92.

***t*-Butyl Chromate Oxidation of 4.**—A solution of **4** (150 mg) in CCl_4 (1.5 ml) was refluxed and then treated with *t*-butyl chromate (1.2 ml) containing Ac_2O (0.15 ml) according to the method described by Heusler and Wettstein.[12a] This procedure gave an oily product which was chromatographed on 15 g of Florisil (100–200 mesh). Solvent mixtures of pentane–benzene eluted 50 mg of intractable oils, but further elution with 20% Et_2O in benzene gave colorless prisms (23 mg) of **11**: mp 166–167°; ir ($CHCl_3$) 1675 cm^{-1}; uv (EtOH) 236 mμ (ε 11,000); nmr ($CDCl_3$) δ 0.76 (s, 3 H, 18-Me), 3.68 (m, 1 H, 17α-H), 5.68 (s, 1 H, 6-H). *Anal.* Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.55; H, 8.32.

Conversion of 11 to 12.—A solution of **11** (60 mg) was exhaustively reduced with $LiAlH_4$ in THF, and the resulting mixture was acetylated by the usual procedures to give a crystalline mixture of acetates. This broad-melting mixture was dissolved in anhydrous $EtNH_2$ (10 ml), added to a solution of Li (60 mg) in $EtNH_2$ (50 ml), and allowed to stand for 5 min at room temperature.[13] The blue color was then removed by slow addition of solid NH_4Cl, and the solvent was allowed to slowly evaporate to near dryness. Addition of H_2O was followed by extraction with ether; evaporation of the dried ($MgSO_4$) extract gave an oil (41 mg) which was chromatographed on 4 g of silica gel (Davison 60–200 mesh). Benzene eluted 9 mg of an oily substance; further elution with Et_2O gave a oil which crystallized from Me_2CO–petroleum ether, mp 172–174°, and gave no depression in melting point when mixed with **12**. Mass spectral fragmentation, R_f on tlc, and nmr spectra of this product and **12** were also identical with data obtained from the hydrolysis product of **5**.

Hydrolysis of 5 to 12.—A solution of **5** (500 mg) in CH_3OH (25 ml) and H_2O (2.5 ml) containing $KHCO_3$ (370 mg) was refluxed for 2 hr, evaporated to half-volume, and treated with 0.25 ml of AcOH. After extraction with three portions of CH_2Cl_2 (100 ml each) and washing with H_2O, the organic layer was dried ($MgSO_4$). Evaporation of solvent gave a white powder (**12**), mp 174–175° (Me_2CO–petroleum ether). *Anal.* Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 77.97; H, 10.09.

Attempted Photooxygenation of 4.—A solution of **4** (300 mg) in pyridine (40 ml) containing 10 mg of eosin bluish was agitated in a slow stream of oxygen for 4.5 days while being irradiated by a fluorescent desk lamp according to the method outlined by Nickon.[14] Only unreacted starting material was isolated under these conditions.

Attempted Methylation of 9.—A solution of **9** (150 mg) in THF (12 ml) was treated with 1.7 *N* CH_3MgI (4 ml) for 32 hr under reflux.[8] After the residual Grignard reagent was destroyed with NH_4Cl, H_2O was added; the solution was extracted with ether. The extracts were washed with H_2O and dried ($MgSO_4$). Evaporation of solvent gave 123 mg of a colorless gum which was chromatographed on silica gel to give only desacetyl **9**, mp 140–141° (Me_2CO), nmr ($CDCl_3$) δ 2.97 ppm (d, J = 4 Hz, 1 H, C-6 proton). *Anal.* Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.91; H, 9.73.

Registry No.—**2**, 19684-86-7; **3**, 19684-87-8; **4**, 19684-88-9; **5**, 19684-89-0; **6**, 19684-90-3; **7**, 19684-91-4; **9**, 19684-92-5; desacetyl **9**, 19684-93-6; **10**, 19684-94-7; **11**, 19684-95-8; **12**, 19684-96-9.

Notes

Lead Tetraacetate Oxidation of Steroidal Hydrazones

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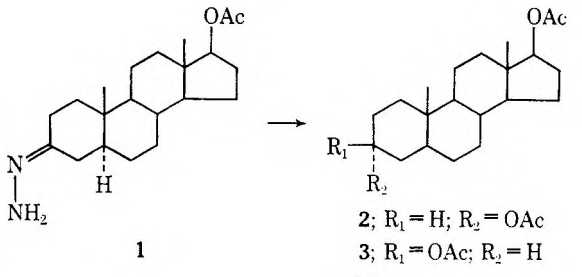
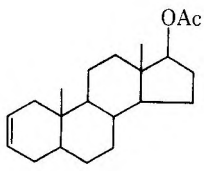
Received October 13, 1968

The purpose of this study is to examine the products formed when steroidal hydrazones are oxidized with lead tetraacetate, and compare these to products of other oxidative deamination reactions of steroidal amines.[1]



1

2; R_1 = H; R_2 = OAc
3; R_1 = OAc; R_2 = H



4

Oxidation of the 3-hydrazone of 17β-acetoxy-5α-androstan-3-one (1) with lead tetraacetate resulted in the immediate evolution of nitrogen.[2] The olefinic and ester products from this reaction were analyzed by vapor phase chromatography and then isolated by column chromatography. These products are tabulated in Table I.

TABLE I

	% olefin	% ester	% composn 3α	% composn 3β
Reaction products from the oxidation of **1**[a]	25[c]	52	65	35
3α-Nitrosoamide of cholestane decomposition products[b]	69–89	8–16	76–83	24–17

[a] Average of five runs. [b] Data reported by White and Bachelor; see ref 1. [c] A mixture of olefins containing 85% of the Δ^2 isomer.

The ratio of epimeric acetates in the present study shows a predominance of 3α-acetate **2** and is in qualitative agreement with the results obtained by White for nitrosoamide decompositions[1] (see Table I).

This reaction requires the conversion of the hydrazone into a reactive species which can readily lose nitrogen and either react with the acetic acid formed in the reaction to afford ester products or lose a proton to give olefinic products. Furthermore, the predominance of the 3α-acetate indicates that factors may be present which result in some measure of stereoselectivity in the formation of those esters, possibly in the protonation step.[3] Owing to the essentially instantaneous rate of reaction, no direct study of the mechanism could be made. Attempts to show solvent change effects by varying the acetic acid concentration and by using pyridine showed the product ratios quite unresponsive to changes in conditions (see Table II, Experimental Section).[4]

Experimental Section[5]

17β-Acetoxy-5α-androstan-3-one Hydrazone.—A solution of 5 g of 5α-androstan-17β-ol-3-one 17-acetate in 70 ml of EtOH, 1 ml of triethylamine, and 1 ml of hydrazine hydrate was refluxed for 2 hr and cooled.[6] The solvents were removed under vacuum, and the white residue was carefully recrystallized once from EtOH–H_2O to give 4 g of colorless crystals, mp 215–219°, which were suitable for subsequent oxidation: ir (mull) 3330, 3500 ($-NH_2$), 1640 cm^{-1} (C=N). Azine formation became apparent when this material was recrystallized several times. *Anal.* Calcd for $C_{21}H_{34}O_2N_2$: C, 72.79; H, 9.89; N, 8.09. Found: C, 72.38; H, 9.98; N, 7.82.

Lead Tetraacetate Oxidation of 1.—A solution of 1.39 g (2.9 mmol) of lead tetraacetate (dried under vacuum over KOH) was dissolved in 75 ml of dry CH_2Cl_2 and cooled to 0° in an ice bath. A solution of 1.0 g (2.8 mmol) of **1** in 75 ml of CH_2Cl_2 was added dropwise. Instantaneous evolution of nitrogen resulted, and a white precipitate of lead acetate formed. The theoretical volume of nitrogen was evolved. After the addition was complete, the ice bath was removed; the reaction mixture was allowed to warm with stirring for 0.5 hr. H_2O was added, stirring continued for a few minutes, and the mixture was filtered through a cake of filter aid. CH_2Cl_2 was added to the filtrate, as well as additional H_2O; the organic layer was separated, washed with saturated $NaHCO_3$ solution, saturated salt solution, and dried over $MgSO_4$. Evaporation of solvent gave an oily solid. The crude oil (0.962 g) was chromatographed on 20 g of Florisil (100–200 mesh). Three major components were isolated: 5α-androst-2- (and 3-) en-17β-ol 17-acetate (**4**) from petroleum ether (bp 30–60°) (cuts 4–83, 0.22 g, mp 96–106°); 5α-androstan-3α,17β-diol diacetate (**2**), 5% through 30% benzene in petroleum ether (cuts 84–302, 0.356 g, mp 159–160°[7] 32.4%); 5α-androstane-3β,17β-diol diacetate (**3**), 30% through 50% benzene in petroleum ether (cuts 302–1063, mp 126–127°,[8] 19%). This isolation was monitored by glpc; combination of cuts were made on this basis.

(1) E. H. White and F. W. Bachelor, *Tetrahedron Lett.*, 77 (1965), and references cited therein.

(2) D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Amer. Chem. Soc.*, **83**, 747 (1961).

(3) A recent study by W. Kirmse and R. Siegfried, *J. Amer. Chem. Soc.*, **90**, 6564 (1968), illustrates that 2-diazonorpinane can undergo *exo* protonation stereospecifically to give reaction products that are best explained by the occurrence of 2-*endo*-norpinyldiazonium ion as an intermediate.

(4) The low activation energy for this type of reaction minimizes the effect of solvation. See G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(5) All melting points were determined on a Mel-Temp apparatus and are uncorrected. Nmr spectra were taken on a Varian HR-60 instrument with tetramethylsilane as an internal standard. Ir spectra were obtained on a Beckman IR-9 spectrophotometer. A Barber–Coleman gas chromatograph, equipped with 1% XE-60 on Gas Chrom 80/100 column in the vicinity of 200°, was used.

(6) D. H. R. Barton, R. E. O'Brien, and S. Sternhell, *J. Chem. Soc.*, 470 (1962).

(7) A. Butenandt and K. Tscherning, *Z. Physiol. Chem.*, **234**, 224 (1935).

(8) C. W. Shoppee, *Helv. Chim. Acta*, **23**, 740 (1940).

The oxidation was carried out with several concentrations of AcOH in CH_2Cl_2 and also in pyridine. Some representative runs are shown in Table II. Estimates of ester ratios were made by glpc.

TABLE II

	% olefin	% ester	% composn 3α	% composn 3β
10 mol % acetic acid–CH_2Cl_2	28.9	60.7	65	35
100 mol % acetic acid–CH_2Cl_2	31.8	53.2	70	30
Pyridine	23.8	50.3	70	30

Registry No.—Lead tetraacetate, 546-67-8; **1**, 19640-01-8.

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Tetramethyl Bismethylenedioxy Steroids. I. A Novel Protective Group

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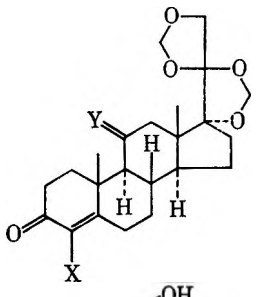
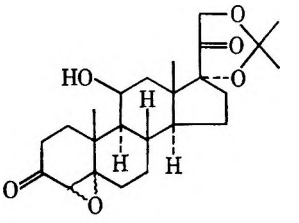
Received November 6, 1968

It is widely known that a bismethylenedioxy group (BMD)[3] has outstanding advantages as a protective group for the dihydroxyacetone side chain of adrenocortical hormones. Regarding the limitations, Sarett, *et al.*,[3a] noticed that a ketonic group at C_{11} retarded the BMD hydrolysis to a marked extent. We have noticed that 4-chlorohydrocortisone-BMD (**1b**), 4-chlorohydrocortisone-BMD-11-methoxy methyl ether (**1d**), and 4-chlorocortisone-BMD (**1f**) could not be hydrolyzed by acetic acid, formic acid, or perchloric acid to the corresponding 4-chlorocorticoids. This finding supports Hirschmann's observation[4] that "a variation at an even more remote position of the corticoid—for example, in the A ring—can have a marked effect on the rate of BMD hydrolysis." It may be mentioned in this connection that a chloro substituent at C_4 did not affect the hydrolysis of a 17α,21-acetonide linkage. In fact, 4-chlorohydrocortisone[5] could be prepared directly by the hydrogen chloride treatment of 4ξ,5ξ-oxido-11β-hydroxy-17α,21-isopropylidenedioxypregnane-3,20-dione (**2**). Now we have discovered that the hydrolysis of a tetramethyl bismethylenedioxy (TMBMD) group (or in other words 17,20-20,21-acetonides) is unaffected by an 11-ketone and also by a 4-chloro substituent in a steroid molecule. In fact, hydrocortisone-TMBMD (**3a**), 4-chlorohydrocortisone-TMBMD (**3b**), cortisone-TMBMD (**3c**), and 4-chlorocortisone-TMBMD (**3d**) could smoothly be hydrolyzed by acetic acid (50%) on a steam bath (3–4 hr) to the corresponding corticoids (yields, 80–90%). The faster rate of hydrolysis of the TMBMD grouping may be attributed to the hypercon-





2

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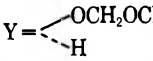
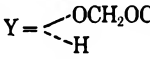
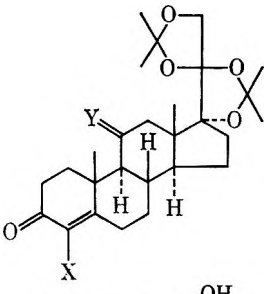
b, X = Cl; Y = 

c, X = H; Y = 

d, X = Cl; Y = 

e, X = H; Y = O

f, X = Cl, Y = O



3a, X = H; Y = 

b, X = Cl; Y = 

c, X = H; Y = O

d, X = Cl; Y = O

jugation effect of the acetonide methyl groups. The nmr spectrum ($CDCl_3$) of the TMBMD compounds showed signals which supported the presence of six methyl groups (τ 8.2–9.1) and one OCH_2 group (5.9–6.0). **3a** and **3c** also showed the vinyl proton (τ 4.3–4.35). The ultraviolet (uv) absorptions of the 4-chloro derivatives (**1b**, **1d**, **1f**, **3b**, and **3d**) were in the region of 254–255 mμ. The TMBMD compounds showed absorptions at 1370–1390 (*gem*-dimethyl) and 1220–1230 cm^{-1} (asymmetric C—O—C stretching) in addition to the symmetric stretching around 1070 cm^{-1}. The BMD derivatives, on the other hand, exhibit only symmetric C—O—C stretching at 1100 cm^{-1}.[3a] The chlorine substituent at C_4 of the corticoids and their derivatives (BMD and TMBMD) makes significant shifts (20–25 cm^{-1}) of Δ^4-3-keto band toward higher and C=C band toward lower frequencies. Satisfactory elemental analyses were obtained for all the new compounds.

In the preparation of the TMBMD compounds, steroids were dissolved in dry acetone, a few drops of perchloric acid (70%) were added, and the solution was stirred overnight at room temperature (yield 60–65%). Chlorination of the corticoid derivatives was effected

(1) To whom all enquiries regarding this paper should be directed.

(2) Recipient of a Roswell Park Memorial Institute summer fellowship from The National Institute of Health, Training Grant CA06183, 1967.

(3) (a) R. E. Beyler, F. Hoffman, R. M. Moriarty, and L. H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961), and other papers in this series; (b) *ibid.*, **26**, 2426 (1961); (c) *J. Amer. Chem. Soc.*, **81**, 1235 (1959); (d) *ibid.*, **82**, 170 (1960).

(4) See ref 7 on p 2423 of ref 3a.

(5) H. J. Ringold, E. Batres, O. Mancera, and G. Rosenkranz, *J. Org. Chem.*, **21**, 1432 (1956).

either by epoxidation followed by acidification (HCl)[6] or by sulfuryl chloride treatment in pyridine solution.[6]

Experimental Section

Melting points (uncorrected) were determined on Fisher-Johns apparatus. The uv spectra (measured on a Cary 14 instrument) are for 95% EtOH solution unless otherwise stated. Infrared (ir) spectra were obtained with a Beckman IR-9 instrument. Microanalyses were carried out by Galbraith Laboratories, Inc. Nuclear magnetic resonance (nmr) spectra are for deuteriochloroform solutions, with tetramethylsilane as internal reference on a Varian A-60 instrument. R_f values were calculated from thin layer chromatographic mobilities on glass plates coated with silica gel G (0.25 mm). Mixtures of chloroform–acetone (9:1) (solvent system A) or chloroform–benzene–ethyl alcohol (9:1:1) (solvent system B) were used for developing. Aqueous solution of orthophosphoric acid (50%) and ethanolic solution of phosphomolybdic acid (1.5%) were used as spray reagents.

Hydrocortisone-BMD (1a), Hydrocortisone-BMD-11-methoxy Methyl Ether (1c), and Cortisone-BMD (1e).—These were prepared by the method of Sarett, *et al.*[3a]

4-Chlorohydrocortisone-BMD (1b).—1a, on epoxidation,[5] followed by hydrochloric acid treatment,[5] gave **1b**. 1a (2 g), mp 220–222° (lit.[3a] mp 220–223°), was dissolved in methanol (100 ml) and cooled to 0°. The solution was successively treated with hydrogen peroxide (12 ml, 30%) and cold aqueous sodium hydroxide (5 ml, 10%). After stirring for 20 hr at 0°, the solution was neutralized by acetic acid (1:1) to pH 7. Concentration of the solution *in vacuo* below 40° gave a mixture of epoxides (1.7 g) which was dissolved in acetone (25 ml) and treated with concentrated hydrochloric acid (1 ml, 37%). The solution was stirred for 45 min at room temperature. Crushed ice was added to turbidity and the mixture was chilled overnight. The solid material (1.72 g), isolated by filtration on recrystallization from methanol–chloroform mixture, afforded **1b** (1.6 g): mp 243–245°; uv max (MeOH) 254.5 mμ (ε 14,320); ir (KBr) 3590 (11-OH), 1685 (3-keto), 1575 (C=C), and 1090 cm^{-1} (C—O—C); R_f 0.56 (solvent system A).

Anal. Calcd for $C_{23}H_{31}O_6Cl$: C, 62.92; H, 7.12. Found: C, 62.40; H, 7.04.

4-Chlorohydrocortisone-BMD-11-methoxy Methyl Ether (1d).—Chlorination of 1c at C_4 was effected by the method of Mori.[6] Freshly distilled sulfuryl chloride (1.4 ml) was added dropwise to an ice-cooled (5°) solution of 1c (1 g) in dry pyridine (10 ml). The solution was stirred for 1 hr. The contents were poured onto crushed ice and the solid (1.02 g) obtained was purified by column chromatography on neutral alumina (20 g). Elution of the column with benzene (80 ml) afforded 1d (0.85 g, 80%): mp 162–164°; uv max 255 mμ (ε 14,940); ir ($CHCl_3$) 1695 (3-keto), 1592 (C=C), 1090 (C—O—C), and 1050 cm^{-1} (11-ketal); R_f 0.81 (solvent system A).

Anal. Calcd for $C_{25}H_{35}O_7Cl$: C, 62.17; H, 7.30. Found: C, 62.27; H, 7.18.

4-Chlorocortisone-BMD (1f).—Cortisone-BMD (1e, 1 g) was dissolved in dry pyridine (10 ml). Freshly distilled sulfuryl chloride (1.2 ml) was added to the solution dropwise at 5° over a period of 5 min. Stirring was continued for an additional 1 hr. The reaction mixture was poured onto crushed ice and the precipitate was collected, washed with water, dried, and crystallized from aqueous acetone to yield 1f (0.83 g, 77%): mp 290–295°; uv max 254 mμ (ε, 15,670); ir (KBr) 1700 (11- and 3-keto), 1585 (C=C), and 1100 cm^{-1} (C—O—C); R_f 0.82 (solvent system A).

Anal. Calcd for $C_{23}H_{29}O_6Cl$: C, 63.23; H, 6.70. Found: C, 63.19; H, 6.86.

4ξ,5ξ-Oxido-11β-hydroxy-17α,21-isopropylidenedioxypregnane-3,20-dione (2).—A methanolic solution (100 ml) of 17α,21-acetonide of hydrocortisone (2 g) [mp 184–186° (lit.[7] mp 194–195°); ir ($CHCl_3$) 3610 (11-OH), 1720 (20-keto), 1665 (3-keto), 1622 (C=C), 1372 and 1385 (*gem*-dimethyl), and 1225–1230 cm^{-1} (asymmetric C—O—C)], on treatment with aqueous NaOH (6 ml, 10%) and hydrogen peroxide (14 ml, 30%), for 20 hr at 0°, gave an epoxide mixture (2, 1.6 g, 78%) which on recrystallization from aqueous acetone had mp 118–122°; ir ($CHCl_3$) 3610 (11-OH), 1718 (20- and 3-keto), and 1225–1230 (asymmetric C—O—C); R_f 0.47 (solvent system A) (R_f of hydrocortisone-17α,21-acetonide, 0.34).

Hydrochloric Acid Treatment of 2.—A solution of 2 (1 g) in acetone (18 ml) was treated with hydrochloric acid (1 ml, 37%) for 45 min. Water was added to turbidity and the mixture was allowed to stand overnight at 5°. The residue on recrystallization from an acetone–benzene mixture afforded 4-chlorohydrocortisone (0.71 g, 75%): mp 224–226° (lit.[5] mp 225–227°); uv max 254 mμ (ε 14,280); ir (KBr) 3400–3470 (11-, 17-, and 21-OH), 1712 (20-keto), 1685 (3-keto), and 1575 cm^{-1} (C=C); R_f 0.42 (solvent system B).

Cortisone-TMBMD (3c).—Perchloric acid (1.25 ml, 70%) was added to a solution of cortisone (5.8 g) in dry acetone (340 ml). The solution was stirred for 20 hr at room temperature. The resulting yellow solution was neutralized by aqueous potassium carbonate (20 ml, 2%) until the solution was colorless. The solution was concentrated *in vacuo* when 3c (4.78 g, 65%) separated. Recrystallization from aqueous acetone led to an analytical sample of 3c: mp 250–252°; uv max 241 mμ (ε 16,540); ir (KBr) 1705 (11-keto), 1675 (3-keto), 1618 (C=C), 1370 and 1385 (*gem*-dimethyl), 1225–1230 (asymmetric C—O—C), and 1070 cm^{-1} (symmetric C—O—C); nmr ($CDCl_3$) τ 4.3 (s, 1 H), 6.0 (s, 2 H), and 8.2–9.1 (complex, 18 H); R_f 0.79 (solvent system A) (R_f of cortisone-BMD, 0.71).

Anal. Calcd for $C_{27}H_{38}O_6$: C, 70.71; H, 8.35. Found: C, 70.78; H, 9.00.

Hydrocortisone-TMBMD (3a).—Treatment of hydrocortisone (6.2 g) as above, with dry acetone (400 ml) and perchloric acid (1.28 ml, 70%) for 20 hr followed by recrystallization from aqueous acetone, furnished 3a (4.65 g, 60%): mp 235–238°; uv max 241 mμ (ε 15,820); ir (KBr) 3405 (11-OH), 1660 (3-keto), 1620 (C=C), 1375 and 1382 (*gem*-dimethyl), 1225–1230 (asymmetric C—O—C), and 1070 cm^{-1} (symmetric C—O—C); nmr ($CDCl_3$) τ 4.35 (s, 1 H), 5.95 (s, 2 H), and 8.2–9.1 (complex, 18 H); R_f 0.65 (solvent system A) (R_f of hydrocortisone-BMD, 0.46).

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75. Found: C, 70.57; H, 9.05.

4-Chlorocortisone-TMBMD (3d).—A solution of cortisone-TMBMD (3c, 0.85 g) in dry pyridine (9.5 ml) was treated with freshly distilled sulfuryl chloride (0.9 ml) and worked up as described in the preparation of 1f. The solid material, isolated by filtration, on recrystallization from a chloroform–methanol mixture, afforded 3d (0.68 g, 75%): mp 252–255°; uv max 254 mμ (ε, 16,240); ir (KBr) 1710 (11-keto), 1700 (3-keto), 1595 (C=C), 1375 and 1390 (*gem*-dimethyl), 1225–1230 (asymmetric C—O—C), and 1080 cm^{-1} (symmetric C—O—C); nmr ($CDCl_3$) τ 5.95 (s, 2 H) and 8.2–9.1 (complex, 18 H); R_f 0.89 (solvent system A).

Anal. Calcd for $C_{27}H_{37}O_6Cl$: C, 65.91; H, 7.58; Cl, 7.00. Found: C, 65.17; H, 7.63; Cl, 7.22.

4-Chlorohydrocortisone-TMBMD (3b).—Treatment[5] of a methanolic solution of hydrocortisone-TMBMD (1.2 g in 75 ml of methanol) with aqueous sodium hydroxide (3 ml, 10%) and hydrogen peroxide (8 ml, 30%), for 20 hr at 0°, gave an epoxide mixture (0.94 g, 76%): mp 215–230°; ir (KBr) 3440 and 3470 (11-OH), 1705 and 1720 (3-keto), 1375 and 1380 (*gem*-dimethyl), 1225–1230 (asymmetric C—O—C), and 1080 cm^{-1} (symmetric C—O—C); R_f 0.75 and 0.81 (solvent system A). Reaction of the epoxide mixture (0.65 g) with acetone (60 ml) and hydrochloric acid (0.6 ml, 37%) for 45 min at room temperature yielded 3b (0.53 g, 80%): mp 283–285°; uv max 254 mμ (ε 14,990); ir (KBr) 3500 (11-OH), 1690 (3-keto), 1590 (C=C), 1225–1230 (asymmetric C—O—C), and 1075 cm^{-1} (symmetric C—O—C); nmr ($CDCl_3$) τ 5.95 (s, 2 H) and 8.2–9.1 (complex, 18 H); R_f 0.76 (solvent system A).

Anal. Calcd for $C_{27}H_{39}O_6Cl$: C, 65.63; H, 7.95; Cl, 6.97. Found: C, 65.34; H, 7.80; Cl, 7.01.

Attempted Bismethylenedioxy Group Hydrolysis of 1b, 1d, and 1f.—A BMD derivative (1b or 1f, 250 mg) was heated in 20 ml of 50% acetic acid at 100° for 6 hr. When the solvent was evaporated to dryness in an atmosphere of nitrogen, only the starting material was obtained in almost quantitative yield (220–230 mg). Attempts to remove the BMD group by formic acid (60%) or glacial acetic acid were also futile. Prolonged acetic acid treatment or use of perchloric acid along with acetic acid gave some decomposed material and the parent compound.

1d, on similar treatment, afforded a mixture of 1b and 1d but no 4-chlorocortisone.

Facile Tetramethyl Bismethylenedioxy Group Hydrolysis of 3a, 3b, 3c, and 3d.—Cortisone-TMBMD (3c, 540 mg) was heated with acetic acid (16 ml, 50%) at 95° for 3 hr. The contents, on removal of solvent, were crystallized from aqueous methanol to

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(7) R. Gardi, R. Vitali, and A. Ercoli, *J. Org. Chem.*, **27**, 668 (1962).

give cortisone (235 mg, 88% yield): mp 223–225°; R_f 0.61 (solvent system B).

4-Chlorocortisone-TMBMD (**3d**, 500 mg) on heating with acetic acid (40 ml, 50%) at steam-bath temperature for 4 hr afforded 4-chlorocortisone (340 mg, 85% yield): mp 212–214° (lit.[5] mp 210–212°; uv max 254 mμ (ε 15,220); ir (KBr) 3500 and 3520 (17- and 21-OH), 1700 and 1710 (11- and 20-keto), 1685 (3-keto), and 1590 cm^{-1} (C=C); R_f 0.64 (solvent system B).

Hydrocortisone-TMBMD (**3a**, 400 mg) was heated with acetic acid (30 ml, 50%) at 90° for 3 hr. The reaction mixture was then taken to dryness *in vacuo*. The residue was crystallized from aqueous ethanol to give hydrocortisone (282 mg, 90% yield): mp 220–221°; R_f 0.37 (solvent system B).

Hydrolysis of 4-chlorohydrocortisone-TMBMD (**3b**, 370 mg) with aqueous acetic acid (50 ml, 50%) for 4 hr as in previous examples, followed by crystallization from benzene–acetone, gave 4-chlorohydrocortisone[5] (245 mg, 83% yield): mp 224–225°; R_f 0.42 (solvent system B). The identity of the material with that prepared by hydrochloric acid treatment of **2** was shown by mixture melting point and uv and ir spectral comparisons.

Registry No.—**1b**, 19551-06-5; **1d**, 19551-07-6; **1f**, 19551-08-7; **2**, 19594-74-2; **3a**, 19551-09-8; **3b**, 19581-61-4; **3c**, 19551-10-1; **3d**, 19551-11-2.

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Catalytic Hydrogenation of 17β-Hydroxyde-A-androst-9-en-5-one, (±)-17β-Hydroxy-18-methylde-A-androst-9-en-5-one, and (±)-17β-Hydroxy-18-methylde-A-D-homoandrost-9-en-5-one

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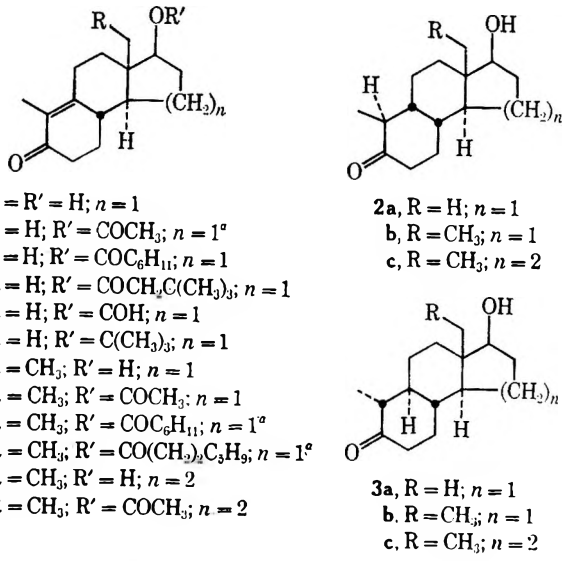
This Note describes the preparation of 17β-hydroxy-9β,10β-de-A-androstan-5-one (**2a**), (±)-17β-hydroxy-9β,10β-18-methylde-A-androstan-5-one (**2b**), and (±)-17β-hydroxy-9β,10β-18-methylde-A-D-homoandrostan-5-one (**2c**) by catalytic hydrogenation of the title compounds (**1a**, **1g**, and **1k**)[3] and their derivatives (Chart I). These compounds were required for our total synthesis of retro steroids (*i.e.*, 9β,10α steroids).[4]

Previous work reported from these laboratories[5] indicated that rhodium on alumina in ethanol–hydrochloric acid would favor formation of **2a** from **1a**, the major by-product being **3a**[6] which has the 9α,10α configuration. The best ratio of **2a**:**3a** obtainable by us under these conditions is shown in Table I (expt 1).

Chart I



1a, R = R′ = H; *n* = 1
b, R = H; R′ = $COCH_3$; *n* = 1[a]
c, R = H; R′ = COC_6H_{11}; *n* = 1
d, R = H; R′ = $COCH_2C(CH_3)_3$; *n* = 1
e, R = H; R′ = COH; *n* = 1
f, R = H; R′ = $C(CH_3)_3$; *n* = 1
g, R = CH_3; R′ = H; *n* = 1
h, R = CH_3; R′ = $COCH_3$; *n* = 1
i, R = CH_3; R′ = COC_6H_{11}; *n* = 1[a]
j, R = CH_3; R′ = $CO(CH_2)_2C_5H_9$; *n* = 1[a]
k, R = CH_3; R′ = H; *n* = 2
l, R = CH_3; R′ = $COCH_3$; *n* = 2

2a, R = H; *n* = 1
b, R = CH_3; *n* = 1
c, R = CH_3; *n* = 2

3a, R = H; *n* = 1
b, R = CH_3; *n* = 1
c, R = CH_3; *n* = 2

[a] Cycloalkyl derivatives.

Experiments with other solvents under neutral, acidic, or basic conditions failed to improve the ratio, and the same was true when palladium on barium sulfate or rhodium on carbon was used as the catalyst. Variation of the amount of hydrochloric acid used indicated that the best results were obtained when *ca.* 3 equiv were used. The optimum yield of **2a** proved to be 40%.

Table I
Hydrogenation of De-A-androst-9-en-5-ones[a]

Expt	Compd 1	Relative ratio 2a:3a
1	a	75–83:25–17
2	b	88–90:12–10
3	c	82:18
4	d	85:15
5	e	75:25
6	f	65:35[b]
		2b:3b
7	g	56:44
8	h	84:16
9	i	94:6
10	j	87:13
		2c:3c
11	k	67:31
12	l	96:4

[a] All hydrogenations were performed using 5% Rh/Al_2O_3 in EtOH–HCl. The formate **1e** hydrolyzed during hydrogenation, the acetates were saponified with KOH—MeOH, and the other esters with NaOMe–MeOH prior to vpc determination of the isomer ratio in the products. The vpc analyses used system A for the products from **1a-f** and system B for the remainder (see Experimental Section). [b] The ether group was first removed with aqueous HCl in EtOH or with *p*-toluenesulfonic acid in benzene.

An improved ratio of **2a**:**3a** was obtained by hydrogenation of acetate **1b** (expt 2), and subsequent saponification. Three other esters (**1c**, **1d**, and **1e**) were also prepared as was the *t*-butyl ether **1f**. Bulky esters **1c** and **1d** (expt 3 and 4) gave results comparable with those obtained with acetate **1b** as regards the ratio of **2a**:**3a**; but the yields of **2a** after saponification and crystallization were only *ca.* 45% as opposed to 70% obtained from **1b**. This almost certainly reflects the strenuous hydrolysis conditions (sodium methoxide in boiling

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(3) It should be noted that all the compounds with R = Me referred to in Chart I are racemic, whereas those with R = H belong to the normal steroid series. Throughout the paper steroid nomenclature is used.
(4) Z. G. Hajos, R. A. Micheli, D. R. Parrish, and E. P. Oliveto, *J. Org. Chem.*, **32**, 3008 (1967); A. M. Krubiner, G. Saucy, and E. P. Oliveto, *ibid.*, **33**, 3548 (1968).
(5) M. Uskokovic, J. Iacobelli, R. Phillon, and T. Williams, *J. Amer. Chem. Soc.*, **88**, 4538 (1966).
(6) M. P. Hartshorn and E. R. H. Jones, *J. Chem. Soc.*, 1312 (1962).

methanol) necessary to effect complete removal of the ester moiety. Ester **1e**, which hydrolyzed during hydrogenation, and ether **1f** led to relatively unfavorable ratios of **2a**:**3a** (expt 5 and 6).

In the cases of **1g** and **1k**[7] none of the expected products was a known compound and it was therefore necessary to consider the likely outcome of the hydrogenations. Formation of **2b** and **2c** requires addition of hydrogen from the β faces of the molecules and the presence of 18-methyl substituents in **1g** and **1k** should hinder this process. However, as noted above, esterification of the 17β-hydroxyl group in **1a** promoted hydrogenation from the β face. This surprising result may be explained by examination of models which reveals that because of the bond angles of the sp^2 hybridized carbon atom of the carbonyl group of the ester function the alkyl moiety of the esters assumes a preferred conformation in which it hinders attack from the α side of the molecule. This is not true of a 17β ether group which hinders approach from the β face and should therefore impede the formation of the desired 9β,10β product. The result (expt 6) with **1f** supports this conclusion.

The hydrogenation products from **1g** and **1k** (expt 7 and 11) were subjected to vpc analysis and the scans obtained were compared to that for the product from **1a**. The only significant differences were in the areas of the major peaks, and on this basis peaks were assigned to **2b**, **2c**, **3b**, and **3c**. The relative ratios of **2b**:**3b** and **2c**:**3c** obtained from the alcohols and various esters are shown in Table I. It will be noted that the results confirm the predictions, the alcohols giving less favorable amounts of the desired 9β,10β compounds than obtained in the case of **1a**. For preparative purposes the acetates proved to be the preferred substrates for hydrogenation and **2b** and **2c** were obtained, by direct crystallization, in yields of 64 and 59%, respectively.

The nmr spectrum[7] of the 18-methyl compound **2b** compared favorably with that of the 9β,10β alcohol **2a**; in particular, the methylene envelopes of the two spectra were almost superimposable, and quite different from that found in the spectrum of the 9α,10α isomer **3a**. Also, the nmr data obtained for the pure D-homo-9β,10β analog **2c** were in agreement with the proposed structure.

Experimental Section

Melting points were determined with a Thomas–Hoover melting point apparatus and are corrected. Ultraviolet data refer to solutions in EtOH, and infrared data to *ca.* 3% solutions in $CHCl_3$. Nmr spectra were measured at 60 MHz in $CDCl_3$ with $SiMe_4$ as internal standard. Two systems were used for vpc measurements, system A [F & M Model 810 with dual flame detector; column 6 ft × 0.25 in. o.d. stainless steel, 2% neopentyl glycol succinate plus 2% fluorosilicone FS-1265 (QF-1) on 60–70 mesh Anakrom ABS; column temperature 200°, with He flow at 120 ml/min] and system B [F & M Model 810R-13N with H_2 flame detector; column 6 ft × 0.25 in. o.d. aluminum, 1% XE60 on 60–70 mesh Anakrom ABS; column temperature 170°, with N_2 flow at 100 ml/min].

The hydrogenations listed in Table I were carried out at room temperature (20–25°) and atmospheric pressure using the methods and proportions described below. Esters **1c**, **1d**, **1i**, and **1j** were prepared from the corresponding acid chloride in pyridine by standard methods. The formate ester **1e** was prepared from HCO_2H and *p*-toluenesulfonic acid.[8] These esters were not completely characterized but they were purified by chromatography on alumina or by crystallization. They were homogeneous on tlc and spectral data were compatible with the assigned structures. The preparations of **1g**, **1h**, **1k** and **1l** are described elsewhere.[7]

Hydrogenation of 17β-Hydroxyde-A-androst-9-en-5-one (1a) (Expt 1).—A suspension of 15 g of 5% Rh/Al_2O_3 in EtOH (benzene free, 300 ml) and 3 *N* HCl (120 ml) was saturated with H_2. To this was added a solution of **1a** (30.0 g) in EtOH (900 ml), and the mixture was shaken in an atmosphere of H_2. After *ca.* 60 min the rate of uptake of H_2 slowed (uptake, 3401 ml, 118.8%; calcd 2865 ml). The catalyst was removed by filtration (Celite), the filtrate neutralized with $NaHCO_3$, and the solution concentrated *in vacuo* (40°) to *ca.* 350 ml. This concentrate was extracted with three 350-ml portions of Et_2O and the extracts were washed with three 225-ml portions of H_2O and two 225-ml portions of saturated NaCl solution. They were dried over Na_2SO_4. Vpc analysis of an aliquot of this solution showed the ratio **2a**:**3a** to be 83:17. The ether solution was concentrated on the steam bath to 80–100 ml and cooled to room temperature, then held at −20° overnight to yield **2a** (12.1 g), mp 135–144° with sintering (vpc assay 97–98%). The melting point of **2a** is not a criterion of purity as a trace of **3a** causes a marked depression. Crystallization from ether gave pure **2a**: mp 143–145.5°; $[\alpha]^{25}D$ −12.9° (*c* 1.065, $CHCl_3$). A further crystallization from CH_2Cl_2–Et_2O gave an analytical sample: mp 144–145.5°; $[\alpha]^{25}D$ −13.0 (*c* 1.0, $CHCl_2$); ir 3610 (OH) and 1705 (C=O) cm^{-1}; nmr δ 0.85 (13β-methyl) and 1.01 ppm (10β-methyl, d, J = 7 Hz).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 75.96; H, 10.21.

Hydrogenation of 17β-Acetoxyde-A-androst-9-en-5-one (1b) (Expt 2).—Compound **1b**[6] (100 g) in EtOH (3.0 l.) was reduced in the presence of 5% Rh/Al_2O_3 (50 g) in EtOH (1.0 l.) and 3 *N* HCl (360 ml), as described above. After H_2 uptake ceased (110% of theory) the catalyst was removed, the solution was adjusted to *ca.* pH 11 with 40% KOH, and heated under reflux in a N_2 atmosphere for 1 hr. The solution was neutralized with 10% HCl and extracted with Et_2O to give crude product (87 g, **2a**:**3a** = 88:12 by vpc). This material was crystallized from CH_2Cl_2–Et_2O–petroleum ether (bp 30–60°) to yield **2a** (60.0 g), mp 137.5–145° (97.5% by vpc).

17β-*t*-Butoxyde-A-androst-9-en-5-one (1f).—A solution of **1a** (10.0 g) in CH_2Cl_2 (100 ml) was allowed to react with isobutylene (200 ml), 47% BF_3–Et_2O[9] (1.0 ml, 8.0 mmol), and 100% H_3PO_4 (0.42 ml. 8.0 mmol) overnight at room temperature. Isolation of the product in the usual manner gave a mixture of **1a** and **1f** (12.0 g), which was triturated with petroleum ether (bp 30–60°) and **1a** (*ca.* 1.0 g) was removed by filtration. Crystallization from EtOH–H_2O of the material in the filtrate gave **1f** (8.7 g): mp 78–80°; $[\alpha]^{25}D$ −12° (c 1.00, $CHCl_3$); uv max 249 mμ (ϵ 15,700); ir 1658 and 1605 cm^{-1}; nmr δ 0.87 (13β-methyl), 1.13 (17β-*t*-butyl) and 1.80 ppm (10-methyl).

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.47; H, 10.61.

Registry No.—**1a**, 19614-34-7; **1b**, 19614-35-8; **1f**, 19614-36-9; **1g**, 18267-52-2; **1k**, 18267-50-0; **2a**, 10072-76-1.

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Novel Ring Openings of Levopimaric Acid Salts[1a]

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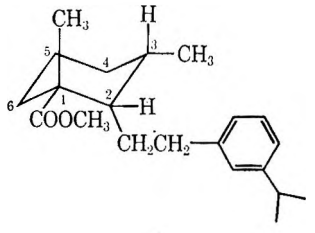
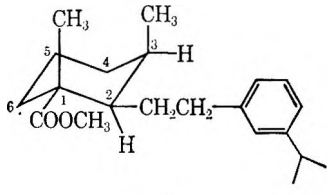
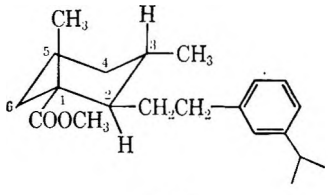
The reaction of levopimaric acid in the presence of 105 mol % potassium hydroxide gives four new compounds, three of which have been isolated and structures postulated.[2] The fourth compound has now been isolated and its structure postulated as indicated in **1**. In the previous work,[2] structure **2** was proposed



1



2



3

for the compound in which only ring B had been opened. Based on a comparison of the nmr spectrum of the two diastereomers, it is now postulated that the structure of the compound ("2") from the previous work[2] is as shown in **3**.

The infrared, ultraviolet absorption, and mass spectra of **1** are very similar to those of **3**. The detailed structure of **1** has been assigned on the basis of its nmr spectrum. The triplet with J = 9 Hz and centered at δ 2.61 was collapsed to a singlet by irradiating at a frequency corresponding to δ 1.41. This same irradiation frequency collapsed the structure at δ 2.05. Integration of the spectrum showed the triplet peaks at δ 2.61 to have a combined area equal to two protons and the absorption at δ 2.05 to have an area equal to one proton. The triplet at δ 2.61 was assigned to the two equivalent benzyl protons. Absorption at δ 1.41 was assigned to the methylene group located next to the benzyl group and the absorption at δ 2.05 was assigned to the tertiary proton at C-2. Following this, the doublet located with its center at δ 0.905 was decoupled by irradiating at a frequency corresponding to δ 1.53. The integration shows the doublet peaks to have a combined area equivalent to three protons. This doublet was thus assigned to the methyl group at C-3 and the unresolved multiplet at δ 1.53 was assigned to the tertiary proton at C-3. The doublet could be partially spin decoupled over a band of frequencies approximately 35 Hz wide. This is to be expected of the splitting of the C-3 proton by six other protons. The singlet absorption at δ 1.15 was assigned to the methyl group at C-1 and the singlet absorption at δ 3.66 was assigned to the methyl group of the ester.

A detailed consideration of compound **3** followed the same pattern as above. The triplet centered at δ 2.55 was assigned to the benzyl protons. This triplet could be collapsed to a singlet by irradiating at a frequency corresponding to δ 1.42. The absorption at δ 1.42 was assigned to the methylene group adjacent to the benzyl group. The absorption by the C-2 proton was not apparent by inspection and could not be located in the spin decoupling experiments. The doublet centered at δ 1.01 could be collapsed by irradiating at a frequency corresponding to 1.42 thus placing the C-3 proton at δ 1.42 with the accompanying assignment of the absorption at δ 1.01 to the C-3 methyl group.

The particular configurations were assigned for the following reasons. The tertiary proton on C-2 in compound **3** was placed at higher fields than the same proton in compound **1** because of the absence of any peaks in the range δ 1.8–2.4 and the absence of any unidentified absorption at still lower fields in **3**. This leads to the belief that the C-2 proton is axial in compound **3** and equatorial[3a] in compound **1**. It is probable that this proton cannot be found in the spectrum of **3** because of intensive splitting introduced by the axial C-3 proton.

The absorption of this proton on C-2 in compound **1** is poorly resolved but a definite triplet is apparent. This triplet has a J value of approximately 4 Hz and this splitting must be caused by interactions from the adjacent methylene group as shown during the spin decoupling. There is further splitting within the triplet which is poorly resolved even by spin decoupling. This has a J value of 2 Hz or less. The predicted value for J_{ea}^{vic} is 1.7 Hz.[4] Thus the C-3 proton is axial and the C-3 methyl group is equatorial.

The configuration at C-1 is the same in both compounds because the bands of these methyl groups do not change. The line width at half-height (W_H) of the resonance of the C-1 methyl group is 1.25 + 0.1 Hz for both **3** and **1**. The W_H for TMS was 0.5. According to Shoppee, *et al.*,[5] this is consistent with the axial nature of the C-1 methyl in both compounds. These methyl groups have the same chemical shift in

(1) (a) Presented at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 4–7, 1968. (b) National Academy of Science, National Research Council Postdoctoral Fellow. (c) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) H. Takeda, W. H. Schuller, and R. V. Lawrence, *J. Org. Chem.*, **33**, 3718 (1968).

(3) (a) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. II, Pergamon Press, New York, N. Y., 1966, p 702; (b) p 701.

(4) J. I. Musher, *J. Chem. Phys.*, **34**, 594 (1961).

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both compounds, *i.e.*, 1.15 *vs.* 1.14 ppm. The constant W_H and δ would lead to the conclusion that there has been no change in the shielding of the C-1 methyl group, implying that the C-3 methyl group is equatorial in both cases. One would expect that an axial C-3 methyl would have strong interactions with the axial C-1 methyl and thus shift both the C-1 methyl and the C-3 methyl bands. The small differences in the δ values of the C-3 substituents between **1** and **3** (compound **1**, δ_H 1.53 and δ_{CH_3} 0.905; compound **3**, δ_H 1.42 and δ_{CH_3} 1.01) are attributed to differing effects from the β-phenethyl group.

Although it is tempting to assume that the downfield shift of the resonance of the C-3 methyl, which occurs between **1** and **3**, is indicative of a change from equatorial to axial conformation of this group, it is not possible to defend an inversion at C-3 using only this information. We, therefore, believe that the conformation at C-3 is the same in **1** and **3** (CH axial, CCH_3 equatorial).

The inversion of the hydrogen at C-3 in **3** may occur during the reaction of the C-3 anion with a proton.[2] The inversion of the hydrogen at C-2 in **1** may result from carbon–carbon cleavage between C-1 and C-2 of the resin acid molecule and a recombination during the reaction.[2] If this is the case, two more isomers could be formed. These isomers do not show up in the glpc analysis of the reaction mixture.

A comparison of the spectral data for **3** and the seco-dehydroabietate compound of Zinkel and Rowe[6] indicated that these compounds were apparently identical. Upon our isolation of **1**, however, a further more detailed comparison of the nmr spectra of **1** and the compound of Zinkel and Rowe showed the latter compounds to be identical. Zinkel, *et al.*, have confirmed this identity by glpc on DEGS and SE-30 columns[7] and concur with the assignment of structure **1**.

It was also found in the present work that methyl levopimarate refluxed in tri-*n*-butylamine for 5 hr gave the same four ring-opened compounds in 32.4% yield. No increase in yield was obtained on further refluxing.

Experimental Section[8]

Methyl 2α-[2′(*m*-Isopropylphenyl)ethyl]-1β,3α-dimethylcyclohexane Carboxylate (1).—Compound **1** was prepared by heating levopimaric acid with 105 mol % of potassium hydroxide for 3 days at 200° as described previously.[2] The compound of relative retention time 0.518 (methyl dehydroabietate, 1.0) was collected from a 10% Versamid 900 on Chromosorb W column (10 ft × 0.25 in. o.d. aluminum tubing F & M 500 instrument) run at 250°. Final purification was accomplished by very careful recollection from a 3.8% SE-30 Chromosorb W column (15 ft. × 0.25 in. o.d. aluminum column) at 200°. Analytical work was carried out on a 5% Versamid 900 on Chromosorb W (60–80 mesh) column (15 ft × 0.25 in. o.d. aluminum column) at 250°. Compound **1** was collected as a colorless oil which gave a single peak on both a Versamid 900 column (250°) and a 3.8% SE-30 column (at 200°). A 1:1 mixture of **2** and **1** was prepared and found to give two peaks on both a Versamid 900 and an SE-30 column. Compound **1** exhibits $[\alpha]^{25}D$ −13° (*c* 0.9, 95% EtOH); uv max (95% EtOH) 264 mμ (ε 284), 271 (253); ir (neat) 1725 (C=O), 1604 (aromatic), 1460 (CH_3), 1213, 1182, 1133 (isopropyl) 1112, 1048, 788 (*meta*-disubstituted aromatic); nmr ($CDCl_3$) δ 0.905 (d, 3, J = 7 Hz, C_3 CH_3), 1.15 (s, 3, C_1 CH_3), 1.245 (d, 6, J = 7 Hz, isopropyl CH_3), 1.41 (m, 2, C_2H CH_2), 1.53 (m, 1, C_3 **H**), 2.05 (t, 1, J = 4 Hz, C_2 **H**), 2.61 (t, 2, J = 9 Hz, C_6H_5 CH_2), 2.87 (quintet, 1, J = 7 Hz, *t*-**H** at isopropyl), 3.66 (s, 3, OCH_3), 7.02 largest peak (m, 4, aromatic **H**); mass spectrum (70 eV) *m/e* (relative intensity) 316 (15), 284 (15), 257 (3.9), 256 (3.2), 192 (7.9), 188 (6.3), 187 (39), 183 (7.9), 173 (3.2), 159 (3.2), 151 (7.9), 147 (15.8), 146 (100), 145 (3.9), 135 (3.9), 134 (28.3), 133 (45.6), 132 (3.9), 131 (14.2), 129 (3.2), 123 (18.9), 121 (3.2), 119 (7.1), 117 (18.9), 116 (7.1), 115 (5.5), 111 (7.9), 110 (3.2), 109 (12.6), 105 (11.8), 102 (3.2), 101 (45.6), 100 (3.2), 97 (3.2), 95 (11.8), 93 (6.3), 92 (23.6), 91 (25), 88 (3.2), 81 (11), 79 (5.9), 77 (3.9), 69 (8.7), 67 (7.9), 59 (3.9), 55 (14.2), 53 (3.2).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.72; H, 10.18. Found: C, 79.62; H, 10.23.

The nmr spectrum of **3** at 100 MHz showed δ 1.013 (d, 3, J = 5.5 Hz, C_3 CH_3), 1.14 (s, 3, C_1 CH_3), 1.235 (d, 6, J = 7 Hz, isopropyl CH_3), 1.42 (m, 2, C_2 CH_2), 1.42 (m, 1, C_3 **H**), <1.8 (definite position could not be found, C_2 **H**), 2.55 (t, 2, J = 7 Hz, $C_6H_5CH_2$), 2.86 (quintet, 1, J = 7 Hz, *t*-**H** at isopropyl), 3.64 (s, 3, OCH_3), 6.96 (m, 4, aromatic **H**).

Methyl Levopimarate Refluxed with Tri-*n*-butylamine.—Methyl levopimarate (0.8 g, 2.5 mmol) was dissolved with tri-*n*-butylamine (10 ml, 42 mmol) and refluxed (216°). After refluxing 5 hr, ether was added, the solution washed twice with aqueous acetic acid and with water five times, dried, and concentrated. The residue was analyzed by glpc (Versamid 900): methyl 9-(*m*-isopropylphenyl)-2,6-dimethyl-*cis*-6-nonenoate[2] (5.8%); mixture of **1** and methyl 9-(*m*-isopropylphenyl)-2,6-dimethyl-*trans*-6-nonenoate[2] (19.1%), **3** (1.75%), levopimarate–palustrate peak (39.8%), unknown (6.1%), dehydroabietate (19.5%), abietate (2.2%). The same composition was obtained on refluxing the sample for 10 hr.

Registry No.—**1**, 19556-80-0; **3**, 19556-81-1.

Acknowledgment.—The authors wish to thank Dr. Ludwig Bauer, of the University of Illinois, College of Pharmacy, Chicago, Ill., for the mass spectrum.

(6) See ref 2, footnote 9.

(7) In the course of communications with D. F. Zinkel, an interpretation of our data was called to our attention which resulted in the postulation of **3** for the compound from ref 2.

(8) The nmr spectra were obtained using a Varian HA-100 nmr spectrometer. Chemical shifts were measured in deuteriochloroform as a solvent relative to tetramethylsilane (TMS) as an internal standard, δ_{TMS} = 0 ppm.

Tumor Inhibitors. XXXVI.[1] Eupatin and Eupatoretin, Two Cytotoxic Flavonols from *Eupatorium semiserratum*[2]

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During a recent study of the cytotoxic constituents of *Eupatorium* species,[3] the isolation and characterization of two previously unreported flavonoids were described. Flavanoid K, mp 243–245°, and flavonoid L, mp 146–148°, which we designate, respectively, as eupatin and eupatoretin, were found to show moderate cytotoxicity against human carcinoma of the nasopharynx carried in cell culture (KB).[3] We report here structural studies leading to assignment of the 3,5,3′-trihydroxy-6,7,4′-trimethoxyflavone structure (**1**) for

(1) Part XXXV in the series: S. M. Kupchan, P. S. Steyn, M. D. Grove, S. M. Horsfield, and S. W. Meitner, *J. Med. Chem.*, **12**, 167 (1969).

(2) This investigation was supported by grants from the National Cancer Institute (CA-04500) and the American Cancer Society (T-275), and a contract with the Cancer Chemotherapy National Service Center (CCNSC), National Cancer Institute, National Institutes of Health (PH-43-64-557). C. W. S. was a N.I.H. Postdoctoral Fellow, 1967–1968.

(3) S. M. Kupchan, C. W. Sigel, R. J. Hemingway, J. R. Knox, and M. S. Udayamurthy, *Tetrahedron*, in press.

TABLE I

NMR SOLVENT SHIFT DATA FOR METHOXY GROUPS IN ETHYL ETHERS OF EUPATIN AND EUPATORETIN

	Benzene-d_6 (TMS)	$CDCl_3$ (TMS)[a]	Δ, ppm
Eupatin			
triethyl ether (**5**)	6.14	6.02	+0.10 ± 0.03 (C-6)
	6.52	6.02, 6.04 ± 0.03	+0.48 ± 0.03 (C-4′)
	6.69	6.07	+0.65 ± 0.03 (C-7)
Eupatoretin			
diethyl ether (**10**)	5.87	5.98	−0.15 ± 0.05 (C-5)
	6.18	6.00	+0.16 ± 0.05 (C-6)
	6.51	6.01, 6.02 ± 0.05	+0.49 ± 0.05 (C-4′)
	6.68	6.07	+0.66 ± 0.05 (C-7)
Quercetagetin			
hexamethyl ether (**3**)[b]	5.88	6.01	−0.13 (C-5)
	6.09	6.01	0.08 (C-6)
	6.20	5.96	0.24 (C-3)
	6.41	6.06	0.35 (C-3′)
	6.57	6.10	0.47 (C-4′)
	6.75	6.01	0.74 (C-7)

[a] The observed chemical shift (τ units) for each signal is given. The value used to calculate Δ is the mean of the two extremes. [b] See ref 6.

eupatin and the 3,3′-dihydroxy-5,6,7,4′-tetramethoxyflavone structure (**8**) for eupatoretin.

Elemental analysis for eupatin (**1**) supported the empirical formula, $C_{18}H_{16}O_8$. The ultraviolet absorption spectrum showed a peak at 366 mμ, indicative that it is a flavonol rather than a flavone. Acetylation afforded a triacetate (**2**), which exhibited three methoxyl and three acetate signals in its nmr spectrum, indicative that eupatin is a trihydroxytrimethoxyflavone.

Methylation of eupatin (**1**) with dimethyl sulfate furnished hexamethylquercetagetin (**3**), which was identified by direct comparison with an authentic sample.[4] The formation of **3** established the oxygenation pattern of eupatin. Methylation of eupatin with diazomethane afforded artemetin (**4**), characterized by comparison of its physical properties and those of its monoacetate with reported values.[5] These experiments established the presence of a hydroxyl at C-5 in eupatin.

Ethylation of eupatin with ethyl iodide afforded the triethyl ether (**5**). The nmr spectrum of this compound was determined in $CDCl_3$ and benzene-d_6 in order to utilize the chemical shift–structural correlations reported by Wilson, *et al.*[6] The solvent shifts observed for the three methoxy groups of eupatin are close to those reported for the C-6, C-7, and C-4′ methoxy groups of hexamethylquercetagetin (see Table I). Finally, the triethyl ether (**5**) was subjected to mild alkaline degradation. The acidic product (**6**) was identified by its melting point and nmr sectrum as the expected 3-ethoxy-4-methoxybenzoic acid. The neutral fraction afforded an acetophenone with physical properties identical with those reported for 2,2′-diethoxy-3′,4′-dimethoxy-6′-hydroxyacetophenone (**7**).[7] The base peak of its mass spectrum at *m/e* 225 corresponded to the loss of $CH_2OCH_2CH_3$ and confirmed the presence of a 2-ethoxyl group.[8]

The results of these structural studies firmly established that eupatin (**2**) possesses hydroxyl groups at C-3, C-5, and C-3′. On this basis the structure of eupatin could be assigned as 3,5,3′-trihydroxy-6,7,4′-trimethoxyflavone (**1**).

Eupatoretin (**8**) was assigned the empirical formula $C_{19}H_{18}O_8$ on the basis of elemental analysis. The ultraviolet spectrum showed a strong absorption at 356 mμ, indicative of a flavonol structure. Acetylation afforded a diacetate (**9**), $C_{23}H_{22}O_{10}$, whose nmr spectrum established the presence of four methoxyl and two acetate groups in the molecule.

Methylation of eupatoretin with either dimethyl sulfate or diazomethane afforded a hexamethyl ether which was identical with hexamethylquercetagetin (**3**). Ethylation of eupatoretin afforded the diethyl ether (**10**). The nmr spectrum was measured in $CDCl_3$ and benzene-d_6 (see Table I). The solvent shifts for the four methoxy groups are close to those observed for C-5, C-6, C-7, and C-4′ methoxyl groups in the model compound hexamethylquercetagetin.[6]

Mild alkaline degradation of eupatoretin diethyl ether (**10**) afforded 3-ethoxy-4-methoxybenzoic acid (**6**) and the acetophenone (**11**), whose nmr spectrum established that it was an ethoxyhydroxytrimethoxyacetophenone. The mass spectrum of **11** showed a base peak at *m/e* 211 (M − $CH_2OCH_2CH_3$). Since this fragmentation defined the location of the ethoxyl, and the conversion of eupatoretin to hexamethylquercetagetin had established the substitution pattern, the structure of acetophenone **11** could be assigned as 2-ethoxy-2′,3′,4′-trimethoxy-6′-hydroxyacetophenone. Identification of the two degradation products located the two hydroxyl groups in eupatoretin at C-3 and C-3′. Thus the structure of eupatoretin is 3,3′-dihydroxy-5,6,7,4′-tetramethoxyflavone (**8**) (Scheme I).

(4) The authors cordially thank Professor T. R. Seshadri for the authentic sample for quercetagetin.

(5) Y. Mazur and A. Meisels, *Bull. Res. Council Israel*, **5A**, 67 (1955).

(6) R. G. Wilson, J. H. Bowie, and D. H. Williams, *Tetrahedron*, **24**, 1407 (1968).

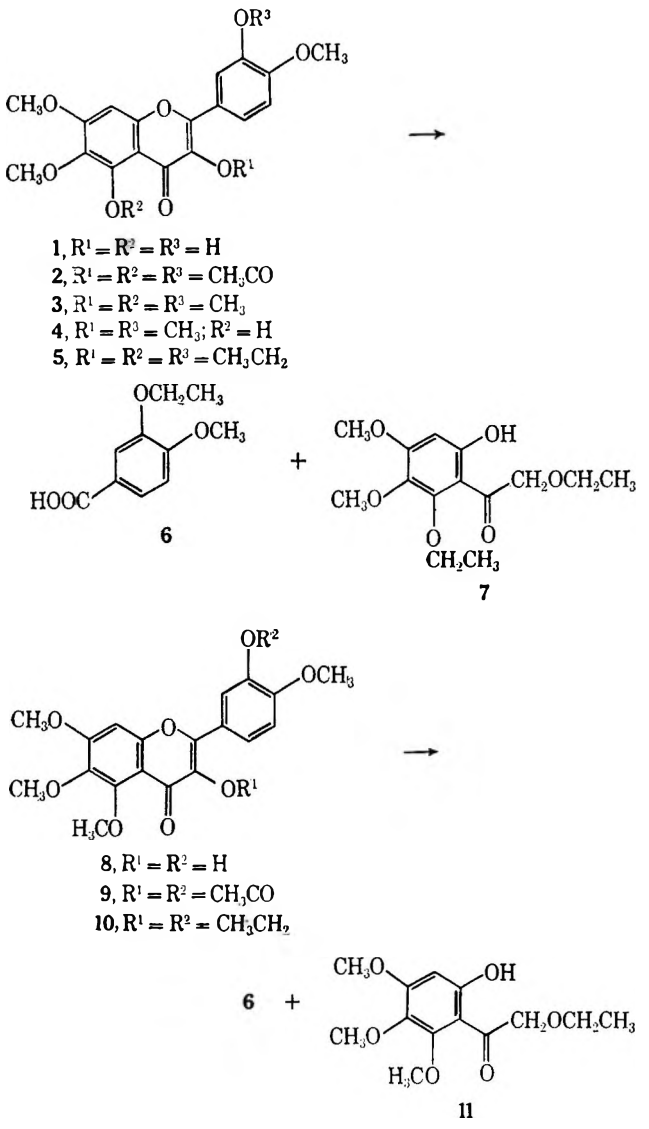
(7) A. K. Kiang, K. Y. Sim, and J. Goh, *J. Chem. Soc.*, 6371 (1965).

(8) We thank Dr. R. D. Brown and Dr. F. W. McLafferty of Purdue Mass Spectrometry Center, supported under U.S. Public Health Service Grant FR-00354, for the mass spectral data.

Experimental Section

Melting points were determined with a Thomas–Hoover Unimelt apparatus and are corrected. Infrared spectra were determined on a Beckman IR-5A double-beam recording spectrophotometer. Ultraviolet spectra were determined on a Beckman DK2A recording spectrophotometer. Nmr spectra were determined on a Varian H-60A spectrometer.

SCHEME I



Eupatin (1).—The isolation of eupatin was reported previously.[3] Eupatin was crystallized from methanol as golden yellow rods: mp 243–245°; uv max (EtOH) 258 mμ (ε 22,100), 273 (15,500), 366 (23,200); ir ($CHCl_3$) 2.85, 3.07, 6.03 μ; nmr (DMSO) τ 2.33 (s, 1), 2.30 (m, 1), 2.93 (d, 1, J = 10 Hz), 3.18 (s, 1), 3.26 (s, 1), 6.05 (s, 3), 6.12 (s, 3), and 6.23 (s, 3).

Anal. Calcd for $C_{18}H_{16}O_8$: C, 60.22; H, 4.58. Found: C, 60.00; H, 4.48.

3,5,3′-Triacetoxy-6,7,4′-trimethoxyflavone (2).—A mixture of eupatin (0.10 g), acetic anhydride (2 ml), and pyridine (0.25 ml) was refluxed for 2 hr, cooled, and poured into ice water. The white insoluble material was filtered, dried, and crystallized from benzene–petroleum ether (bp 60–68°) to yield the triacetate (2) as a colorless powder (0.067 g): mp 219–221°; ir (Nujol) 5.65, 6.10 μ; nmr ($CDCl_3$) τ 2.33 (m, 2), 2.82 (d, 1, J = 10 Hz), 3.15 (s, 1), 6.03 (s, 3), 6.11 (s, 3), 6.15 (s, 3), 7.54 (s, 3), 7.67 (s, 6).

Anal. Calcd for $C_{24}H_{22}O_{11}$: C, 59.26; H, 4.56. Found: C, 59.23; H, 4.65.

3,5,6,7,3′,4′-Hexamethoxyflavone (3). A.—A solution of eupatin (0.10 g) in dry acetone (20 ml) was refluxed for 8 hr with potassium carbonate (2 g) and dimethyl sulfate (0.5 ml). The acetone was evaporated, distilled water was added, and the insoluble material was collected by filtration. Chromatography on alumina (Woelm, grade 1) and elution with 5% ethyl acetate–benzene followed by recrystallization from benzene–petroleum ether (bp 60–68°) afforded eupatin trimethyl ether (3, 45 mg) as colorless needles: mp 141–142°; uv max (EtOH) 242 mμ (ε 20,900), 251 sh (20,900), 266 sh (16,100), 333 (24,500); ir 6.15 and 6.21 μ. Admixture of an authentic sample of hexamethylquercetagetin (mp 141–142°) did not depress the melting point, and the uv and ir spectra were identical with those of the authentic sample.

B.—Eupatoretin (0.050 g) was methylated with dimethyl sulfate by the procedure used for eupatin. The product was crystallized from benzene–petroleum ether to give 0.027 g of pale yellow needles, mp 141–142°. The sample was shown by melting point, mixture melting point, and infrared spectroscopy to be identical with 3,5,6,7,3′,4′-hexamethoxyflavone (3) prepared from eupatin.

C.—A solution of eupatoretin (0.20 g) in ethanol (90 ml) was treated with diazomethane (approximately 1 g) in ether at 0° for 2 hr. The product was crystallized from benzene–petroleum ether (bp 60–68°) to give colorless needles (0.115 g), mp 141–142°, which were shown to be identical with 3,5,6,7,3′,4′-hexamethoxyflavone (3) by melting point, mixture melting point, and infrared spectral comparison.

5-Hydroxy-3,6,7,3′,4′-pentamethoxyflavone (4).—A solution of eupatin (0.10 g) in methanol (50 ml) was treated with an excess of diazomethane in ether at 0° for 2 hr. The solvent was removed and the residue dissolved in chloroform. The chloroform was extracted several times with 3% potassium hydroxide solution. The alkaline extract was acidified and extracted with chloroform. The solution was dried ($MgSO_4$) and evaporated. The residue was crystallized from benzene–petroleum ether (bp 60–68°) to afford the pentamethoxyflavone (4) as pale yellow needles: mp 160–161° (lit.[5] mp 161°); uv max (EtOH) 255 mμ (ε 17,900), 274 (16,400), 346 (20,500); ir (Nujol) 6.00 μ.

3,5,3′-Triethoxy-6,7,4′-trimethoxyflavone (5).—A solution of eupatin (0.179 g), dry potassium carbonate (3 g), and ethyl iodide (3 g) in dry acetone (20 ml) was refluxed for 40 hr. After filtration, the solvent was evaporated and the residue was dissolved in ether, washed with water, and dried (Na_2SO_4). Evaporation of the solvent afforded 0.220 g of a pale yellow solid. Recrystallization from ethyl acetate–cyclohexane afforded yellow needles: mp 105–106°; uv max (95% EtOH) 242 mμ (ε 14,900), 250 sh (14,800), 265 sh (10,100), 233 (16,000); ir (KBr) 6.13, 6.18, 6.22 μ; nmr ($CDCl_3$) τ 2.23 (s, 1), 2.29 (m, 1), 3.0 (d, 1, J = 9 Hz), 3.21 (s, 1), 5.80 (q, 6, J = 7 Hz), 5.98 (s, 3), 6.00 (s, 3), 6.01 (s, 3), 8.46 (t, 6, J = 7 Hz), 8.65 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35. Found: C, 64.68; H, 6.25.

Alkaline Degradation of 3,5,3′-Triethoxy-6,7,4′-trimethoxyflavone (5).—Triethyl ether 5 (0.120 g) in a mixture of 50% potassium hydroxide (30 ml) and ethanol (5 ml) was refluxed under nitrogen for 17 hr. The reaction mixture was cooled, acidified with 20% sulfuric acid, and extracted with ether (200 ml). The ethereal extract was washed with four 50-ml portions of 5% sodium bicarbonate, dried (Na_2SO_4), and evaporated to dryness to afford the acetophenone (7) as a yellow oil. Recrystallization from petroleum ether (bp 35–37°) afforded 20 mg of yellow prisms: mp 59–60° (lit.[7] mp 60–61°); uv max (95% EtOH) 235 mμ (ε 8500), 283 (11,400), 335 (3400); nmr ($CDCl_3$) τ −3.20 (s, 1), 3.74 (s, 1), 5.25 (s, 2), 5.78 (q, 2, J = 7 Hz), 6.12 (s, 3), 6.22 (s, 3), 6.33 (q, 2, J = 7 Hz), 8.55 (t, 3, J = 7 Hz), 8.69 (t, 3, J = 7 Hz); m/e (relative intensity) 284 (24), 226 (11), 225 (100), 197 (31).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 58.95; H, 7.07.

The bicarbonate extract was acidified with dilute hydrochloric acid and extracted with ether which was dried (Na_2SO_4) and evaporated *in vacuo* to afford a white solid (40 mg). Recrystallization twice from methanol–water gave 3-ethoxy-4-methoxybenzoic acid (6) as colorless needles, mp 162–163° (lit.[9] mp 163–164°).

Eupatoretin (8).—The isolation of eupatoretin was reported previously.[3] Eupatoretin was crystallized from benzene to give bright yellow needles: mp 146–148°; uv max (EtOH) 255 mμ (ε 20,500), 356 (23,400); ir ($CHCl_3$) 2.96, 6.15, and 6.22 μ; nmr ($CDCl_3$) τ 2.26 (m, 2), 3.05 (d, 1, J = 9 Hz), 3.23 (s, 1), 5.96 (s, 3), 6.03 (s, 3), 6.05 (s, 3), 6.08 (s, 3).

Anal. Calcd for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85. Found: C, 60.81; H, 4.52.

3,3′-Diacetoxy-5,6,7,4′-tetramethoxyflavone (9).—Eupatoretin (0.16 g) was acetylated in the same manner as for the preparation of eupatin triacetate. The product was crystallized from benzene–petroleum ether (bp 60–68°) to afford 0.11 g of a colorless powder: mp 145–147°; uv max (EtOH) 235 mμ (ε

(9) I. Heilbron, "Dictionary of Organic Compounds," Eyre and Spottswoode, London, 1965.

28,300), 263 (25,000) 316 (31,000); ir ($CHCl_3$) 5.68, 6.14, and 6.21 μ.

Anal. Calcd for $C_{23}H_{22}O_{10}$: C, 60.26; H, 4.84. Found: C, 59.96; H, 5.16.

3,3'-Diethoxy-5,6,7,4'-tetramethoxyflavone (10).—Eupatoretin diethyl ether was prepared in the same manner as for eupatin triethyl ether. The product was crystallized from ethyl acetate–cyclohexane to yield 0.160 g of light yellow prisms: mp 119–120°; uv max (95% EtOH) 242 mμ (ϵ 17,000), 249 sh (13,000), 264 sh (13,000), 233 (18,800); ir (KBr) 6.10, 6.24 μ; nmr ($CDCl_3$) τ 2.19 (s, 1), 2.28 (m, 1), 3.0 (d, 1, J = 9 Hz), 3.24 (s, 1), 5.80 (q, 2, J = 7 Hz), 5.91 (q, 2, J = 7 Hz), 5.98 (s, 3), 6.01 (s, 3), 6.02 (s, 3), 6.07 (s, 3), 8.49 (t, 3, J = 7 Hz), 8.66 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{23}H_{26}O_8$: C, 64.17; H, 6.09. Found: C, 64.27; H, 6.10.

Alkaline Degradation of 3,3'-Diethoxy-5,6,7,4'-tetramethoxyflavone (10).—Alkaline degradation of **10** (0.120 g), using the same conditions as for eupatin triethyl ether, gave an acid and a neutral material. The acid was recrystallized from methanol–water to yield needles (0.030 g) of 3-ethoxy-4-methoxybenzoic acid (**6**), mp 163–164° (lit.[9] mp 164–165°). The neutral material was crystallized from petroleum ether (bp 35–37°) to afford 0.035 g of the acetophenone **11** as colorless needles: mp 60–61°; uv max (95% EtOH) 235 mμ (ϵ 5600), 283 (11,800), 334 (4750); ir (KBr) 6.15, 6.25 and 6.32 μ; nmr ($CDCl_3$) τ −3.02 (s, 1), 3.73 (s, 1), 5.30 (s, 2), 5.95 (s, 3), 6.08 (s, 3), 6.20 (s, 3), 6.32 (q, 2, J = 7 Hz), 8.68 (t, 3, J = 7 Hz); *m/e* (relative intensity) 270 (16), 212 (11), 211 (100), 196 (12), 69 (6).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.94; H, 6.70.

Registry No.—**1**, 19587-65-6; **2**, 19587-66-7; **5**, 19587-67-8; **7**, 4324-56-5; **8**, 19587-69-0; **9**, 19598-22-2; **10**, 19598-23-3; **11**, 19598-24-4.

The Synthesis of the Ring-B Sulfur Analog of Dehydrogriseofulvin

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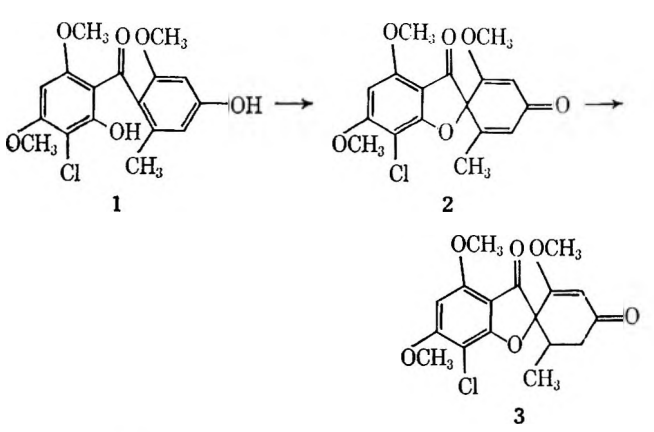
Received January 3, 1969

In 1957, Barton and Cohen,[1] in a classic paper speculating on the role of oxidative phenolic coupling in biogenesis, suggested that griseofulvin (**3**) arises biogenetically *via* oxidative ring closure of benzophenone **1** to dehydrogriseofulvin (**2**) followed by reduction.

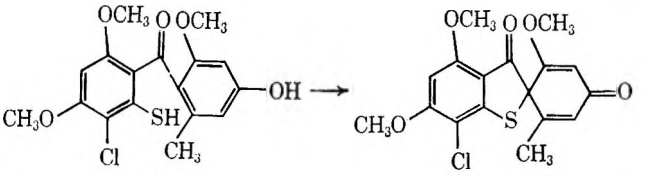


1 **2** **3**

(1) D. H. R. Barton and T. Cohen, "Festschrift A. Stoll," Birkhauser, Basle, Switzerland, 1957, p 117.

A laboratory analogy for the oxidative ring closure was first provided in 1958 by Scott, who accomplished the transformation of **1** to **2** in alkaline medium in the presence of potassium ferricyanide.[2] This coupling reaction was subsequently employed by Scott, *et al.*, in their total synthesis of griseofulvin[3] and in the total synthesis of griseofulvin and a number of its analogs described by Taub, *et al.*[4]

We report here the application of this reaction to the mercapto analog **4** of benzophenone **1** which was thus transformed into **5**, the ring-B sulfur analog of dehydrogriseofulvin **2**.[5]



4 **5**

In Table I the chemical shift values of the various protons in **5** are compared with their counterparts in dehydrogriseofulvin **2** and the ring-B carbon analog of dehydrogriseofulvin **6** ($-CH_2-$ in place of the ring oxygen in **1**). As can be seen, with the exception of the aromatic protons, the chemical shift values of the various corresponding protons are essentially superimposable.

The different chemical shift values observed for the aromatic proton in the three compounds would be expected as a result of the ring substituent change from sulfur to oxygen to methylene. The increase in shielding observed with increasing electron-donating ability of the substituent attached to the aromatic ring (O > S > $-CH_2-$, resulting in an increase in ring electron density) is in accord with earlier observations made on monosubstituted benzenes.[6]

Benzophenone **4** was synthesized according to Scheme I. The commercially available[7] 3,5-dimethoxyaniline (**6**) was converted *via* its diazonium salt into 3,5-dimethoxythiophenol (**7**), which was, in turn, acetylated and chlorinated with N-chlorosuccinimide to give **9**. Acylation of **9** with isoeverninic acid acetate (**10**) in trifluoroacetic anhydride[8,9] gave the diacetylated benzophenone **11** which was hydrolyzed to **4**.

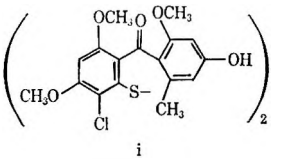
The position of the chlorine in **9** follows from its nmr spectrum in which the aromatic protons appeared as two doublets at δ 6.72 and 6.58 (J = 3 cps) consistent

(2) A. I. Scott, *Proc. Chem. Soc.*, 195 (1958).

(3) A. C. Day, J. Nabney, and A. I. Scott, *ibid.*, 284 (1960); *J. Chem. Soc.*, 4067 (1961).

(4) D. Taub, S. Kuo, and N. L. Wendler, *J. Org. Chem.*, **28**, 3344 (1963), and earlier papers cited there.

(5) At best, the formation of any disulfide i took place to only a very minor extent, and it is interesting that the rate influencing parameters in **4** com-



i

bine to cause intramolecular carbon–sulfur bond formation to dominate over the normally extremely rapid sulfur–sulfur bond-forming reaction.

(6) P. L. Corio and B. P. Dailey, *J. Amer. Chem. Soc.*, **78**, 3043 (1956).

(7) Aldrich Chemical Co., Milwaukee, Wis.

(8) See Table I, footnote *e*.

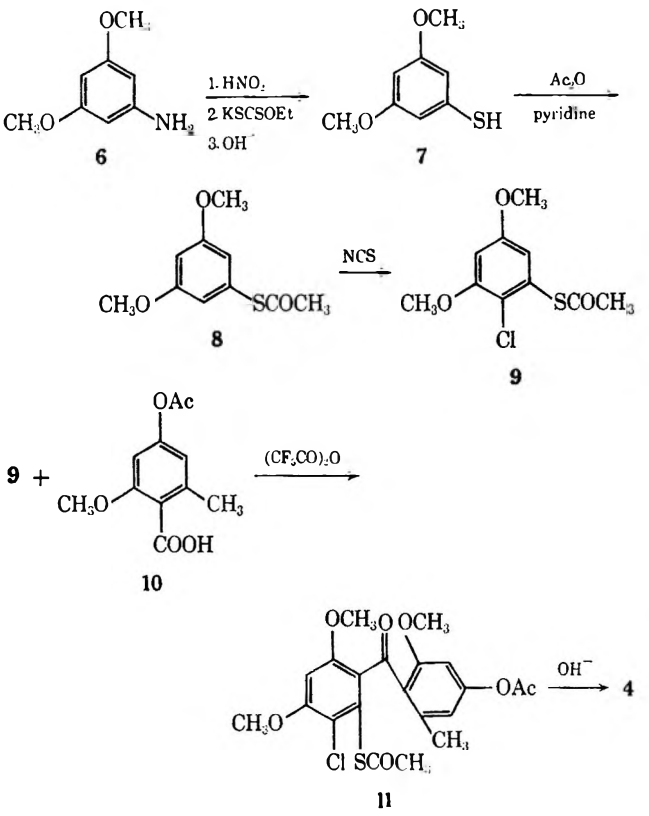
(9) D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Tetrahedron*, **19**, 1 (1963).

TABLE I[a]

	Aromatic proton	Vinyl proton	Aromatic methoxyls	Vinyl methoxyl	Vinyl methyl	Ring-B CH_2[b]
Dehydrogriseofulvin S analog 7	6.37	6.18,[c] 5.71[d]	4.05, 4.00	3.65	1.90 (J = 1 cps)	
Dehydrogriseofulvin[e,g]	6.15	6.15, 5.59	4.04, 3.98	3.63	1.79 (J = 2 cps)	
Dehydrogriseofulvin C analog[f]	6.52	6.17,[c] 5.70[d]	4.07, 4.00	3.62	1.74 (J = 1 cps)	3.40, 3.32

[a] Chemical shift values are in parts per million from tetramethylsilane (internal standard). Solvent–$CDCl_3$. [b] H. Newman and R. B. Angier, *J. Org. Chem.*, **31**, 1462 (1966), Table I. [c] Triplet (J = <1 cps). [d] Doublet (J = <1 cps). [e] H. Newman and A. Durante, *J. Org. Chem.*, **31**, 2291 (1966). [f] B. H. Arison, *et al.*, *J. Amer. Chem. Soc.*, **85**, 627 (1963).

SCHEME I



with their being *meta* oriented in an unsymmetrical environment.[10] (The symmetrical 4 analog would be expected to show a single two-proton peak.)

Depending on the catalyst and conditions employed, dehydrogriseofulvin (2) is reported to undergo either predominant hydrogenolysis to benzophenone **1** or predominant reduction to griseofulvin **3**.[8,9] The latter reaction course could be realized[9] (this was confirmed by us) by using a prepared Pd–C catalyst, in relatively large amounts and conducting the hydrogenation in a nonhydroxylic solvent. However, an attempt to convert **5** into the sulfur analog of griseofulvin under these conditions gave, instead, exclusive hydrogenolysis to benzophenone **4**.[11]

Experimental Section[12]

3,5-Dimethoxythiophenol (7).—To a stirred, cooled (ice–water) suspension of 37 g (0.24 mol) of 3,5-dimethoxyaniline[7] in 200 ml of water containing 50 ml of concentrated hydrochloric acid (0.6 mol) was added a solution of 16.6 g (0.24 mol) of sodium nitrite in 50 ml of water, the rate of addition being adjusted so as not to allow the reaction temperature to exceed 5°. The resulting red-purple, moderately thick solution of diazonium salt was added, over a 30-min period, to a stirred solution of 250 g (1.7 mol) of potassium ethyl xanthate in 200 ml of water at 85–90°. After cooling, the almost black reaction mixture was extracted with ether and the ethereal extracts were washed with dilute sodium hydroxide, water, dried, and evaporated. The crude xanthate (49 g) was heated under reflux in 200 ml of 90% ethanol containing 100 g of potassium hydroxide for 15 hr, the mixture extracted with ether (to remove any base insoluble material), and the basic aqueous phase acidified (concentrated hydrochloric acid). The water insoluble product which separated was extracted with ether and the ethereal extracts were washed, dried, and evaporated to yield a 23-g crude liquid residue. Distillation *in vacuo* from zinc dust gave 12.8 g (31%) of the thiophenol: bp 111° (0.1 mm); $n^{25}D$ 1.5830. The analytical sample was a colorless liquid: $n^{25}D$ 1.5834; λ_{max}^{film} 3.90 μ (–SH).

Anal. Calcd for $C_8H_{10}O_2S$ (170.18): C, 56.46; H, 5.92; S, 18.84. Found: C, 56.78; H, 5.99; S, 18.43.

3,5-Dimethoxythiophenol Acetate (8).—A cooled solution of 2 g (0.012 mol) of the thiophenol in 4 ml of dry pyridine was treated with 4 ml of acetic anhydride. The reaction mixture was kept at room temperature overnight, poured into ice water, and the product extracted with ether. The ethereal extracts were washed successively with cold dilute hydrochloric acid, cold water, aqueous bicarbonate, dried, and evaporated to yield 2.4 g (96%) of a colorless crystalline solid: mp 61–62.5°; λ_{max}^{Nujol} 5.85 μ.

Anal. Calcd for $C_{10}H_{12}O_3S$ (212.27): C, 56.58; H, 5.71; S, 15.11. Found: C, 56.40; H, 5.88; S, 14.80.

2-Chloro-3,5-dimethoxythiophenol Acetate (9).—To a solution of 7.8 g (0.037 mol) of 3,5-dimethoxythiophenol in 135 ml of dry benzene was added 5 g (0.037 mol) of N-chlorosuccinimide. The reaction mixture was stirred and irradiated for 23 hr with a 150-W G.E. projector lamp placed 4–6 in. from the side of the flask. The heat generated by the lamp raised the temperature of the reaction mixture to 77° and gave a homogeneous system. (N-Chlorosuccinimide is only partially soluble in benzene at room temperature.) The course of the reaction was followed by periodic testing of the reaction mixture for active halogen (starch–iodide paper). The test was still weakly positive after 18 hr, but was essentially negative after 21 hr. The orange solution was washed with water, dried, and evaporated to yield an oily solid residue which was heated and partially dissolved in a relatively small amount of ether and kept at room temperature overnight. The beige solid obtained (5.3 g) melted at 87–90° (softens *ca.* 84°). An additional 0.87 g, mp 81–86°, was isolated by concentrating the mother liquors giving a total yield of 6.2 g (68%). The analytical sample was obtained by partially dissolving a sample of the product in boiling ether and collecting after 1 hr at room temperature: mp 87–89.5° (softens 85°); λ_{max}^{Nujol} 5.90 μ.

Anal. Calcd for $C_{10}H_{11}ClO_3S$ (246.73): C, 48.68; H, 4.50; S, 13.00. Found: C, 48.78; H, 4.62; S, 12.70.

The nmr spectrum of the product in deuteriochloroform showed two one-proton doublets at δ 7.72 (J = 3 cps) and 6.58 (J = 3 cps) (aromatic protons), two three-proton singlets at 3.90 and 3.82 (aromatic methoxyl), and a three-proton singlet at 2.47 (–$SCOCH_3$).

(10) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 96.

(11) The reduction of **5** to the sulfur analog of griseofulvin has been accomplished microbiologically (unpublished results with W. W. Andres, *et al.*). The details of this conversion will appear elsewhere.

(12) Melting points were taken in a Hershberg apparatus using a 3-in. immersion thermometer. Infrared spectra were determined either neat (liquids or oils) or in Nujol mulls (solids) on a Perkin-Elmer Infracord spectrophotometer. Nmr spectra were determined on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Ultraviolet spectra were measured in methanol on a Cary 11MS spectrophotometer. Magnesium sulfate was used for drying. The petroleum ether used boiled at 30–60°.

4-Hydroxy-2'-mercapto-3-chloro-2,4',6'-trimethoxy-6-methylbenzophenone Diacetate (11).—A mixture of 4.4 g (0.018 mol) of 9 (above) and 4.0 g (0.018 mol) of isoeverninic acid acetate (10)[8,9] in 60 ml of trifluoroacetic anhydride was heated in a pressure bottle at 55–60° for 20 hr. The dark solution was evaporated *in vacuo*, the residue dissolved in methylene chloride, and the solution washed with aqueous bicarbonate, dried, and evaporated to yield a gummy residue which solidified on trituration with ether. The purple tinged colorless solid obtained, 2.8 g (34%), melted at 163–166°. Heating, partially dissolved, in boiling methanol furnished the analytical sample: mp 168–170°; λ_{max}^{Nujol} 5.67 (OAc), 5.87 (thioacetate), and 6.00 μ (ArCOAr); λ_{max}^{MeOH} 311 mμ (ϵ 7720), 242 sh (17,000), and 209 (50,000).

Anal. Calcd for $C_{21}H_{21}ClO_7S$ (452.91): C, 55.69; H, 4.67; S, 7.08. Found: C, 55.94; H, 5.09; S, 7.06.

Only partial conversion into **11** was realized when the reaction was conducted at room temperature.[13]

4'-Hydroxy-2-mercapto-3-chloro-2',4,6-trimethoxy-6'-methylbenzophenone (4).—Nitrogen was bubbled through a stirred suspension of 2.5 g (0.055 mol) of **11** in 40 ml of methanol at room temperature and 40 ml of 2 *N* aqueous sodium hydroxide was added in *ca.* 3 min. By the end of 10–15 min the reaction mixture was homogeneous. The nitrogen passage was terminated, and the flask stoppered and kept at room temperature for an additional 1.25 hr. Ice was added to the solution which was then acidified with cold, fairly concentrated hydrochloric acid. The practically colorless gum which separated solidified almost immediately and was collected after 15 min and air dried overnight; yield 2 g (99%); mp 195–199°. Recrystallization from aqueous methanol furnished the analytical sample: mp 198–199; λ_{max}^{Nujol} 290 and 6.33 μ. The latter band showed two inflections at 6.13 and 6.23 μ: λ_{max}^{MeOH} 300 mμ (ϵ 9250), 240 sh (21,300), and 210 (40,800).

Anal. Calcd for $C_{17}H_{17}ClO_5S$ (368.78): C, 55.36; H, 4.65; S, 8.70. Found: C, 55.05; H, 4.83; S, 8.43.

7-Chloro-2',4,6-trimethoxy-6'-methylspiro[benzo(*b*)thiophene-2(3H),1'-(2,5)-cyclohexadiene]-3,4'-dicne (5).—A solution of 1.7 g (0.0046 mol) of **4** (above) in 150 ml of water containing 25 g of potassium carbonate was added dropwise, over *ca.* a 10-min period, to a stirred solution of 6 g (0.018 mol) of potassium ferricyanide in 75 ml of water. The solid which began separating almost immediately was collected after stirring for 1 additional hr and heated, suspended, in boiling ethanol: yield 1.3 g (77%); mp 235–238°. A portion of this product was again heated in boiling ethanol to furnish the analytical sample: mp 236–238°; λ_{max}^{Nujol} 5.90 and 6.02 μ; λ_{max}^{MeOH} 348 mμ (ϵ 4550), 306 (18.700) and 235 (43,300). The nmr spectrum is presented in Table I.

Anal. Calcd for $C_{17}H_{15}ClO_5S$ (366.82): C, 55.66; H, 4.12; Cl, 9.67; S, 8.74. Found: C, 55.66; H, 4.41; Cl, 9.84; S, 863.

Attempted Reduction of 5 to the Ring-B Sulfur Analog of Griseofulvin.—A solution of 0.2 g (0.54 mmol) of **5** in a minimum of methylene chloride was prepared and diluted with 25 ml of ethyl acetate. The resulting solution was added to a suspension of 0.4 g of prereduced 10% Pd–C (prepared according to the procedure in ref 14) in 5 ml of ethyl acetate and the mixture was stirred under hydrogen at room temperature and atmospheric pressure until 10 ml of hydrogen was consumed (30 min) (0.54 mmol = 13.3 ml of H_2). The catalyst was separated by filtration through Celite and the filtrate evaporated to yield 0.18 g of a light yellow opaque gum which was separated into a base-soluble and base-insoluble fraction by dissolving in methylene chloride and extracting with cold dilute sodium hydroxide. The nmr spectrum of the base-insoluble fraction [isolated by drying and evaporating the methylene chloride solution (0.12 g, mp 237–240°)] was identical with that of pure **5**. The base-scluble material [obtained by acidifying the dilute sodium hydroxide extract and collecting the solid which separated (45 mg, mp 194–197°)] was identified by ir and thin layer chromatography as benzophenone **4**.

(13) As might have been anticipated, **8** proved more reactive. It was acylated by **10** in trifluoroacetic anhydride at a reasonable rate at room temperature.

(14) "Organic Syntheses, Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 687. (Darco-G-60 was the support employed.)

Registry No.—**4**, 19689-64-6; **5**, 19689-65-7; **7**, 19689-66-8; **8**, 19689-67-9; **9**, 19689-68-0; **11**, 19689-69-1.

Acknowledgment.—We thank Mr. L. Brancone and staff for the microanalyses and Mr. W. Fulmor and staff for the ultraviolet and nmr spectra.

A 1,4-Pyran Compound from Condensation of Pulegone and Ethyl Acetoacetate

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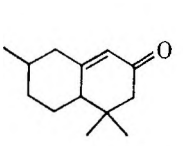
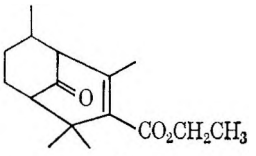
Received November 14, 1968

The zinc chloride catalyzed condensation of pulegone[1,2] with ethyl acetoacetate has been reported to yield two major crystalline compounds having mp 74–76°, proved[1,3] to possess structure **1**, and mp 37–39°, respectively.[1] Bicyclo[3.3.1]nonenone **2** was proposed as a possible structure for the compound of mp 37–39° in our early communication.[4] New chemical evidence and spectroscopic data now confirm that the compound of mp 37–39° is 2,4,4,7-tetramethyl-3-carbethoxy-5,6,7,8-tetrahydrobenzopyran[5] (**3**).



1



2

In our earlier condensation experiments it was noticed that although the yield of enone **1** did not fluctuate appreciably, the yield of pyran ester **3** varied from 12 to 0% depending on the conditions of the condensation. It was shown that a prolonged heating of the reaction eventually gave only enone **1** and no pyran ester **3**. Shorter reaction time or milder reaction conditions did not improve the yield of pyran ester **3**, but also resulted in recovery of a substantial amount of the starting material. Under the condensation conditions pyran ester **3** was gradually rearranged to enone **1**. Pyran ester **3** is, therefore, formed by a kinetically controlled process and reversibly rearranges to the thermodynamically more stable enone **1**.

Elemental analysis and mass spectroscopy established the molecular formula of the compound of mp 37–39° as $C_{16}H_{24}O_3$. In the absence of a deep-seated rearrangement, two structures **2** and **3** can be formulated for the compound of mp 37–39°. The chemical transformations summarized in Scheme I would

(1) Y. L. Chow, *Acta Chem. Scand.*, **16**, 205 (1962).

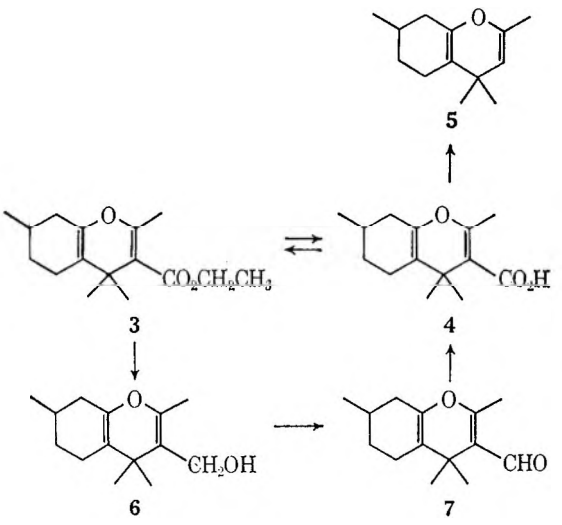
(2) P. Barbier, *C. R. Acad. Sci., Paris*, **127**, 870 (1898); L. G. Jupp, G. A. R. Kon, and E. H. Lockton, *J. Chem. Soc.*, 1639 (1928).

(3) J. Wolinsky and M. A. Tyrell, *Chem. Ind.* (London), 1104 (1960).

(4) Y. L. Chow, *Tetrahedron Lett.*, 1337 (1964).

(5) Professor J. Wolinsky has independently proved that the compound of mp 37–39° has structure **3**. We thank Professor Wolinsky for calling our attention to his paper [J. Wolinsky and H. S. Hauer, *J. Org. Chem.*, **34**, 380 (1969); Abstract, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968].

SCHEME I

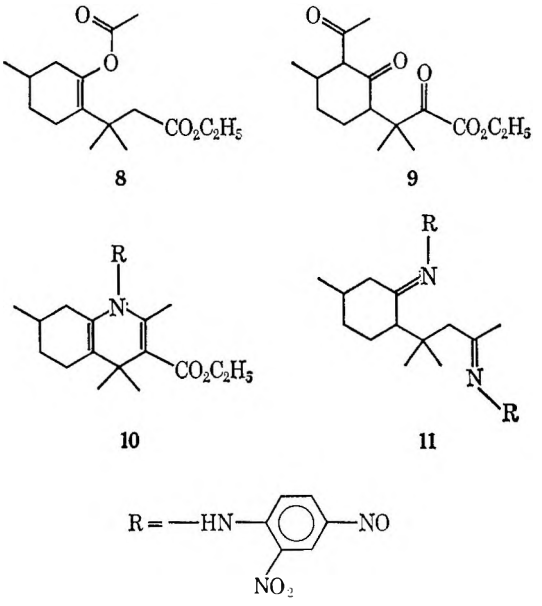


eliminate structure **2** but do not unambiguously prove the correctness of pyran structure **3**.

The primary aim of the chemical transformations (Scheme I) was to remove the conjugated carbethoxy group from parent compound **3** in order to simplify the chromophore system. The hindered nature of the ester grouping in **3** was indicated by the observation that **3**, after being vigorously refluxed in ethanolic potassium hydroxide solution, was only partially hydrolyzed to acid **4**. The carboxylic acid was re-esterified to **3** proving that no skeletal rearrangement had occurred during the vigorous base treatment. Carboxylic acid **4** was decarboxylated in hot quinoline to give pyran **5** which showed one olefinic proton at abnormally high field[6-9] at τ 5.82 (quartet) in the nmr spectrum and intense ir absorption at 1715 cm^{-1}. Vigorous treatment of **3** in ether with lithium aluminium hydride gave alcohol **6**. Although survival of a carbonyl group was unlikely under the reduction conditions, alcohol **6** showed the intense ir absorption at 1710 cm^{-1} and ultraviolet maxima at 235 and 285 mμ. While alcohol **6** could be oxidized by Sarett reagent in good yield to aldehyde **7**, the latter was converted into carboxylic acid **4** only by air oxidation, but not by other oxidizing agents.

The best proof that a carbonyl was absent in **5** and **6** came from the ORD curves[10] of these two compounds which exhibited plain positive curves regardless of the determination in isooctane or in ethanol. This argument was further supported by the failure of the deuterium incorporation into the carboxylic acid **4** in a basic condition. A literature search reveals that a 1,4-pyran usually exhibits fairly intense infrared absorption at about 1710- and 1660-cm^{-1} regions.[7,9,11] However, the ultraviolet maxima shown by **3**–**6** cannot be readily reconciled with the pyranoid structure since no data of a good model system can be found. Uptake of 2 mol equiv of hydrogen under vigorous hydrogenation finally proved that the compound of mp 37–39° contained two olefinic bonds (which must be tetrasubstituted) and therefore should be represented by **3**.

An unambiguous proof of pyran **3** was secured by ozonolysis of the conjugated double bond followed by mild reductive decomposition in which the probability of a skeletal rearrangement could be kept to a minimum. The expected ozonolysis products from structures **3** and **2** were **8** and **9**, respectively, wherein substantial



structural differences were obvious. The major component from this cleavage reaction, though obtained in only 18% yield, was shown to be **8** by spectroscopic data. The infrared absorption at 1750 and 1180 cm^{-1} and the strong mass peaks at 237 (corresponding to $M^+ - CH_3CO_2$) prove the presence of a vinyl acetate group. The ultraviolet[12] and the nmr[13] spectra do not show a maximum at the 250-mμ region nor a signal at low field typical for a 1,3 diketone. Thus the compound of mp 37–39° is proven to be pyran ester **3**.

The mass spectrum of pyran ester **3** shows the dominant peak at *m/e* 249 equivalent to $M^+ - 15$. The driving force for the tendency to loose a methyl group (from *gem*-dimethyl) is no doubt provided by the aromatization to a pyrylium ion. Elimination of either C_2H_4 (*m/e* 221) or C_2H_5OH (*m/e* 203) species from the pyrylium ion are readily conceivable *via* a similar transition state proposed in McLafferty rearrangement.[14]

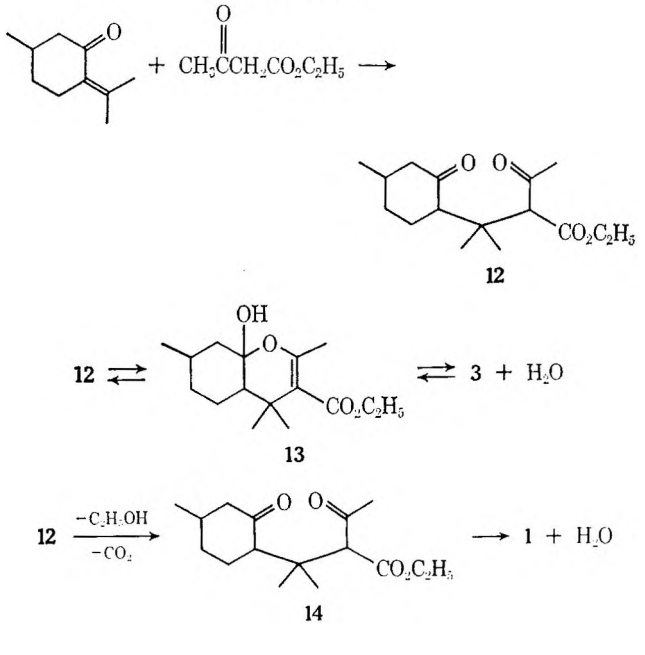
It is now in order to comment on the products obtained from the reaction of 2,4-dinitrophenylhydrazine with pyran ester **3** and pyran **5**. On treatment of pyran ester **3** with Brady's reagents, beautifully crimson needles were obtained which exhibited an ultraviolet maximum at 325 mμ. Since the nmr spectrum of the needles retained the typical ethyl signals of the carbethoxy group, the derivative was obviously not the corresponding acyl 2,4-dinitrophenylazide as pro-

(6) J. Feeney, A. Ledwith, and L. H. Sutcliffe, *J. Chem. Soc.*, 2021 (1962).
(7) S. Masamune and N. T. Castellucci, *J. Amer. Chem. Soc.*, **84**, 2452 (1962).
(8) "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, No. 111.
(9) H. W. Whitlock, Jr., and N. A. Carlson, *Tetrahedron*, **20**, 2101 (1964).
(10) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.
(11) M. J. Jorgenson, *J. Org. Chem.*, **27**, 3224 (1962).
(12) Most of the 1,3-diketones show an intense absorption at 250–270 mμ (ϵ 10,000) region in an alcoholic solution obviously due to enolization [E. G. Meek, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 2891 (1953)].
(13) L. M. Jackman "Application of NMR Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p 70.
(14) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1967, p 22.

posed previously.[4] On the other hand, the ultraviolet maximum of the needles is very similar to the maxima of diethyl 1-(2′,4′-dinitrophenylamino)pyrrole 3,4-dicarboxylate.[15] Dihydropyridine **10** is, therefore, assigned to the crimson needles. Although the purity of dihydropyridine **10** was fully established by tlc analysis,[16] the nmr signal of the *gem*-dimethyl group displays many sharp singlets and that of vinylic methyl a closely located doublet. In pyridine solution **10** showed singlets (τ 8.01 and 8.60) for vinylic methyl and one of the *gem*-dimethyl groups and a doublet (τ 8.46) for the other *gem*-dimethyl group. The latter doublet did not collapse when the temperature was raised to 100°. Interaction of Brady's reagent with pyran **5** readily gave yellow crystals analyzed as $C_{25}H_{30}N_8O_8$. The ultraviolet absorption of 361 mμ (ϵ 30,100) displayed by this compound demonstrated the presence of two 2,4-dinitrophenylhydrazone groups. Under the reaction conditions the hydrolysis of pyran **5** to the corresponding diketone was apparently possible. The yellow crystals are, therefore the bishydrazone (**11**).

It is now possible to suggest a mechanism of condensation of pulegone with the acetoacetate as shown in Scheme II. The formation of pyran ester **3** *via* **12** and **13** may be facilitated by the presence of the hindered carbethoxyl group which promotes the enolization of **12** and eventually the pyran ring closure. A steric acceleration of the pyran ring closure may also be suggested by the presence of the methyl and carbethoxyl substitutions. As soon as the carbethoxyl group is eliminated, such effects are no longer present in **14** and enone **1** is formed.

SCHEME II



Experimental Section[17]

Condensation of Pulegone and Ethyl Acetoacetate.—A solution consisting of pulegone (Fluka AG., [α]D +22.1, 150 g), ethyl acetoacetate (137 g), freshly fused zinc chloride (150 g), and glacial acetic acid (500 g) was heated over a water bath for 5 hr. The reaction mixture was poured into ice water (1.5 l.) and the oil was extracted with ether. The ether extract was washed with water and dried to afford a residue (145 g) after evaporation. The residue was subjected to fractional distillation under 10 mm vacuum. The forerun (35 g, bp up to 102°) was the recovered starting material. The second fraction (56 g, bp 102–130°) solidified on standing and was shown to contain mostly enone **1**.

The third fraction (39 g, bp 130–144°) partially crystallized on standing. A part of the crystals (1 g) was chromatographed on an alumina column. Elution with light petroleum gave a crystalline fraction (830 mg) which was recrystallized from light petroleum three times to afford an analytical sample of the pyran ester **3**: mp 37–39°; [α]D +47.8 (in EtOH); λ_{max} 206 mμ (ϵ 5900) and 272 (2500). The uv absorption of **3** is not appreciably changed in 5% NaOEt solution. Compound **3** has the infrared absorption at 1712, 1635, 1310, 1170, and 1050 cm^{-1}; the nmr signals (CCl_4) at τ 5.89 (q, J = 7 Hz, 2 H), 8.10 (s, 3 H), 8.72 (t, J = 7 Hz, 3 H), 8.77 (s, 3 H), 8.80 (s, 3 H), and 9.03 (d, J = 5 Hz, 3 H).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.74; H, 8.93.

The yields of pyran ester **3** and enone **1** varied considerably depending on the experimental conditions and were usually poorer than that shown above. Pyran ester **3** consumed bromine in carbon tetrachloride and exhibited red color with tetranitromethane. Pyran ester **3** showed negative for iodoform test and semicarbazone formation and was stable toward a hot 10% ethanolic potassium hydroxide solution for several hours.

Reaction of Pyran Ester 3 with 2,4-Dinitrophenylhydrazine.—To a solution of **3** (106 mg) in ethanol (4 ml) was added Brady's reagent (5 ml). Red needles precipitated slowly and were recrystallized three times from ethanol to give a crimson crystal (176 mg): mp 182–184°; λ_{max} 326 mμ (ϵ 17,700); the ir absorptions at 3320, 1700, 1618, 1592, 1534, 1515, 1500 and 1335 cm^{-1}; and the nmr signals at τ 0.90 (d, J = 2.5 Hz, 1 H), 1.65 (d of d, J = 2.5 and 10 Hz, 1 H), 2.70 (m, 3 H), 5.78 (q, J = 7 Hz, 2 H), 8.69 (t, J = 7 Hz, 3 H), and 9.10 (d, J = 5 Hz, 3 H). At room temperature, the $=CCH_3$ protons (τ 8.17) showed an unequal doublet and the CH_3CCH_3 protons (τ 8.7) an irregular multiplet.

Anal. Calcd for $C_{22}H_{28}N_4O_6$: C, 59.44; H, 6.35; N, 12.61. Found: C, 59.14; H, 6.22; N, 12.53.

Acid-Catalyzed Isomerization of the Pyran.—A solution of pyran ester **3** (570 mg), fused zinc chloride (500 mg), and glacial acetic acid (10 ml) was heated over a water bath for 15 hr. The reaction mixture was worked in the usual manner to afford enone **1** (85 mg), mp and mmp 74–76° with an authentic sample[1].

Carboxylic Acid 4.—The pyran ester **3** (300 mg) and potassium hydroxide (1.5 g) in ethanol (10 ml) were vigorously refluxed for 30 hr. The hydrolysate was worked up in a usual manner to give unreacted starting material (60 mg) and a crystalline acidic fraction (190 mg). The acidic fraction was recrystallized from chloroform and then from ethanol to afford the carboxylic acid **4**: mp 205–206° (evolution of gas on melting in a sealed tube); [α]D +61° (in EtOH); λ_{max} 209 mμ (ϵ 6500) and 270 (2600). The carboxylic acid shows the ir absorption ($CHCl_3$) at 2300–3500, 1710, 1685, 1620, and 1320 cm^{-1} and the nmr signals at τ 7.94 (s, 3 H), 8.67 (s, 6 H), and 9.04 (d, J = 5 Hz, 3 H). In a DMSO solution the *gem*-dimethyl groups show two singlets at τ 8.67 and 8.68. The mass spectrum of the acid shows peaks at m/e 236 (2) 221 (94), 203 (5), 192 (5), 177 (100).

Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 70.90; H, 8.41.

The carboxylic acid (130 mg) was treated successively with sulfonyl chloride (5 ml) at room temperature and then with ethanol in the presence of pyridine to give an oil. This oil was chromatographed on alumina (5 g) to give a crystalline fraction

(15) T. D. Binns and R. Brettle, *J. Chem. Soc., C*, 341 (1966).

(16) The original 2,4-DNP derivatives were further purified to give mp 182–184°.

(17) Unless specified otherwise the following experimental conditions prevail. The nmr spectra were recorded in $CDCl_3$ solution with respect to an internal TMS reference with the Varian Associates A-60 spectrometer. The mass spectra were measured with an Hitachi-Perkin Elmer RMU-6E mass spectrometer at ionization voltage 80 eV. The ultraviolet spectra were recorded in 95% ethanol with a Cary 14 spectrophotometer and the infrared spectra in Nujol mull or liquid film with Perkin-Elmer Model 421 and 457. The ORD curve was measured with a Rudolph spectropolorimeter. All melting points are uncorrected. The elemental analyses were performed by Dr. A. Bernhardt, West Germany. The splitting patterns of the nmr spectra are expressed by s (singlet), d (doublet), t (triplet), q (quartet), and the number of hydrogen by H.

(125 mg) which was recrystallized from ethanol to afford pyran ester **3**, mp and mmp 37–39°.

A clean piece of sodium (350 mg) was dissolved in D_2O (5 ml). The carboxylic acid (226 mg) was dissolved in the solution and was refluxed for 3 hr under nitrogen atmosphere. Acetic anhydride was added dropwise until pH ~6. The precipitate was recrystallized from ethanol three times to afford the carboxylic acid, mp 205–206°. The infrared and mass spectra of this sample were completely indistinguishable from those of an authentic sample of carboxylic acid **4**.

Decarboxylation of the Carboxylic Acid.—A solution of the carboxylic acid (870 mg) in redistilled quinoline (20 ml) was refluxed for 1 hr. Upon a usual working up, the unreacted carboxylic acid (370 mg) and a neutral oil (310 mg) were obtained. The oil was recrystallized from ethanol–water (5:1) three times to give pyran **5**; mp 32.7–33.5° (sealed tube); $[\alpha]_D$ +63.9 (in EtOH); λ_{max} 221 mμ (ε 4600), 230 (2770), 275 (157), 286 (142), 303 (36), and 318 (21) in cyclohexane. The crystalline compound of **5** sublimed quickly on exposure to the air and gave red color with tetranitromethane in CCl_4. Pyran **5** shows their absorptions at 1715, 1678, and 812 cm^{-1}; nmr τ 9.03 (d, J = 4 Hz, 3 H), 8.96 (s, 6 H), 8.32 (d, 1 Hz, 3 H), 5.82 (q, J = 1 Hz, 1 H); plain positive ORD curve φ (mμ) 32 (550), 41 (500), 50 (450), 70 (400), 95 (350) and 160 (300) in ethanol and 70 (550), 95 (500), 119 (450), 155 (400), 234 (350) and 415 (300) in isooctane.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.32; H, 10.48.

On treatment with Brady's reagent, pyran **5** gave a yellow precipitate which was recrystallized from ethanol–ethyl acetate three times to afford bishydrazone **11**: mp 184–186°; λ_{max} 229 mμ (ε 23,300), 260 (15,700), and 361 (30,100). The molecular weight determination by Rast method was 601.

Anal. Calcd for $C_{25}H_{30}N_8O_8$: C, 52.65; H, 5.35; N, 19.67. Found: C, 52.46; H, 5.30; N, 19.47.

Reaction of Pyran Ester 3 with $LiAlH_4$.—Pyran **3** was recovered unchanged on treatment with potassium borohydride in aqueous methanol solution overnight. A solution of **3** (850 mg) and lithium aluminum hydride (700 mg) in dry ether (100 ml) were refluxed for 5 hr. The reaction mixture was decomposed with ethyl acetate and was further treated with 20% ammonium hydroxide solution. The product was extracted with light petroleum in the usual manner to give a residue which was recrystallized from light petroleum several times to afford alcohol **6** (425 mg): mp 80–82.5°; $[\alpha]_D$ +62.5 (EtOH); λ_{max} 235 mμ (ε 2660), 285 (20), and 300 (10). Alcohol **6** exhibits the ir absorption (CCl_4) at 3640, 3520, 1710, 1665, and 1195 cm^{-1}; nmr signals at τ 5.82 (s, 2 H), 4.8 (broad, 1 H), 8.09 (s, 3 H), 8.85 (s, 6 H) and 9.02 (d, J = 5 Hz, 3 H); and a plain positive ORD curve of φ (mμ) 102 (550), 130 (500), 165 (450), 222 (400), 335 (350), 585 (300) and 850 (280) in ethanol and 105 (550), 130 (500), 170 (450), 225 (400), 340 (350), 655 (300), and 940 (280) in isooctane.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97; active H, 0.45. Found: C, 75.60; H, 9.76; active H, 0.40.

Although alcohol **6** was recovered unchanged on treatment in hot 1 *N* ethanolic sodium hydroxide solution, it decomposed on storage or on treatment in ethanol solution containing a trace of hydrochlorice acid. Amorphous precipitates were obtained on attempts to prepare 2,4-DNPH, semicarbazone, and thiosemicarbazone.

The acetate of alcohol **5** was formed (acetic anhydride–pridine) as an oil which showed the infrared absorption at 1740, 1715, 1670, 1235, and 1220 cm^{-1} and the nmr signals at τ 5.40 (s, 2 H), 8.02 (s, 3 H), 8.17 (s, 3 H), and 8.9 (s, 6 H).

Oxidation of Alcohol 6.—A solution of the alcohol (1 g) in pyridine (30 ml) was oxidized with a chromic oxide (900 mg) solution in pyridine (5 ml) overnight at 0–5°. After the usual working up, an oil (780 mg) was obtained as the neutral fraction but no material could be obtained from sodium hydroxide (2 *N*) extraction. This oil showed their peaks at 2750, 1712, and 1615 cm^{-1} and was oxidized with a slow stream of air in ethanol (100 ml) for several days. The solvent was evaporated and the remaining residue was triturated with light petroleum to give a crystalline precipitate (145 mg). The crystals were recrystallized from ethanol to give the carboxylic acid **4**. The oil remained from the isolation of the carboxylic acid was oxidized with air in the similar manner to give additional amounts of carboxylic acid **4**.

Hydrogenation of Pyran Ester 3.—A preliminary experiment showed that pyran ester **3** did not absorb hydrogen in ethanol in the presence of palladized carbon (10%) over 48-hr period. Pyran ester **3** (80 mg) platinum oxide (30 mg) in glacial acetic acid (10 ml) were hydrogenated at atmospheric pressure for 20 hr at room temperature. The product was isolated in the usual manner to give an oil. This oil was taken up in light petroleum and percolated through an alumina column to give a colorless oil which was distilled from bulb to bulb under 10 mm pressure. The distillate showed the infrared absorption at 1735 and 1715 cm^{-1} (medium) and, in the nmr region, complex multiplet at τ 5.85–6.75 and many singlets at 9.1–8.7. The mass spectrum showed the intense M^+ peak at 268.

Ozonolysis of Pyran Ester 3.—A solution of **3** (789 mg) in chloroform (30 ml) was ozonized at 0° for 15 min followed by a zinc dust decomposition.

The neutral fraction was taken up in chloroform and was chromatographed on a silicic acid column (10 g). The major component was eluted as the second fraction (125 mg) with chloroform and was distilled from bulb to bulb. This oil showed single spot on a tlc plate (alumina) with chloroform or 2% methanol in chloroform as eluents. Oil **8** possesses their absorption at 1750, 1715, 1180, and 1070 cm^{-1}, the mass spectral peaks at *m/e* 296 (M^+, 12%), 281 (10), 251 (13), 237 (12), 223 (35), 198 (32) and 171 (100); λ_{max} 207.5 mμ (ε 3600); nmr signals at τ 8.98 (d, J = 6 Hz, 3 H), 8.70 (s, 3 H), 8.82 (s, 3 H), 8.67 (t, J = 7 Hz, 3 H), 8.06 (s, 3 H), and 5.80 (q, J = 7 Hz, 2 H). At the ionization voltage of 15 eV the intensity of the mass peaks at 296, 281, and 237 are enhanced.

From a tlc analysis the acidic fraction was shown to be a mixture of at least six components and was not investigated further.

Registry No.—Pulegone, 89-82-7; ethyl acetoacetate, 141-97-9; **3**, 18600-02-7; **4**, 19614-44-9; **5**, 19614-45-0; **6**, 19614-46-1; **8**, 19640-43-8; **10**, 18588-73-3; **11**, 19614-47-2.

Acknowledgment.—The authors are indebted to the National Research Council of Canada for financial support of this project and the purchase of an Hitachi-Perkin Elmer RMU-6E.

The Hydroxylamine Route to 3-Unsubstituted Isoxazolium Salts

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Received November 19, 1968

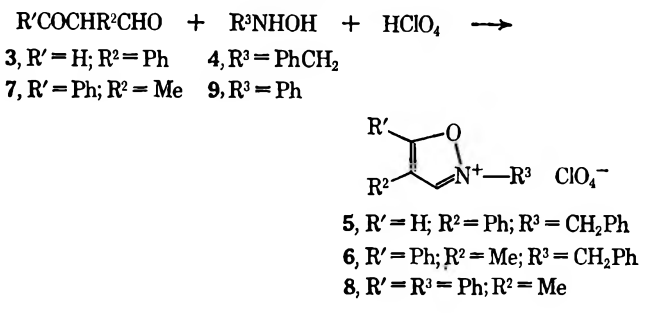
The importance of 3-unsubstituted isoxazolium salts in the synthesis of peptides[2] has spurred the improvement of preparative methods for the heterocyclic cations[3] and the development of routes to new types of the salts. Recently those with bulky groups on nitrogen have been made available by the SN1 alkylation of isoxazoles with alcohols and perchloric acid,[4,5] while the first N-aryl compounds **1** were obtained by a new pathway to the heterocyclic ring.[4] Our study of the latter route has now provided a one-step synthesis of 3-unsubstituted isoxazolium perchlorates directly from α-formyl derivatives of carbonyl compounds and N-substituted hydroxylamines.

(1) National Science Foundation Graduate Trainee, 1966–1969.
(2) R. B. Woodward and D. J. Woodman, *J. Amer. Chem. Soc.*, **90**, 1371 (1968).
(3) B. D. Wilson and D. M. Burness, *J. Org. Chem.*, **31**, 1565 (1966).
(4) R. B. Woodward and D. J. Woodman, *ibid.*, **31**, 2039 (1966).
(5) D. J. Woodman, *ibid.*, **33**, 2397 (1968).

In the previous work[4] N-arylhydroxylamines were condensed with hydroxymethyleneacetophenone to give 3-(N-hydroxyanilino)acrylophenones, **2**. Although treatment with aqueous acid was known to lead to simple hydrolysis of compounds of type **2**,[6] it was found that dehydrative cyclization to **1** took place in concentrated sulfuric acid.

Our further examination of this approach with phenylmalonaldehyde, **3**, and N-benzylhydroxylamine, **4**, revealed that cyclization can also be achieved under mildly acidic conditions in nonaqueous media. Moreover, the condensation and cyclization steps can both be carried out simply by adding 70% perchloric acid to a solution of **3** and **4** in ether, from which the insoluble product 2-benzyl-4-phenylisoxazolium perchlorate, **5**, precipitates. The scope of the new method is demonstrated by the preparation of 2-benzyl-4-methyl-5-phenylisoxazolium perchlorate, **6**, from the more hindered dicarbonyl compound 2-benzoylpropanal, **7**, and of 2,5-diphenyl-4-methylisoxazolium perchlorate, **8**, from **7** and N-phenylhydroxylamine, **9** (Scheme I).

SCHEME I



Experimental Section

Melting points were determined with a Mel-temp apparatus and are uncorrected. The nmr spectra were run on a Varian A-60 spectrometer, and the uv spectra were recorded with a Cary 14 spectrophotometer. Elemental analyses were performed by A. Bernhardt, Mikroanalytisches Laboratorium, West Germany.

2-Benzyl-4-phenylisoxazolium Perchlorate (**5**).—A mixture of 0.6 g (4.1 mmol) of phenylmalonaldehyde, **3**, and 0.5 g (4.1 mmol) of N-benzylhydroxylamine, **4**, in 50 ml of dry ether was stirred while 0.4 ml of 70% $HClO_4$[7] was added dropwise. After 24 hr the ether was decanted, leaving an orange oil. Several precipitations of the oil from MeCN (10-ml portions) with ether (75-ml portions) gave 0.85 g (62%) of white crystals: mp 125–125.5°; nmr (MeCN) δ 5.93 (s, 2), 7.4–7.82 (unresolved, 10), 9.37 (s, 1), 9.77 (s, 1).

Anal. Calcd for $C_{16}H_{14}ClNO_5$: C, 57.24; H, 4.20; N, 4.18. Found: C, 57.06; H, 4.24; N, 4.03.

2-Benzyl-4-methyl-5-phenylisoxazolium Perchlorate (**6**).—A solution of 4.0 g (24.7 mmol) of 2-benzoylpropanal, **7**, and 3.0 g (24.7 mmol) of **4** in 1 l. of ether was stirred vigorously at 0° while 2.6 ml of 70% $HClO_4$ was added dropwise. After 24 hr the crystals of **6**, 7.2 g (84%), were filtered and washed with ether. Precipitation of the product from 50 ml of MeCN with 800 ml of ether gave white crystals: mp 138–140°; uv max (CH_2Cl_2) 300 mμ (ϵ 19,000); nmr (98% H_2SO_4, positions upfield relative to H_2SO_4) δ 2.62 (s, 1), 3.7 (broad, 10), 5.5 (s, 1), 8.72 (s, 3).

Anal. Calcd for $C_{17}H_{16}ClNO_5$: C, 58.38; H, 4.61; Cl, 10.14; N, 4.00; O, 22.87. Found: C, 58.42; H, 4.65; Cl, 10.07; N, 4.18; O, 22.95.

(6) J. Thesing, A. Müller, and G. Michel, *Chem. Ber.*, **88**, 1027 (1955).

(7) In view of the explosion hazard associated with the use of perchloric acid, all reactions were carried out behind a sturdy safety shield. Although no detonations were encountered in the present work, it should be noted that some isoxazolium perchlorates have been found to be impact-sensitive explosives.[3]

2,5-Diphenyl-4-methylisoxazolium Perchlorate (**8**).—A solution of 4.5 g (27.8 mmol) of **7** and 3.0 g (28 mmol) of N-phenylhydroxylamine, **9**, in 1 l. of ether was stirred vigorously with protection from the light while 3 ml of 70% $HClO_4$ was added dropwise. After 3 hr a grey precipitate, 7 g (75%), was filtered, washed with ether, and dried. Precipitation of the product from MeCN with ether gave off-white, light-sensitive crystals: mp 166–167° dec; uv max (CH_2Cl_2) 332 mμ (15,900); nmr (98% H_2SO_4, positions upfield relative to H_2SO_4) δ 3.18–3.62 (m, 10), 2.05 (s, 1), 8.6 (s, 3).

Anal. Calcd for $C_{16}H_{14}NO_5Cl$: C, 57.24; H, 4.20; N, 4.18; Cl, 10.55; O, 23.82. Found: C, 57.30; H, 4.23; N, 4.28; Cl, 10.59; O, 23.79.

Registry No.—**5**, 19614-31-4; **6**, 19614-32-5; **8**, 19614-33-6.

Reaction of 2-Trichloroacetamido-5-chlorobenzhydrol with Potassium Hydroxide to Give 4-Phenyl-6-chloro-1,4-dihydro-2H-3,1-benzoxazin-2-one

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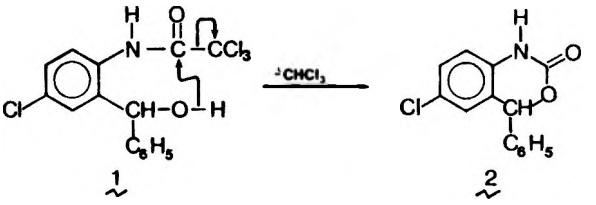
Several examples have been recently reported of cyclizations of 2-chloroacetamidobenzhydrols under basic conditions to give 1,5-dihydro-5-phenyl-4,1-benzoxazepin-2(3H)-ones.[1-4]

In the present study we investigated the reaction of 2-trichloroacetamido-5-chlorobenzhydrol (**1**) with alcoholic base. A crystalline compound $C_{14}H_{10}ClNO_2$ was the only product obtained; ir bands at 1705 and 3210 cm^{-1} suggested the presence of a RNHCOOR group,[5] and the nmr results established the oxazine structure **2**.[6] The formation of **2** might be considered as an intramolecular displacement of chloroform by the neighboring benzhydrilic function (Scheme I).

SCHEME I



An alternative mechanism, involving formation and cyclization of the intermediate isocyanate, could also be considered. To clarify this matter, we planned the synthesis of 2-(N-methyltrichloroacetamido)-5-chlorobenzhydrol, which cannot lead to an isocyanate. Unexpectedly, the reaction of 2-methylamino-5-chlorobenzhydrol with trichloroacetyl chloride in the presence

(1) E. Testa, L. Fontanella, and M. Bovara, *Farmaco, Ed. Sci.*, **18**, 815 (1963).

(2) G. I. Poos, U. S. Patent 3,122,554 (1964); *Chem. Abstr.*, **60**, 12036 (1964).

(3) Lepetit S.p.A., French Patent 1,405,271 (1965); *Chem. Abstr.*, **63**, 13298 (1965).

(4) E. Testa and L. Fontanella, *Farmaco, Ed. Sci.*, **20**, 323 (1965).

(5) L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen & Co. Ltd., London, 1962, pp 221–222.

(6) E. Testa and L. Fontanella, *Farmaco, Ed. Sci.*, **21**, 549 (1966).

of triethylamine directly yielded benzoxazinone **3**, also obtained by methylation of **2**.[6,7] The isolation of **3** in the reaction of 2-methylamino-5-chlorobenzhydrol with trichloroacetyl chloride could be explained only by the intermediate formation of 2-(N-methyltrichloroacetamido)-5-chlorobenzhydrol, in which only intramolecular nucleophilic displacement of chloroform by the neighboring benzhydrylic function could lead to **3**. These results suggest a similar mechanism for the formation of benzoxazinone **2**.

Experimental Section

Melting points were determined in open capillary tubes. Ir spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Nmr spectra were determined with a Varian HA-100 spectrophotometer in the indicated solvent using TMS as internal standard. Thin layer chromatograms were run on silica gel G. Spots were detected with sulfuric acid. The solvent systems used were solvent A, benzene–methanol (95:5); solvent B, carbon tetrachloride–methanol (95:5); solvent C, chloroform–ethyl acetate–diethylamine (70:10:10).

2-Trichloroacetamido-5-chlorobenzhydrol (1).—A solution of 18.2 g (0.1 mol) of trichloroacetyl chloride in 60 ml of anhydrous ether was added dropwise over 30 min to an ice-cooled stirred solution of 23.35 g (0.1 mol) of 2-amino-5-chlorobenzhydrol[1] and 10.1 g (0.1 mol) of triethylamine in anhydrous ether. After stirring at 5° for 2 hr, the resultant suspension was filtered from triethylamine hydrochloride (13.6 g); the filtrate was concentrated to dryness; and the residue was recrystallized from benzene–cyclohexane to give 30.5 g (80%) of white crystals, mp 130–131°. Tlc using solvents A and C showed single spots with R_f 0.79 and 0.70, respectively.

Anal. Calcd for $C_{15}H_{11}Cl_4NO_2$: C, 47.52; H, 2.93; Cl, 37.47; N, 3.69. Found: C, 47.68; H, 2.96; Cl, 37.17; N, 3.59.

4-Phenyl-6-chloro-1,4-dihydro-2H-3,1-benzoxazin-2-one (2).—A solution of 18.95 g (0.05 mol) of 1 and 8.4 g (0.15 mol) of potassium hydroxide in 350 ml of absolute ethanol was heated at reflux for 4 hr. The resultant suspension[8] was concentrated to *ca.* 100 ml, and 50 ml of 1 *N* HCl and 500 ml of water were added with stirring. The precipitate was filtered, washed with water, and recrystallized from ethanol to give 8.4 g (65%) of white crystals: mp 191–193° dec; ir (KBr) 3395 and 3210 (NH), 1705 cm^{-1} (C=O); nmr ($CDCl_3$–DMSO-d_6 9:1) δ 10.08 (1, s, NH), 7.36 (5, s, C_6H_5), 6.75–7.25 (3, m, the aromatic protons of the benzoxazine ring), 6.28 (1, s, CH–O); tlc, single spots with R_f 0.47, 0.62, and 0.59 in solvents A, B, and C, respectively.

Anal. Calcd for $C_{14}H_{10}ClNO_2$: C, 64.74; H, 3.88; Cl, 13.65; N, 5.39. Found: C, 64.83; H, 3.87; Cl, 13.72; N, 5.52.

4-Phenyl-6-chloro-1-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (3). A. From 2-Methylamino-5-chlorobenzhydrol.—A solution of 17.7 g (0.097 mol) of trichloroacetyl chloride in 60 ml of anhydrous ether was added dropwise at −5° over 30 min to a stirred solution of 24.0 g (0.097 mol) of 2-methylamino-5-chlorobenzhydrol[1] and 9.8 g (0.097 mol) of triethylamine in 200 ml of anhydrous ether. After stirring at −5° for 2 hr, the resultant suspension was filtered, and the precipitate was washed twice with 50 ml of a hot mixture of tetrahydrofuran–ether (3:1); the insoluble triethylamine hydrochloride (13.2 g) was discarded. The filtrates were combined and the solvents evaporated. Recrystallization of the residue from ethanol gave 14.6 g (55%) of white crystals: mp 185–187° dec; ir (KBr) 1705 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.38 (5, s, C_6H_5), 6.80–7.30 (3, m, the aromatic protons of the benzoxazine ring), 6.18 (1, s, CH–O), 3.34 (3, s, N–CH_3); tlc, a single spot with R_f 0.84 in the solvent A.

Anal. Calcd for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; Cl, 12.95; N, 5.12. Found: C, 65.78; H, 4.44; Cl, 13.01; N, 5.23.

B. From 2.—A mixture of 52.0 g (0.20 mol) of 2 and 10.6 g (0.22 mol) of sodium hydride (50% oily suspension) was treated with a solution of 56.5 g (0.33 mol) of methyl iodide in 100 ml of anhydrous dimethylformamide. As the exothermic reaction that initially took place had subsided, the mixture was refluxed for 2.5 hr to give a clear solution. Upon standing overnight at 5°, a crystalline product separated, which was washed and recrystallized from ethanol to give 34.0 g (60%) of **3**, mp 185–187°. This product was identical in all respects (ir spectra, tlc, and mixture melting point) with the substance obtained from procedure A.

(7) R. L. Dannley and M. Lukin, *J. Org. Chem.*, **22**, 268 (1957).

(8) Filtration after cooling at room temperature gave 9.3 g (0.125 mol) of potassium chloride.

Registry No.—**1**, 19639-69-1; potassium hydroxide, 1310-58-3; **2**, 13213-86-0; **3**, 13213-94-0.

Acknowledgments.—We wish to thank Professor V. Rosnati of the University of Milan for helpful discussion through the experiment and Professor C. J. Cavallito of the University of North Carolina for his valuable comments to the manuscript.

The 6-Hydroxy-5,6-dihydro-4H-1,2-oxazine 2-Oxide System. Absence of Ring–Chain Tautomerism in 5,5-Dinitro-2-pentanone

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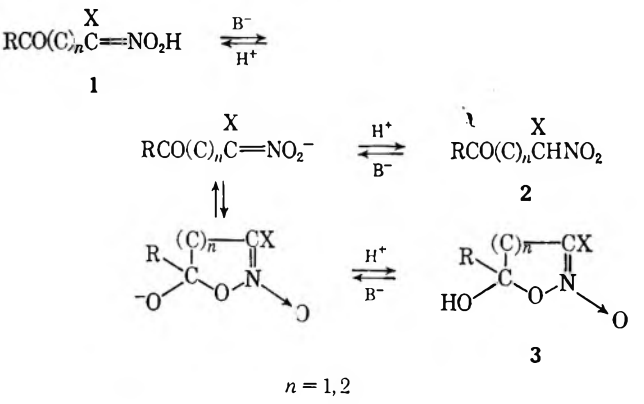
Many 3- and 4-keto-1-nitro- (and 1,1-dinitro-) alkanes are known.[2,3] Their nitronate salts on mild acidification may undergo very rapid O protonation to form the corresponding 3- and 4-ketonitronic acids (**1**) (Scheme I), which usually are consumed in solution by relatively slower C protonation of their nitronate

SCHEME I



anions leading ultimately to ketonitroalkanes (**2**). Spectra and other properties which have been determined for 3- and 4-keto-1-nitroalkanes and 3-keto-1,1-dinitroalkanes indicate that they exist in the chain form.[3-5] Reported ring–chain tautomerism with these substances is limited to two examples; the rings are

(1) National Research Council Postdoctoral Research Associate, 1967–1968.

(2) E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10**, 179 (1959).

(3) (a) D. J. Glover and M. J. Kamlet, *J. Org. Chem.*, **26**, 4734 (1961); (b) M. J. Kamlet and D. J. Glover *ibid.*, **27**, 537 (1962).

(4) M. E. Kuehne and L. Foley, *ibid.*, **30**, 4280 (1965).

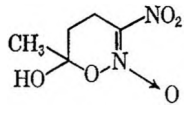
(5) (a) A. Risaliti, M. Forchiassin, and E. Valentin, *Tetrahedron*, **24**, 1889 (1968); (b) G. F. Tereshchenko, B. I. Lonin, L. I. Bagal, and G. I. Koldobskii, *Zh. Org. Khim.*, **4**, 1125 (1968); (c) K. V. Altukhov, V. A. Tartakovskii, V. V. Perekalin, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 197 (1967); (d) K. V. Altukhov and V. V. Perekalin, *Zh. Org. Khim.*, **3**, 2003 (1967).

6-hydroxy-5,6-dihydro-4H-1,2-oxazine 2-oxides (**3**, n = 2).[6-8] We have reexamined these reports and have corroborated one of them. No other examples of ring–chain tautomerism of this type have been found.

5,5-Dinitro-2-pentanone (**4**) has been reported to exist in methanol solution to a large extent as 6-hydroxy-6-methyl-3-nitro-5,6-dihydro-4H-1,2-oxazine 2-oxide (**5**).[6] This conclusion rests principally on the observation that the rate of sodium borohydride reduction of **4** to the corresponding nitro alcohol in 1:1 methanol–water at pH 3–4 is slow, relative to rates of reduction of other 4-keto-1,1-dinitroalkanes lacking a C-1 proton.

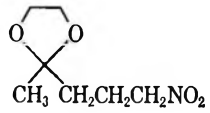
$CH_3COCH_2CH_2CH(NO_2)_2$

4



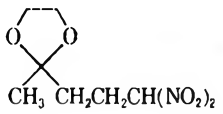
5

The preparation of **4** itself has not been described in the literature, although the potassium salt has been made from 5,5,5-trinitro-2-pentanone.[3] We found direct oxidative nitration of 5-nitro-2-pentanone to yield **4** in only 5% yield, but ethylene ketal **6** could be converted into ketal **7** in 43% yield; acid hydrolysis of **7** led to an 83% yield of **4**.



6

$\xrightarrow[AgNO_3]{NaOH,\ NaNO_2}$



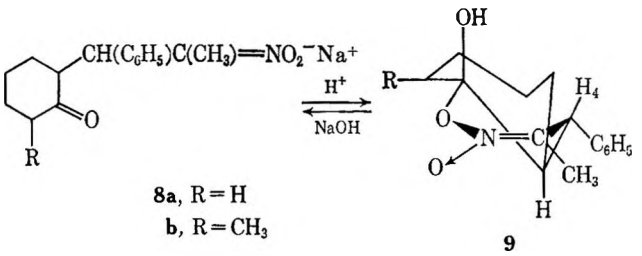
7

$\xrightarrow{H_3O^+}$ **4**

Properties of **4** reveal no evidence of its existence as ring form **5**. Infrared spectra determined neat and in carbon tetrachloride or dimethyl sulfoxide-d_6 reveal no absorption in the region 3100–4000 cm^{-1} (no hydroxyl stretching bands); characteristic strong asymmetric and symmetric nitro bands appear at *ca.* 1560 and 1350 cm^{-1}, respectively, and a normal carbonyl stretching band is found at 1720 cm^{-1}. No C=N stretching bands are evident (no bands near 1630–1690 cm^{-1}).[9] The nmr spectra of **4** determined in 1:1 methanol–water at pH 5 and 3.5, in deuteriochloroform and dimethyl sulfoxide-d_6 agree with chain structure **4**. The ultraviolet spectra of **4** determined in water, ethanol, or 1:1 methanol–water show the same absorption maximum as the corresponding nitronate anion determined in aqueous or ethanolic potassium hydroxide solution (*ca.* 380 mμ). Ketal **7** and other 1,1-dinitroalkanes have very similar absorption maxima (*ca.* 380 mμ).[3] Cyclic α-nitronitronic esters such as **5** would be expected to absorb at wavelengths 40–60 mμ lower than the corresponding 1,1-dinitronate anions.[9] In 1:1 methanol–water at pH 3.5 the ionization of **4** is almost completely repressed as evidenced by the absence of significant electronic absorption above 250 mμ.

The ionization constant of **4** was determined by rapid potentiometric titration in water at 25° and revealed only one equivalence point (pK_a = 4.84);[10] 1,1-dinitro-n-alkanes have pK_a values of 5.2–5.6.[11] There appears to be no acid weakening of **4** which would be associated with a stable ring form **5**. Rather, an expected acid strengthening owing to an inductive effect of the β-acetyl group is apparent (calculated for **4**, $pK_a \cong$ 4.85[3,11b]). The observation that reduction of **4** in methanol at pH 3–4 is slow and requires a large excess of sodium borohydride may possibly be explained by the fact that this reducing agent is destroyed exceedingly rapidly in this medium.[12]

Many 2-(2-nitroalkyl)cyclohexanones are known.[2-5,13] One of these has been reported to exist as a ring tautomer.[7] Condensation of cyclohexanone with 2-nitro-1-phenylpropene in aqueous sodium hydroxide led to a Michael adduct (**8a**), which on acidification with methanolic acetic acid gave a crystalline solid, tentatively assigned structure **9a** (no stereochemistry); **8a** could be regenerated from **9a**.[7]



8a, R = H
b, R = CH_3

9

Structure **9a** is in agreement with its infrared spectrum and chemical behavior, previously reported,[7] and its ultraviolet spectrum which we have determined, λ_{max}^{EtOH} 228 mμ (ϵ 17,000).[14] We find that the nmr spectrum of **9a** establishes its structure and stereochemistry, assuming a *trans*-fused chair form of cyclohexane ring as shown. A ten-cycle coupling of the C-4 proton with the adjacent bridgehead proton supports a structure having a pseudoequatorial C-4 phenyl. Cyclic structure **9a** must be considered unique. Low solubility coupled with high crystallinity and melting point facilitates its isolation. Its ease of formation and stability may be associated, in part, with the slow rate of C protonation of **8a**, and slow proton removal from the axial hydroxyl in **9a**. Slow C protonation is observed with α,β,β-substituted nitronic acids.[14,15]

(6) H. Shechter, D. E. Ley, and L. Zeldin, *J. Amer. Chem. Soc.*, **74**, 3664 (1952).

(7) (a) E. B. Hodge and R. Abbott, *J. Org. Chem.*, **27**, 2254 (1962); (b) E. B. Hodge, U. S. Patent 3,024,232 (1962); *Chem. Abstr.*, **57**, 8501 (1962).

(8) P. R. Jones, *Chem. Rev.*, **63**, 461 (1963).

(9) 3-Nitro-2-isoxazoline 2-oxide has $\lambda_{max}^{H_2O}$ 320 mμ (ϵ 8366); ν 1640–1650 cm^{-1} (C=N). (a) V. I. Slovetskii, A. I. Ivanov, A. A. Fainzilberg, S. A. Shevelev, and S. S. Novikov, *Zh. Org. Khim.*, **2**, 937 (1966); *Chem. Abstr.*, **65**, 16827 (1966); (b) A. I. Ivanov, I. E. Chlenov, V. A. Tartakovskii, V. I. Slovetskii, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1491 (1965); *Chem. Abstr.*, **63**, 16152 (1965); (c) V. A. Tartakovskii, B. G. Gribov, I. A. Arostyanova, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1644 (1965); *Chem. Abstr.*, **64**, 2080 (1966).

(10) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley & Sons, Inc., New York, N. Y., 1962.

(11) (a) V. I. Slovetskii, A. A. Fainzilberg, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 989 (1962); *Chem. Abstr.*, **58**, 5487 (1963); (b) V. I. Slovetskii, S. A. Shevelev, V. I. Erashko, L. I. Biryukova, A. A. Fainzilberg, and S. S. Novikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 655 (1966); *Chem. Abstr.*, **65**, 3714 (1966).

(12) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, pp 242–247.

(13) V. V. Perekalin and K. S. Parfenova, *Zk. Obshch. Khim.*, **30**, 388 (1960); *Chem. Abstr.*, **54**, 24582 (1960).

(14) Ultraviolet spectra of acyclic or cyclic aliphatic nitronic esters lacking an α-nitro or aryl substituent have not been reported; *cf.* N. Kornblum and R. A. Brown, *J. Amer. Chem. Soc.*, **86**, 2681 (1964). The spectra of these substances should resemble those of the corresponding nitronic acids. For octane-2-nitronic acid λ_{max}^{EtOH} 226 mμ (ϵ 12,800); for the corresponding nitronate anion λ_{max}^{EtOH} 232 mμ (ϵ 12,800); A. T. Nielsen and H. F. Cordes, *Tetrahedron Suppl.*, **20** (1), 235 (1964).

(15) E. B. Hodge, *J. Amer. Chem. Soc.*, **73**, 2341 (1951).

2-Methylcyclohexanone and 2-nitro-1-phenylpropene gave a solid (**9b**) which was too unstable to characterize. Attempts to prepare other 5,6-dihydro-4H-1,2-oxazine 2-oxides were unsuccessful. Normal Michael adducts or recovered reactants are usually obtained in the condensation of 2-nitro-1-phenylpropene and other nitro olefins with various ketones under conditions whereby **9a** is formed.[7,16]

Ring-chain tautomerism of 3- and 4-ketonitronic acids in which both ring and chain forms coexist in solution in stable equilibrium is unknown. It is unlikely to be observed. The ring form (**3**) should be only slightly less acidic (0.5–1 pK_a) than the nitronic acid (**1**).[17] With nitronic acids derived from the weakly acidic mononitroalkanes (**2**, X = H, alkyl) pK_a^{nitro}–$pK_a^{aci} \cong$ 3–7.[18] Even 1-nitro-3- and -4-ketoalkanenitronic acids derived from the more acidic 1,1-dinitroalkanes (**2**, X = NO_2; pK_a^{nitro}–$pK_a^{aci} \cong$ 1–2),[18] or certain nitronic acids stabilized by substitution of bulky groups, should be expected to behave like 3- and 4-ketoalkanoic acids and exist in the chain form.[5c,d,8,16,17] On the other hand, an intramolecular addition of nitronate anion oxygen to carbonyl can occur in certain systems if a stable product results. This process is observed in the formation of **9a** and **b**, and the reaction of 1,3-cyclohexanedione with some nitro olefins to yield 3-oxo-2,3-dihydro-4H-1,2-benzoxazines.[19,20]

Experimental Section

2-Methyl-2-(3-nitropropyl)-1,3-dioxolane (**6**) was prepared from 5-nitro-2-pentanone and ethylene glycol:[21] 44% yield; bp 87–90° (0.5 mm); $n^{25}D$ 1.4523; $\nu_{neat}^{cm^{-1}}$ 1560, 1380 (NO_2), 1060 (ether), no bands between 1600 and 1800. The nmr spectrum (neat) showed a methylene triplet signal at τ 5.94 (J = 7 Hz, two protons), methylene singlet at 6.41 (four protons), multiplet methylene signal centered at 8.5 (four protons), and a methyl singlet at 9.2 (three protons).

Anal. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00; mol wt, 175.18. Found: C, 48.13; H, 7.75; N, 7.85; mol wt, 175 (mass spectroscopy).

2-Methyl-2-(3,3-dinitropropyl)-1,3-dioxolane (**7**).—A solution of 15.6 g (0.089 mol) of ketal **6** in 100 ml of methanol was added to a solution of 3.6 g of sodium hydroxide and 5.0 g of sodium nitrite in 50 ml of water. This solution was allowed to stand for 30 min at 25°, cooled to 0°, and added slowly to a cold solution of 30 g of silver nitrate in 75 ml of water covered with 60 ml of ether. When addition was complete, the reaction mixture was kept at 0° for 30 min, filtered, and extracted three times with 100 ml of ether. The combined ether extracts were evaporated and the residue distilled to yield 8.5 g (43%) of ketal **7**: bp 110–114° (0.3 mm); $n^{25}D$ 1.4604; $\nu_{neat}^{cm^{-1}}$ 1580, 1340 (NO_2); λ_{max}^{EtOH} 381 mμ (ε 4590); λ_{max} in ethanolic potassium hydroxide (1 × 10^{-4} *M* hydroxide, 5 × 10^{-5} *M* compound **7**) 238 mμ (ε 7000), 381 (17,200). The nmr spectrum ($CDCl_3$) showed a triplet methine signal at τ 3.60 (J = 7 Hz, one proton), methylene signals at 6.08 (s, four protons), 7.40 (m, two protons), and 8.05 (m, two protons), and a methyl singlet at 8.70 (three protons).

Anal. Calcd for $C_7H_{12}N_2O_6$: C, 38.18; H, 5.49; N, 12.72; mol wt, 220. Found: C, 37.92; H, 5.75; N, 12.97; mol wt, 213 (in acetone by osmometry).

5,5-Dinitro-2-pentanone (**4**).—A solution of 5.4 g (0.025 mol) of ketal **7** in 50 ml of ethanol and 50 ml of 2.9 *M* hydrochloric acid, after standing at 25° for 76 hr, was concentrated to a small volume and extracted three times with 75-ml portions of ether. The combined ether extracts were evaporated and the residue was distilled to yield 3.6 g (83%) of 5,5-dinitro-2-pentanone: bp 123–125° (0.5 mm); $n^{25}D$ 1.4594; $\nu_{neat}^{cm^{-1}}$ 1560, 1350 (NO_2), and 1720 (C=O); $\nu_{CCl_4}^{cm^{-1}}$ 1550, 1720; $\nu^{cm^{-1}}$ (DMSO-d_6) 1570, 1340, 1720; λ_{max}^{EtOH} 379 mμ (ε 9000); λ_{max} in ethanolic potassium hydroxide (1.0 × 10^{-3} *M* hydroxide, 5 × 10^{-5} *M* compound **4**) 379 mμ (ε 17,200); $\lambda_{max}^{H_2O}$ 382 mμ (ε 8200); λ_{max} in aqueous potassium hydroxide (1.0 × 10^{-3} *M* hydroxide, 5 × 10^{-5} *M* compound **4**) 382 mμ (ε 16,500) [lit.[3] 379 mμ (ε 16,600)]; in 1:1 methanol–water, λ_{max} 377 mμ (ε 5700); in methanol–water containing sulfuric acid (pH 3.5), λ_{max} 377 mμ (ε 26). No change in these spectra occurred during 1 hr. The nmr spectrum ($CDCl_3$) showed a complex methine signal at τ 3.49, methylene singlets at 7.21 and 7.26 (four protons), and a methyl singlet at 7.79 (three protons). The same proton signals were observed neat, in acetone-d_6, and in DMSO-d_6. However, in $CDCl_3$–benzene (1:1) there appeared a normal methine triplet at τ 3.93 (J = 7 Hz, one proton), a complex methylene signal centered at τ 7.6 (four protons), and a methyl singlet at 8.12 (three protons). The proximity of the methylene chemical shifts in $CDCl_3$ solution explains the virtual coupling effect observed for the methine proton signal in this solvent. A 10% solution of **4** in 1:1 methanol–water (pH *ca.* 5) showed the C-1 proton multiplet centered at τ 3.25 (one proton), a complex methylene signal centered at 7.22 (four protons), and a methyl singlet at 7.82 (three protons). In the same solvent adjusted to pH 3.5 with sulfuric acid the spectrum was essentially the same with a slight increase in the intensity of the C-1 proton signal. These solutions are similar to those employed in the reported sodium borohydride reductions.[6] In a 1:1 methanol-d_4–D_2O solution of **4** the C-1 methine signal was absent owing to very rapid exchange of the C-1 proton in this solvent; the remainder of the spectrum was similar to that observed for **4** in methanol–water. The observed spectra remained unchanged during 24 hr.

Anal. Calcd for $C_5H_8N_2O_5$: C, 34.09; H, 4.58; N, 15.91; mol wt, 176.13. Found: C, 34.32; H, 4.93; N, 15.62; mol wt, 176 (mass spectroscopy).

A 2,4-dinitrophenylhydrazone derivative of **4** was prepared and crystallized from ethanol, mp 114–115°.

Anal. Calcd for $C_{11}H_{12}N_6O_8$: N, 23.59. Found: N, 23.46.

8a-Hydroxy-3-methyl-4-phenyl-4a,5,6,7,8,8a-hexahydro-4H-1,2-benzoxazine 2-Oxide (**9a**).—2-Nitro-1-phenylpropene (6.0 g, 0.037 mol) in 20 ml of cyclohexanone was treated with a solution of 2.0 g of sodium hydroxide in 3 ml of water and the mixture stirred for 2 hr (after *ca.* 10 min an exothermic reaction occurred and a homogeneous solution resulted). The mixture was poured into 100 ml of acetone containing 20 ml of acetic acid. The solid which precipitated was removed by filtration and recrystallized from ethanol to yield 3.9 g (40%) of **9a**, colorless prisms, mp 137–139° dec (lit.[7] mp 137–139° dec). The nmr spectrum ($CDCl_3$) revealed an aryl multiplet centered at τ 2.74 (five protons), a broad singlet at 3.11 (OH, one proton), a doublet centered at 6.53 (J = 10 Hz, one proton), a complex multiplet at 7.4–8.9 (nine protons), and a methyl doublet at 8.15 (J = 1 Hz, three protons). Owing to the very slight solubility of **9a** in water and ethanol we were unable to determine its pK_a in these solvents.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.96; H, 7.21; N, 5.19.

The above procedure employed with 2-methylcyclohexanone gave an unstable solid product upon acidification with acid. However, it decomposed very rapidly and could not be characterized. It is believed to be an impure sample of **8a-hydroxy-3,8-dimethyl-4-phenyl-4a,5,6,7,8,8a-hexahydro-4H-1,2-benzoxazine 2-oxide** (**9b**). Unsuccessful attempts were made to extend the reaction, employing the above procedure and various modifications of it, to the reaction of 2-nitro-1-phenylpropene with cyclopentanone, acetone, 3-pentanone, 2,4-pentanedione, 1-indanone, 1,3-indandione, dimedone, 1,3-cyclohexanedione, and 2,6-dimethylcyclohexanone. β-Nitrostyrene, 1-nitropropene, and 2-nitro-1-butene were also allowed to react with some of these ketones. Products obtained were usually the normal 1:1 adducts,[2,7,12] recovered reactants, or intractable tars. Some of these reactions gave previously unreported compounds which will be described in a forthcoming publication.[20] Michael

(16) (a) F. Boberg and G. R. Schultze, *Chem. Ber.*, **90**, 1215 (1957); (b) F. Boberg and A. Kieso, *Ann.* **626**, 71 (1959).

(17) C. Pascual, D. Wegmann, U. Graf, R. Scheffold, P. F. Sommer, and W. Simon, *Helv. Chim. Acta*, **47**, 213 (1964).

(18) A. T. Nielsen in "Chemistry of Functional Groups, Chemistry of the Nitro and Nitroso Groups," H. Feuer and S. Patai, Ed., Interscience Publishers, New York, N. Y., in press, Chapter 7.

(19) H. Stetter and K. Hoehne, *Chem. Ber.*, **91**, 1344 (1958).

(20) A. T. Nielsen and T. G. Archibald, *Tetrahedron*, **25** (1969), in press.

(21) Procedure of W. D. S. Bowering, V. M. Clark, R. S. Thakur, and Lord Todd, *Ann.*, **669**, 106 (1963).

addition of nitromethane and nitroethane to benzalacetone and chalcone gave the normal 1:1 adducts.[2] No evidence of 6-hydroxy-5,6-dihydro-4H-1,2-oxazine 2-oxides was found upon examination of the infrared and nmr spectra of product mixtures or selected fractions thereof from each of these reactions.

Registry No.—**4**, 19639-72-6; **4** (2,4-dinitrophenylhydrazone), 19639-73-7; **6**, 19639-74-8; **7**, 19639-75-9; **9a**, 19640-00-7.

Acknowledgment.—The authors are indebted to Donald W. Moore for helpful discussions.

Some Reactions of 2,4,4-Trimethyl-1-pyrroline 1-Oxide

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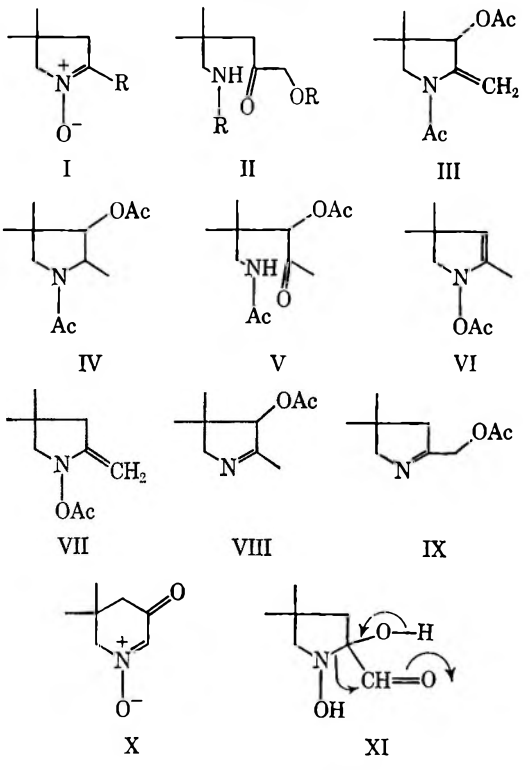
Received December 3, 1968

In connection with other work we had need to investigate some reactions of the title compound. Many of the interesting properties of cyclic nitrones have already been delineated.[1,2] For example, treatment of 2,4,4-trimethyl-1-pyrroline 1-oxide (I, R = Me) with benzoyl chloride under Schotten–Baumann conditions gave smoothly a ketobenzoate to which the structure II (R = PhCo) was assigned.[1] We were interested in carrying out the corresponding process of acetylation to give II (R = Ac).[3]

Treatment of the nitrone (I, R = Me) with acetic anhydride in carbon tetrachloride at −20° gave in reasonable yield a crystalline derivative of the composition $C_{11}H_{17}O_3N$ and therefore not the diacetyl compound (II, R = Ac) (Chart I). The new derivative showed in the ^1H nmr spectrum two acetyl groups, two vinyl hydrogens, and one hydrogen on a carbon to which an acetoxyl (or equivalent) function was attached. This, and other spectroscopic evidence, suggested structure III. The following experiments confirmed the correctness of this suggestion. Hydrogenation of derivative III over palladized charcoal (1-mol uptake) gave a compound (IV) which showed an additional secondary methyl group in its nmr spectrum. Treatment of derivative III with aqueous acetic acid containing a little hydrochloric acid at 0° gave smoothly ketoamide V in which the methyl ketone function could be readily recognized in the nmr spectrum. Ketoamide V was characterized as its crystalline 2,4-dinitrophenylhydrazone derivative, a compound which could be prepared directly by treating III with acidic 2,4-dinitrophenylhydrazine solution. The acid-catalyzed hydration of III to give V is a conventional enamide reaction, but the acetylation process itself deserves brief comment. Acetylation of nitrone I should give either enamine VI or its analog VII. The rearrangement of this type of compound to the corresponding imines (VIII and IX,

CHART I



respectively) has much precedent.[4] The N acetylation of VIII and concommitant loss of methyl proton would furnish III directly. A route from IX would require a further allylic rearrangement which would be improbable in the presence of only a small amount of acetic acid at −20 to 0°. The driving force for such an additional rearrangement would also appear to be lacking. We favor, therefore, the direct route I (R = Me) → VI → VIII → III.

Since the methyl group of nitrone I (R = Me) was not functionalized by the acetylation process, we considered also a direct oxidation procedure to give aldehyde I (R = CHO), or other equivalent derivative. It had been shown earlier[5] that oxidation of I (R = Me) with selenium dioxide in methanol[6] under reflux gave a dark oil which with dilute hydrochloric acid afforded crystalline nitrone X. We have found that the selenium dioxide oxidation of I (R = Me) will proceed smoothly at room temperature in ether to give I (R = CHO) in satisfactory (65%) yield. This aldehyde readily afforded a crystalline dimedone derivative and showed the expected aldehyde proton in the nmr spectrum. Oxidation of the aldehyde with silver oxide afforded the corresponding crystalline acid (I, R = CO_2H). A by-product from the selenium dioxide oxidation was the rearranged nitrone X. Indeed if the initial selenium dioxide oxidation solution was left to stand at room temperature substantial amounts of nitrone X were formed. An attempted formation of the 2,4-dinitrophenylhydrazone of aldehyde I (R = CHO) afforded only the known derivative of X. The facile rearrangement of I (R = CHO) to X

(1) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 2094 (1959), and sequential papers.

(2) J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964); G. R. Delpierre and M. Lamchen, *Quart. Rev.* (London), **19**, 329 (1965).

(3) Compare F. Agolini, R. Bonnett, D. E. McGreer and G. F. Stephenson, *J. Chem. Soc., C*, 1491 (1966).

(4) *Inter alia* T. Cohen and J. H. Fager, *J. Amer. Chem. Soc.*, **87**, 5701 (1965); T. Cohen and G. L. Deets, *ibid.*, **89**, 3939 (1967); R. F. C. Brown, W. D. Crow, L. Subrahmanyan, and C. S. Barnes, *Aust. J. Chem.*, **20**, 2485 (1967); R. Bodalski and A. R. Katritzky, *Tetrahedron Lett.*, 257 (1968).

(5) R. F. C. Brown, V. M. Clark, and A. Todd, *J. Chem. Soc.*, 2105 (1959).

(6) Compare M. Lamchen, *J. Chem. Soc.*, 2300 (1966).

must involve hydration of the nitrone function to give XI followed by a conventional α-hydroxy–carbonyl rearrangement (XI, see arrows) and subsequent dehydration of the intermediate α-carbinolhydroxylamine.

Experimental Section

General.—All melting points were taken on a Kofler block and are uncorrected. Infrared spectra were measured on a Perkin-Elmer 137 Infracord spectrometer and ultraviolet spectra on a Cary Model II spectrometer. Nmr spectra were taken in $CDCl_3$ on a Varian A-60 spectrometer. Microanalyses were done by Dr. A. Bernhardt, Max Planck Institute, Mülheim (Ruhr), Germany.

Acetylation of 2,4,4-Trimethyl-1-pyrroline 1-Oxide (I, R = Me).—The nitrone (I, R = Me,[1] 5.0 g) in carbon tetrachloride (120 ml) was treated with ice-cold acetic anhydride (18.8 ml) added dropwise with stirring at −20° and held at this temperature for 5 hr. The solution was then left at room temperature for 16 hr, poured into ice–water, and extracted with methylene dichloride. After it was washed with aqueous sodium hydrogen carbonate solution and with water the solvent was removed *in vacuo* to furnish a viscous red oil. This was chromatographed in methylene dichloride over Florisil to give a pale yellow oil which crystallized on trituration with ether–hexane. Recrystallization from hexane afforded acetate III (3.0 g): mp 49°; ν_{max}^{Nujol} 1745, 1675, and 1640 cm^{-1}; τ 8.95 (3 H), 8.89 (3 H), 7.89 (3 H), 7.82 (3 H), 6.61 and 6.46 (2 H, J = 10 cps), 5.21 (1 H), 4.80 (1 H), and 4.02 1 (H).

Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.74; H, 8.32; N, 6.61.

Acetate III (800 mg) in benzene (150 ml) was hydrogenated over 5% palladized charcoal (800 mg) for 5.5 hr (1-mol uptake). The resultant suspension was filtered through "Hyflo Supercel" and the benzene removed *in vacuo*. The resultant oily product was chromatographed in benzene over Florisil to give a trace of starting material and then dihydroacetate IV as an oil: $\nu_{max}^{thin\ film}$ 1745 and 1640 cm^{-1}; τ 8.96 (6 H), 8.83 and 8.71 (3 H, J = 7 cps), 7.95 (3 H), 7.87 (3 H), 6.69 (2 H), 5.69 (1 H), and 4.97 (1 H).

Acid-Catalyzed Hydrolysis of Acetate III.—Acetate III (1.33 g) in glacial acetic acid (20 ml) and water (2 ml) was treated with concentrated hydrochloric acid (3 drops) at 0° for 45 min. The solution was poured into water and extracted with methylene dichloride. The organic phase was washed with aqueous sodium hydrogen carbonate and with water and the solvent removed *in vacuo* to furnish ketoamide V (730 mg). The aqueous phases were combined; excess sodium hydrogen carbonate and sodium borate were added; the mixture was extracted with methylene dichloride to furnish additional ketoamide V (202 mg). Ketoamide V was an oil: $\nu_{max}^{thin\ layer}$ 3400, 1750, 1725, and 1665 cm^{-1}, τ 8.99 (6 H), 8.01 (3 H), 7.80 (6 H), 6.80 (2 H).

Ketoamide V was characterized as the 2,4-dinitrophenylhydrazone. Recrystallized from ethanol, this had mp 113–115°; ν_{max}^{Nujol} 3340, 3150, 1740, 1640, 1625, 1590, and 1515 cm^{-1}.

Anal. Calcd for $C_{17}H_{23}N_5O_7$: C, 49.87; H, 5.66; N, 17.11; mol wt, 409.4. Found: C, 49.88; H, 5.52; N, 17.06; mol wt (Rast), 381.

Treatment of acetate III with acidified 2,4-dinitrophenylhydrazine in the usual way gave the same 2,4-dinitrophenylhydrazone.

Selenium Dioxide Oxidation of 2,4,4-Trimethyl-1-pyrroline 1-Oxide (I, R = Me).—The pyrroline 1-oxide (1.0 g) in ether (30 ml) was treated with selenium dioxide (970 mg) at room temperature for 20 min. The suspended selenium was removed by filtration through a small pad of Florisil and the solvent removed *in vacuo*. Chromatography in methylene dichloride over Florisil gave, as minor product, rearranged nitrone X (identical in all respects with a specimen prepared by the standard method[6]). Further elution afforded as the major product (715 mg) the aldehyde (I, R = CHO, 715 mg), which was an oil: $\nu_{max}^{thin\ film}$ 1665 and 1545 cm^{-1}; τ 8.70 (6 H), 7.30 (2 H), 6.09 (2 H), and −0.07 (1 H). The aldehyde readily afforded a dimedone derivative in aqueous methanol at room temperature. Recrystallized from aqueous methanol this had mp 175–180°.

Anal. Calcd for $C_{23}H_{33}O_5N$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.39; H, 8.37; N, 3.34.

When aldehyde I (R = CHO) in methanol was treated with acidic 2,4-dinitrophenylhydrazine solution in the usual manner it afforded the 2,4-dinitrophenylhydrazone of keto nitrone X.

Oxidation of Aldehyde I (R = CHO) with Silver Oxide (with Dr. D. R. Brittain).—Aldehyde I (R = CHO) [prepared from nitrone I (R = Me, 1.7 g)], suspended in water (20 ml), was treated with stirring with silver oxide [prepared from silver nitrate (4.64 g) and sodium hydroxide (2.18 g)] at room temperature for 2 hr. The mixture was extracted with chloroform. The pH of the aqueous phase was then adjusted to 1.0 and extraction with chloroform was repeated. This second chloroform extract was evaporated *in vacuo* and the residue crystallized from ether–*n*-hexane to give carboxylic acid I (R = CO_2H, 700 mg): mp 80–92°; λ_{max}^{MeOH} 266 mμ (ϵ 6700); ν_{max}^{KBr} 1520 cm^{-1}

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.50; H, 7.20; N, 9.64.

Registry No.—I (R = Me), 6931-11-9; I (R = CHO) dimedone derivative, 19689-70-4; I (R = CO_2H), 19713-63-4; III, 19689-71-5; IV, 19689-72-6; V, 19689-73-7; V (2,4-dinitrophenylhydrazone), 19689-74-8.

2,2-Dichlorocyclopropyl Acetates as Intermediates for the Preparation of Pyrazoles and Pyrimidines

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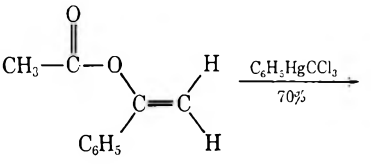
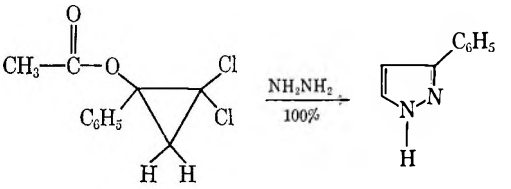
Received November 20, 1968

The reaction of *gem*-dihalocyclopropyl acetates with hydrazine and substituted hydrazines provides a new synthetic route to pyrazoles.[3] In order to define further the scope of this synthesis, reactions of compounds of type 2 with a variety of nucleophiles have been examined; the results of this study constitute the subject of this report.

α-Acetoxystyrene (1) was treated with excess phenyl(trichloromethyl)mercury and 2,2-dichloro-1-phenylcyclopropyl acetate (2) was obtained in 70% yield. The cyclopropyl acetate (2) was shown to undergo facile ring opening with 4.5 equiv of 95% hydrazine in hot ethanol, and gave an essentially quantitative yield of 3-phenylpyrazole (3).



1



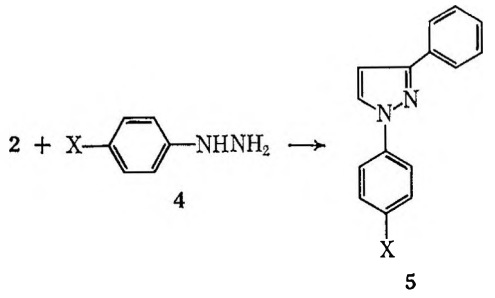
2 3

(1) Supported by the National Science Foundation Grant GP-6169X.

(2) Taken in part from the Ph.D. Thesis of J. F. Dooley, University of Minnesota, 1967.

(3) (a) W. E. Parham and J. F. Dooley, *J. Amer. Chem. Soc.*, **89**, 985 (1967); (b) W. E. Parham and J. F. Dooley, *J. Org. Chem.*, **33**, 1476 (1968).

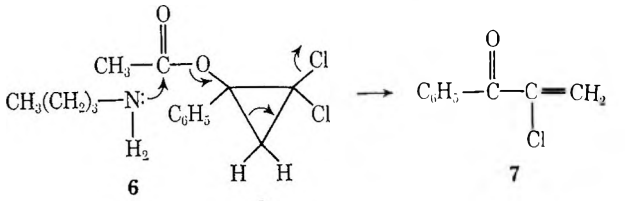
Reaction of 2 with excess phenylhydrazine in hot ethanol for 13.5 hr gave 1,3-diphenylpyrazole (**5a**) in 35% yield. However, attempts to extend this reaction to include *p*-bromo- or *p*-nitrophenylhydrazine were unsuccessful; no reaction occurred under conditions essentially identical with those used with phenylhydrazine.



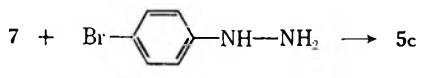
4 5

a, X = H
b, X = NO_2
c, X = Br

The inability of **4b** or **4c** to react with ester 2 suggested that the substituent had lowered the nucleophilicity of the substituted phenylhydrazine to the point that ester aminolysis was unable to occur under the conditions employed. In order to test this assumption, the reaction of 2 with 1.5 equiv of *p*-bromophenylhydrazine was carried out as before, but in the presence of excess *n*-butylamine. *n*-Butylamine is known to react[4,5] readily with esters, and it was anticipated that aminolysis of 2 by the more nucleophilic amine would give the α,β-unsaturated chloro ketone (**7**), which would in turn react irreversibly with the weakly nucleophilic hydrazine in the system to give the pyrazole. Under these conditions the pure pyrazole **5c** was obtained in 27% yield; somewhat improved yields of **5c** were obtained (38%) when only a slight excess of *n*-butylamine was employed. In this case potassium acetate was used to neutralize the hydrogen chloride formed in the reaction.

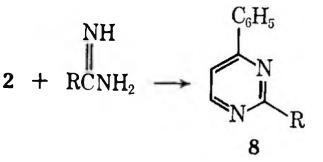


6 2 7



4c

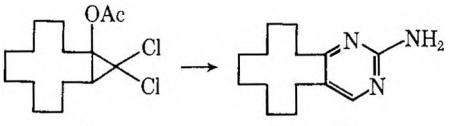
Cyclopropane 2 did not react with excess urea or thiourea in hot ethanol;[6] however, condensation of 2 with an excess of the more basic guanidine gave 2-amino-4-phenylpyrimidine (**8a**) in 63% yield. The reaction of cyclopropane 2 with benzamidine afforded



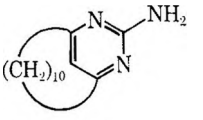
8

a, R = NH_2
b, R = C_6H_5

2,4-diphenylpyrimidine (**8b**), isolated in 64% yield. Attempts to extend this pyrimidine synthesis to methacyclophane **10b** were unsuccessful. Reaction of **9** with excess guanidine gave a viscous mixture which was purified by chromatography. 2-Amino-4,5-cyclododecapyrimidine (**10a**) was isolated in 12% yield as the only identifiable product. Reaction of **9** with hydrazine under similar conditions is known to give the corresponding 1,3-bridged pyrazole in >49% yield together with some of the 3,4-bridged pyrazole, and the duality of mechanism leading to these products has been discussed.[3] The structure of **10a** was established by its independent synthesis (see Experimental Section).

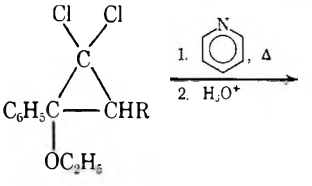


9 10a

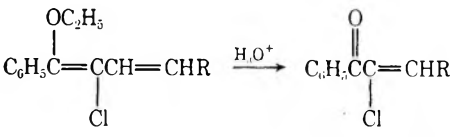


10b

α-Chloro ketones of type **7**, which are intermediates[3] in the synthesis of heterocycles from dichlocyclopropyl acetates, are also readily available from 2,2-dihalocyclopropyl ethers.[7] The preparation of chloro ketones **13a** and **13b**, and the conversion of **13a** into 3-phenyl-5-



11a, R = CH_3
b, R = C_4H_9



12a, R = H
b, R = C_3H_7

13a, R = CH_3
b, R = C_4H_9

methylpyrazole (74% yield) are described in the Experimental Section. Attempts to dehydrohalogenate **12b** to the corresponding triene with potassium *t*-butoxide, by a process analogous to that described for the prepara-

(4) W. H. Watanabe and L. R. De Donso, *J. Amer. Chem. Soc.*, **78**, 4542 (1956).

(5) P. A. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1965, p 29.

(6) These reagents are known to form pyrimidines with a variety of unsaturated carbonyl compounds or their analogs; *cf* D. J. Brown, "The Pyrimidines," John Wiley & Sons, Inc., New York, N. Y., 1962, Chapters II and III; C. H. Covallito, C. M. Matine, and F. C. Nachod, *J. Amer. Chem. Soc.*, **73**, 2544 (1951).

(7) W. E. Parham, R. W. Soeder, J. R. Throckmorton, K. Kuncl, and R. M. Dodson, *J. Amer. Chem. Soc.*, **87**, 321 (1965); W. E. Parham and R. J. Sperley, *J. Org. Chem.*, **32**, 926 (1967); L. Skattebøl, *ibid.*, **31**, 1454 (1966).

tion of ethoxy cyclohexatriene,[7] led to an unstable product which was not characterized.

Experimental Section

2,2-Dichloro-1-phenylcyclopropyl Acetate (2).—A solution of α-acetoxystyrene (1, 16.2 g, 0.10 mol) and phenyl(trichloromethyl)mercury[8] (51.5 g, 0.13 mol) in benzene was heated for 52 hr. The mixture was processed in the usual way,[3] and the product was distilled to give 17.1 g (70%) of **2**: bp 93° (0.01 mm); $n^{25}D$ 1.5310; ir 1760 cm^{-1} (C=O); nmr (CCl_4) τ 8.10 (s, 3, $OCOCH_3$), 7.90 (q, 2, J = 9 Hz, CH_2), and 2.70 (m, 5, C_6H_5). The acetate was crystallized from petroleum ether (bp 60–68°) and melted at 45–46.5°.

Anal. Calcd for $C_{11}H_{10}Cl_2O_2$: C, 53.90; H, 4.12; Cl, 28.93: Found: 53.55; H. 4.02; Cl, 28.70.

1. Reaction of 2 with Hydrazine.—A solution of hydrazine (95%, 1.52 g, 0.045 mol) in ethanol (5 ml) was added dropwise with cooling to a solution of 2,2-dichloro-1-phenylcyclopropyl acetate (**2**, 2.46 g, 0.010 mol) in ethanol (10 ml) and the resulting mixture was heated at the reflux temperature for 12 hr. A solution of sodium hydroxide (1.40 g, 0.040 mol) in water (10 ml) was added and the resulting mixture was heated at the reflux temperature for 1 additional hr. The solution was poured into water (50 ml) and extracted with three 30-ml portions of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated on a rotary evaporator to give a yellow oil (1.55 g, $n^{25}D$ 1.6075). The oil was triturated with carbon tetrachloride (5 ml) and stored in the cold overnight. Filtration of the mixture gave 1.43 g (100%) of 3-phenylprazole (**3**): mp and mmp 77–78° (lit.[9] mp 78°); nmr (CCl_4) τ 3.69 (d, 1, J = 2.2 Hz, CH—CN), 2.70 (d, 1, J = 2.2 Hz, C=CHN), 2.43–2.99 (m, 5, C_6H_5), and −3.17 (1, NH).

2. With Phenylhydrazine.—The oil obtained subsequent to heating (13 hr at reflux) a solution of **2** (5.8 g, 0.024 mol), phenyl hydrazine (9.8 g, 0.10 mol), and 30 ml of absolute ethanol was chromatographed over silica gel (60 g); elution with petroleum ether (bp 60–68°) afforded the crude product. Crystallization of this material from absolute ethanol afforded 1.9 g (35%) of the pale yellow, crystalline 1,3-diphenylpyrazole (**5a**): mp 85.5–87° (lit.[10] mp 84–85°); nmr (CCl_4) τ 6.51 (d, 1, J = 2 Hz (CH=CHN), 2.08–3.15 (m, 11, C_6H_5 and CH=CHN).

3. With *p*-Nitrophenylhydrazine.—The reaction of *p*-nitrophenylhydrazine (2.82 g, 0.0184 mol) with **2** (1.00 g, 0.0041 mol) in ethanol (70 ml) was carried out as described in **1**. After the solution had been heated at the reflux temperature for 16 hr, a reference compound (*m*-chlorobenzoic acid, 1.00 g) was added, and the homogeneous solution was subjected to glpc (20% silicone oil DC 710 on Chromosorb W, 150°, He, 50 ml/min). The presence of 1.00 g of starting ester (**2**) was demonstrated.

4. With *p*-Bromophenylhydrazine.—The results were essentially identical with those described with *p*-nitrophenylhydrazine.

5a. With *p*-Bromophenylhydrazine and *n*-Butylamine.—A solution of **2** (5.00 g, 0.021 mol), *p*-bromophenylhydrazine (5.27 g, 0.027 mol), and *n*-butylamine (6.14 g, 0.084 mol) was heated at the reflux temperature for 15 hr. A solution of sodium hydroxide (3.68 g, 0.092 mol) in water (50 ml) was added and the mixture was heated at the reflux temperature for an additional 0.5 hr. The cherry red reaction mixture was poured into water (100 ml) and extracted with three 100-ml portions of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated on a rotary evaporator to give 10.0 g of a red oil. Crystallization of the oil from ethanol afforded 1.88 g (30%) of the crude 1-(*p*-bromophenyl)-3-phenylpyrazole, mp 129–132°. Recrystallization of this material afforded 1.72 g (27%) of pure **5c**: mp and mmp 139–140° (lit.[11] mp 137–138°); nmr ($CDCl_3$) τ 3.31 (d, 1, J = 2.5 Hz, CH=CHN), 2.21 (d, 1, J = 2.5 Hz, CH=CHN), 2.47 (m, 5, C_6H_5), and 2.38 (m, 4, BrC_6H_4).

5b. With *p*-Bromophenylhydrazine and *n*-Butylamine.—A solution of potassium acetate (1.5 g, 0.015 mol), *p*-bromophenylhydrazine (1.25 g, 0.0056 mol), and **2** (1.0 g, 0.0041 mol) in ethanol (15 ml) was heated at the reflux temperature for 50 min. To the solution was added dropwise a solution of *n*-butylamine (0.35 g, 0.0049 mol) and ethanol (4 ml) and the resulting solution was heated at the reflux temperature for 16 hr. The mixture was processed essentially as described above and gave 423 mg (35%) of the pale yellow, crystalline pyrazole, mp and mmp 139–140°. Chromatography of the residue on silica gel using benzene as the eluent afforded an additional 35 mg (3%) of **5c**, mp 139–140°.

6. Reaction of 2 with Guanidine.—A solution of sodium hydroxide (3.68 g, 0.092 mol) in water (10 ml) was added to a solution of guanidine hydrochloride (8.78 g, 0.092 mol) in water (10 ml). One drop of phenophthalein solution was added and the mixture stirred until the red color disappeared (*ca.* 10 min). Ethanol (70 ml) and a solution of **2** (5.00 g, 0.021 mol) in ethanol (10 ml) were added. The solution was heated at the reflux temperature for 2 hr, a solution of sodium hydroxide (3.68 g, 0.092 mol) in water (50 ml) was added, and the reaction mixture was heated at the reflux temperature for 0.5 hr. The mixture was cooled, poured into water (200 ml), and extracted with five 50-ml portions of ether. The combined ether extracts were washed once with a saturated sodium chloride solution (100 ml), dried ($MgSO_4$), and the solution was concentrated on a rotary evaporator to give 2.25 g (63%) of the yellow, crystalline 2-amino-4-phenylpyrimidine (**8a**), mp 164–165° (lit.[12] mp 165°, 164°). Vacuum sublimation of the product afforded the white, crystalline product: mp and mmp 165–166.5°; nmr ($DCCl_3$) τ 4.69 (2, NH_2), 0.03 (d, 1, J = 5.3 Hz, NCH=), 2.68 (d, 1, J = 5.3 Hz, HC=CHN), and 2.31 (m, 5, C_6H_5).

7. Reaction of 2 with Benzamidine.—To a solution of sodium ethoxide prepared from 0.480 g (0.0208 g-atom) of sodium and absolute ethanol (25 ml) was added 4.74 g (0.027 mol) of benzamidine hydrochloride hydrate. The solution was heated at the reflux temperature for 0.5 hr, cooled, and the excess benzamidine hydrochloride was removed by filtration. To the filtrate was added 1.10 g (0.0045 mol) of 2,2-dichloro-1-phenylcyclopropyl acetate in absolute ethanol (10 ml). The resulting solution was heated at the reflux temperature for 44 hr, poured into water (100 ml), and extracted with two 100-ml portions of ether. The combined ether extracts were dried (calcium chloride), filtered, and the solvent removed *in vacuo*. Crystallization of the residue from absolute ethanol afforded 0.693 g (64%) of the crude 2,4-diphenylpyrimidine, mp 68–71.5°. Recrystallization of this material afforded 0.470 g (43.5%) of 2,4-diphenylpyrimidine (**8b**), mp 71–73° (lit.[13] mp 71–72°).

2-Amino-4,5-cyclododecapyrimidine (10).—Chromatography of the product obtained by reaction of **9** with guanidine on neutral alumina (see section 6) gave 2-amino-4,5-cyclododecapyrimidine (**11**, 320 mg, 12% yield) as a yellow oil. Crystallization of this product from petroleum ether gave 312 mg of **11**: mp and mmp 198–200°; nmr (CCl_4) τ 8.59 (m, 16, CH_2), 7.40 (m, 4, CH_2C=C) 2.68 (s, 1, C=CH), 1.95 (2, NH_2); ir (Nujol) 3280 and 3110 (NH), 1660 cm^{-1} (C=N).

Anal. Calcd for $C_{14}H_{23}N_3$: C, 72.04; H, 9.95. Found: C, 72.28; H, 10.05.

2-Amino-4,5-cyclododecapyrimidine (10a) from 2-Hydroxymethylenecyclododecanone (12).—To a solution of 2-hydroxymethylenecyclododecanone[14] (**12**, 11.6 g, 0.055 mol) was added dropwise to a guanidine solution [0.01 mol in water (20 ml)] prepared as described above. After the addition was completed the solution was heated at the reflux temperature for 15 hr, cooled, and extracted with three 100-ml portions of ether. The combined ether extracts were dried ($MgSO_4$) and the solvent was removed *in vacuo*. Crystallization of the residue from chloroform–petroleum ether (bp 60–68°) afforded 0.60 g (5%) of the crystalline product **11**, mp 200°.

2,2-Dichloro-1-ethoxy-3-methyl-2-phenylcyclopropane (11a).—The reaction of 1-ethoxy-1-phenyl-1-propene (50 g, 0.308 mol) with sodium methoxide (21.6 g, 0.40 mol) and ethyl trichloroacetate (66.2 g, 0.346 mol) was carried out for 6 hr at 0°. The mixture was processed in the usual way,[7,15] and the residue was distilled, taking care to keep the temperature of the distillation flask below 100°, to give 39.2 g (69%) of **11a**: bp 62–67° (0.01–0.03 mm); $n^{25}D$ 1.5265; nmr (CCl_4) τ 2.67 (s, 5, C_6H_5),

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6.66 (m, 2, OCH_2CH_3), 8.10 (q, 1, J = 6 Hz, $CHCH_3$), 8.62 (d, 3, J = 6 Hz, $CHCH_3$), and 9.01 (t, 3, J = 7.0 Hz, OCH_2CH_3).

Anal. Calcd for $C_{12}H_{14}Cl_2O$: C, 58.79; H, 5.76. Found: C, 58.79; H, 5.40.

α-Chlorocrotonophenone (13a).—A mixture of 11a (44.8 g, 0.183 mol) and pyridine (1 mol) was heated at 110–120° for 2.5 hr. The cooled mixture was poured into cold water, extracted with petroleum ether (bp 30–60°), and the combined petroleum ether extracts were washed with 1.8% hydochloric acid (*ca.* 800 ml) and water. The extract was dried and concentrated to afford an oil (39.0 g) containing 2-chloro-1-ethoxy-1-phenyl-1,3-butadiene (12a). The oil was dissolved in a solution of acetone (340 ml), water (17 ml), and hydrochloric acid (17 ml) and heated at the reflux temperature for 2.5 hr. Water was added to the cooled mixture and the solution was extracted with petroleum ether. The combined extracts were washed with water, aqueous bicarbonate solution, and dried ($MgSO_4$). The petroleum ether was removed *in vacuo* and the resulting solid was crystallized from petroleum ether to give 19.4 g (60%) of **13a**: mp 70.5–71°; nmr (CCl_4) τ 2.20–2.85 (m, 5, C_6H_5), 3.36 (q, 1, J = 7 Hz, $C{=}CHCH_3$), 8.02 (d, 3, J = 7 Hz, $CHCH_3$); uv max (95% C_2H_5OH) 250 mμ (ε 12,000); ir 1660 and 1620 cm^{-1} (COC=C).

Anal. Calcd for $C_{10}H_9ClO$: C, 66.49; H, 5.02; Cl, 19.63. Found: C, 66.19; H, 5.34; Cl, 19.68.

The 2,4-dinitrophenylhydrazone of 13a was prepared in a solution of methanol and hydrochloric acid and was recrystallized from chloroform–menthanol and ethanol–ethyl acetate to give the pure product (45%): mp 198–200°; uv max (95% C_2H_5OH) 375 mμ (ε 31,000).

Anal. Calcd for $C_{16}H_{13}ClN_4O_4$: C, 53.27; H, 3.63; N, 15.53; Cl, 9.83; Found: C, 53.33; H, 3.41; N, 15.57; Cl, 9.88.

5-Methyl-3-phenylpyrazole.—Reaction of **13a** with hydrazine in ethanol (95%) was exothermic at room temperature and afforded the pyrazole in 74% yield, mp 127–128° [from petroleum ether C, bp 100–105° (lit.[16] mp 127–128°]; the picrate had mp 159° (lit.[16] mp 159°).

1,1-Diethoxy-1-phenylhexane.—The reaction of caprophenone (75 g, 0.43 mol, from caproic anhydride) with ethyl orthoformate in absolute ethanol (58 ml) was carried out[17] with hydrogen bromide and afforded the ketal in 90–95% yields: bp 79–81.5° (0.60–0.65 mm); $n^{25}D$ 1.4750.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.99; H, 10.59. Found: C, 76.75; H, 10.47.

1-Ethoxy-1-phenyl-1-hexene.—A solution of 1,1-diethoxy-1-phenylhexane (30 g, 0.12 mol) and *p*-toluenesulfonic acid (0.08 g) was heated with stirring at the reflux temperature for 1.5 hr allowing ethanol to distil. Distillation of the residue afforded the vinyl ether in >90% yield: bp 75–76° (0.45–0.50 mm); $n^{25}D$ 1.5085; ir (neat) 1645 cm^{-1} (C=C).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.57; H, 10.05.

3-*n*-Butyl-2,2-dichloro-1-ethoxy-1-phenylcyclopropane (11b).—The method was essentially that described for the preparation of 11a; however, the crude product could not be purified by distillation since it was thermally unstable. Chromatography of the crude product on silica gel (100–200 mesh) and elution with petroleum ether–benzene (3:1) afforded the nearly pure product. Short-path distillation of a small sample of this material at a bath temperature of 62° (0.002 mm) gave the analytically pure product, $n^{28.5}D$ 1.5090.

Anal. Calcd for $C_{15}H_{20}Cl_2O$: C, 62.72; H, 7.02. Found: C, 62.63; H, 7.07.

2-Chloro-1-ethoxy-1-phenyl-1,3-heptadiene (12b).—The reaction of 11b (6.00 g, 0.021 mol) with pyridine was carried out essentially as that described for the reaction with 11a. The crude product was distilled to give 3.27 g (62.5%) of **12b**: bp 92–94° (0.03–0.04 mm); $n^{25}D$ 1.5566; nmr (CCl_4) τ 2.66 (s, 5, C_6H_5), 3.98 (m, 2, CH=CH), 6.38 (q, 2, J = 7 Hz, OCH_2CH_3), 7.98 (m, 2, $C{=}CH_2$), 8.86 (m, 8, CH_3CH_2 and OCH_2CH_3); uv max (95% C_2H_5OH) 285 mμ (ε 13,000).

Anal. Calcd for $C_{15}H_{19}ClO$: C, 71.84; H, 7.64. Found: C, 71.57; H, 7.87.

The over-all yield of heptadiene **12b** from 1-ethoxy-1-phenyl-1-hexene, without purification (chromatography) of the intermediate cyclopropane **11b**, was 36%. The diene slowly turned into a glass upon standing.

2-Chloro-1-phenyl-2-hepten-1-one (13b).—The hydrolysis of **12b** was effected as described for **12a**. The crude yellow product was distilled to give **13b** in 82% yield: bp 74–83° (0.005 mm); $n^{24}D$ 1.5424; nmr (CCl_4) τ 2.46 (m, 5, C_6H_5), 3.46 (t, 1 $C{=}CHCH_2$ 7.57 (m, 2, $C{=}CCH_2$), 8.58 (m, 4, CH_2), and 9.07 (m, 3, CH_3); ir (neat 1670 and 1615 cm^{-1} (COC=C); uv max (95% C_2H_5OH) 251 mμ (ε 13,000).

Anal. Calcd for $C_{13}H_{15}ClO$: C, 70.11; H, 6.79. Found: C, 69.91; H, 6.82.

The 2,4-dinitrophenylhydrazone of 13b was prepared from the diene and from the ketone in ethanolic hydrogen chloride. Crystallization of the crude product from ethyl acetate afforded the analytically pure hydrazone: mp 163–165°; uv max (95% C_2H_5OH) 374 mμ (ε 28,900).

Anal. Calcd for $C_{19}H_{19}ClN_4O_4$: C, 56.65; H, 4.75; N, 13,91; Cl, 8.80. Found: C, 56.25; H, 4.75; N, 13.98; Cl, 8.95.

Registry No.—**2**, 19689-75-9; **10a**, 19689-76-0; **11a**, 19689-77-1; **11b**, 19713-64-5; **12b**, 19713-65-6; **13a**, 19689-78-2; **13a** (2,4-dinitrophenylhydrazone), 19689-79-3; **13b**, 19689-82-8; **13b** (2,4-dinitrophenylhydrazone), 19689-83-9; 1,1-diethoxy-1-phenylhexane, 19689-80-6; 1-ethoxy-1-phenyl-1-hexene, 19689-81-7.

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The Synthesis of 2-Azetidinones[1a]

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In continuing our search for small-ring heterocycles having biological activity,[2,3] we have synthesized a few *cis*-3-azido-4-aryl-2-azetidinones (I). This Note describes their synthesis and reaction with lithium aluminum hydride. The formation of 2-azidoacetyl-2,4,5-triphenyl-2-imidazoline under modified conditions is also described.

N-Substituted 2-azetidinones have been synthesized by the cycloaddition of azidoacetyl chloride to Schiff bases[4] to yield both *cis* and *trans* isomers, the ratio being dependent on the order of addition of reactants. There is, however, no general method available for the preparation of N-unsubstituted 2-azetidinones. Lack of N substitution has been reported to be a structural requirement[5] for reduction of 2-azetidinones to azetidines which were our ultimate goal. The synthesis of N-unsubstituted 2-azetidinones (I) was achieved by the cycloaddition of acidoacetyl chloride (II) to the corresponding α,α-dibenzylideniminotoluene (hydrobenzamide) (III) in the presence of triethylamine followed by hydrolysis.

(1) (a) From the Ph.D. Thesis of R. E. Lee. (b) To whom all correspondence should be addressed.

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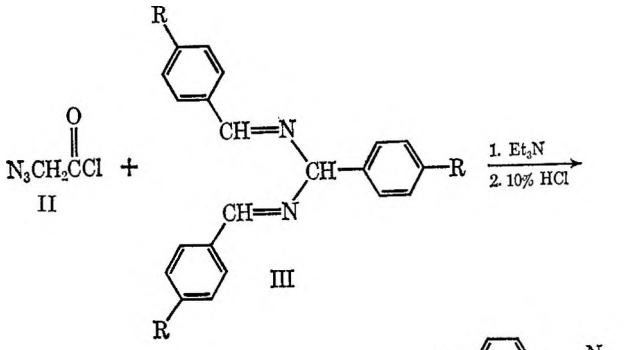
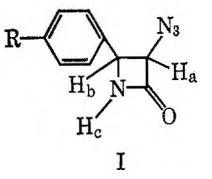


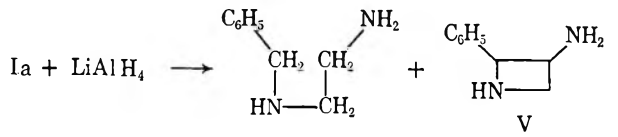


I

a, R = -H
b, R = -OCH3
c, R = -CH3

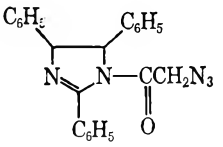
The nmr spectrum of Ia exhibited a five-proton aromatic singlet (H_{Ar}) at δ 7.36, a broad, one-proton signal (H_c) at 6.92 which is exchangeable with deuterium oxide, and a two-proton multiplet from 4.7 to 5.1 (H_a, H_b). This latter multiplet resolved (upon exchange with deuterium oxide) into two doublets at δ 4.94 (H_b) and 4.86 (H_a) (J_{ab} = 5 Hz). This value of J_{ab} is consistent with *cis* vicinal coupling in the 2-azetidinones.[6] Compounds Ib and Ic also exhibited characteristic nmr spectrum.

Compound Ia yielded a two-component mixture upon reaction with lithium aluminum hydride. The mixture was composed of N-benzylethylenediamine (IV) which was isolated by fractional crystallization of the hydrochloride salts and a second component which is assigned the 3-amino-2-phenylazetidine structure (V) on the basis of nmr data. The nmr after subtraction of the spectrum of N-benzylethylenediamine showed an aromatic signal between δ 7.0 and 7.5, a one-proton multiplet centered at 4.93, a two-proton multiplet between 3.7 and 4.15, a one-proton quartet centered at 3.13, and a three-proton singlet at 1.38 which is exchangeable with D_2O.



IV V

If, instead of adding the acid chloride to a methylene chloride solution of the hydrobenzamide and triethylamine, the triethylamine was added to a mixture of the acid chloride and hydrobenzamide, a compound identified as an imidazoline derivative was isolated. The mass spectrum (mol wt 381) and elemental analysis indicated the molecular formula $C_{23}H_{19}N_5O$. The imidazoline structure would result from intramolecular reaction of the intermediate formed by reaction of the acid chloride with hydrobenzamide. Spectral data are consistent with the structure postulated. The infrared spectrum (KBr) showed strong azide absorption at 2095 cm^{-1} and a strong carbonyl band at 1655 cm^{-1}. The infrared also showed aromatic absorption in the 2000–1660-cm^{-1} region and bands at 758 and 697 cm^{-1} characteristic of a monosubstituted phenyl ring. The nmr spectrum showed broad one-proton singlets at δ 3.33 and 3.42 (methylene), a fifteen-proton aromatic multiplet between δ 7.7 and 7.9, and a two-proton doublet of doublets at δ 6.1 and 7.2 (methine). On the basis of this information we postulate the compound to be 1-azidoacetyl-2.4.5-triphenyl-2-imidazoline (VI). Lactam carbonyl absorption was absent in an ir spectrum of the methylene chloride fraction, indicating that cycloaddition to the azetidinone did not occur in this reaction.



VI

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Experimental Section[7]

cis-**3-Azido-4-phenyl-2-azetidinone** (**Ia**).—A solution of 2.4 g (0.02 mol) of II in 75 ml of methylene chloride was added dropwise over 40 min to a stirred solution of 6.0 g (0.02 mol) of III and 2.0 g (0.02 mol) of triethylamine cooled between 0 and 5°. After the addition was complete, the reaction mixture was allowed to warm to room temperature. Acid (100 ml of 10% HCl) was added to the reaction mixture. The resulting precipitate was removed by filtration to yield 3.27 g of a beige solid, mp 152–157°. Recrystallization from methanol and water yielded 1.31 g (40%) of pure white Ia: mp 90–91.5°; ir (KBr) 1742 (lactam C–O) and 2110 cm^{-1} (N_3).

Anal. Calcd for $C_9H_8N_4O$: C, 57.44; H, 4.29. Found: C, 57.67; H, 4.27.

cis-**3-Azido-4-(*p*-methoxyphenyl)-2-azetidinone** (**Ib**) was prepared from IIIb according to the procedure described for the preparation of Ia. The reaction gave a 44% yield of pure Ib: mp 131–132.5° (MeOH and HOH); nmr ($CDCl_3$) δ 7.08 (d of d, 5, Ar, –NH), 4.85 (m, 2, –CHCH–), and 3.79 (s, 3, $-OCH_3$); ir (KBr) 1750 (C=O) and 2125 cm^{-1} (N_3).

Anal. Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04: H, 4.62. Found: C, 54.86; H, 4.60.

cis-**3-Azido-4-(*p*-methylphenyl)-2-azetidinone** (**Ic**) was prepared from IIIc according to the procedure described for the preparation of Ia. The reaction gave 36% yield of pure Ic: 102–103.5°; ir (KBr) 1750 (C=O) and 2090 cm^{-1} (N_3); nmr ($CDCl_3$) δ 7.16 (s, 4, Ar), 6.75 (broad, 1, –NH), 4.85 (m, 2, –CHCH–), and 2.32 (s, 3, $Ar-CH_3$).

Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98. Found: C, 59.27; H, 5.13.

Lithium Aluminum Hydride Reduction of 2-Azido-4-phenyl-2-azetidinone (**Ia**).—3-Azido-4-phenyl-2-acetidinone (0.76 g, 0.004 mol) was added in small portions through Gooche tubing to a suspension of lithium aluminum hydride (0.92 g, 0.024 mol) in 100 ml of anhydrous ether cooled to 0°. After the addition the reaction mixture was refluxed for 6 hr, then cooled to 0°. Water (1.75 ml, 0.096 mol) was added dropwise from a 2-ml syringe. The mixture was stirred for 30 min at room temperature and then the solid was removed by vacuum filtration. The filtrate was treated with anhydrous HCl and a white precipitate formed which was removed by filtration: mp 140–230°. This solid was recrystallized from absolute ethanol several times to yield a solid that melted at 250–252°; nmr of free base ($CDCl_3$) δ 7.30 (s, 5, Ar), 3.81 (s, 2, $C_6H_5CH_2$–), 2.76 (broad s, 4, NCH_2CH_2N), and 1.5 (s, 3, –NH–, $-NH_2$) exchangeable with D_2O. This compound

(7) Melting points were determined on a Büchi apparatus with open capillary tubes and are uncorrected. The ultraviolet spectrum was obtained using a Bausch and Lomb Model 505 recording spectrophotometer. Nmr spectra were obtained with a Varian Associates A-60A spectrophotometer in $CDCl_3$ with tetramethylsilane as an internal standard. Combustion analyses were conducted by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer and the mass spectrum with a Hitachi RMU-6A at 75 eV.

was identified as N-benzylethylenediamine (lit.[8] mp of hydrochloride, 253°).

If instead of treating the ether filtrate with anhydrous HCl the ether was evaporated, an oil resulted which was shown to be composed of two compounds by tlc. When the signals of the N-benzylethylenediamine were subtracted from the nmr of the mixture, it was determined that the 3-amino-2-phenylazetidine was obtained and that the mixture was composed of 42% azetidine and 58% ethylenediamine. All efforts to separate these compounds failed.

Attempted Synthesis of *trans*-3-Azido-4-phenyl-2-azetidinone.—Hydrobenzamide (11 g, 0.037 mol) and azidoacetyl chloride (4.4 g, 0.037 mol) were dissolved in 200 ml of methylene chloride and treated dropwise at 0° with triethylamine (3.74 g, 0.037 mol) dissolved in 100 ml of methylene chloride. After the addition was complete the reaction mixture was allowed to warm to room temperature. The reaction mixture was then stirred with 100 ml of 10% HCl. The organic layer was separated from the aqueous phase and evaporated to dryness under reduced pressure to yield a dark oil. A small amount of ether was added to this oil and 1.87 g of solid was collected by filtration. Recrystallization from absolute ethanol yielded a solid, mp 218–219°. The structure of this compound was postulated as 1-azidoacetyl-2,4,5-triphenyl-2-imidazoline (VI).

Anal. Calcd for $C_{23}H_{19}N_5O$: C, 72.42; H, 5.02; N, 18.10. Found: C, 72.69: H, 4.99; N, 18.34.

Registry No.—Ia, 19684-83-4; Ib, 19684-84-5; Ic, 19684-85-6; VI, 19689-63-5.

Acknowledgment.—The authors are indebted to Drs. J. M. Cassady and P. E. Manni for helpful discussions during the course of this work.

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Free Carbonium Ions in the Anodic Oxidations of Alkanecarboxylates, Alkaneboronates, and Alkyl Halides[1]

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A free propyl cation[2] is the postulated intermediate leading to cyclopropane in the deoxideation of *n*-propyl alcohol and in the deamination of *n*-propylamine.[3] Formation of cyclopropane in good amount is a criterion for the free *n*-propyl cation.

Anodic oxidation of *n*-butyrate (the Hofer–Moest or abnormal Kolbe reaction) produces cyclopropane.[4,5] The reaction is best explained with a free *n*-propyl cation (eq 1). The detailed description of the steps leading to the propyl cation is not certain.

$$n\text{-PrCO}_2^- \xrightarrow{-2e^-} CO_2 + n\text{-Pr}^+ \longrightarrow \text{cyclopropane} + H^+ \quad (1)$$

(1) Taken from the Ph.D. Thesis of J. T. K., The Pennsylvania State University, Sept 1968. For a review of anodic oxidation, see A. K. Vijh and B. E. Conway, *Chem. Rev.*, **67**, 623 (1967); J. T. Keating and P. S. Skell in "Carbonium Ions," G. A. Olah and P. von R. Schleyer, Ed., Interscience Publishers, New York, N. Y., in press.

(2) A free carbonium ion is one generated in a state not relaxed with respect to neighbor nucleophiles.

(3) P. S. Skell and I. Starer, *J. Amer. Chem. Soc.*, **81**, 4117 (1959); **82**, 2971 (1960). M. S. Silver, *ibid.*, **82**, 2971 (1960).

(4) R. J. Maxwell, M. S. Thesis (Skell), The Pennsylvania State University, 1963.

(5) W. J. Koehl, *J. Amer. Chem. Soc.*, **86**, 4686 (1964).

Alkaneboronic acids are the Lewis acid counterparts of the Brønsted carboxylic acids and would be expected to undergo anodic oxidation also. We have studied the anodic oxidation of propaneboronate. Cyclopropane is among the products, implicating a free propyl cation. Table I gives the results and compares them with our work on butyrate.

TABLE I
ANODIC OXIDATION OF SODIUM BUTYRATE AND POTASSIUM PROPANEBORONATE AT BRIGHT PLATINUM

	%	
Products	Sodium butyrate[a]	Potassium propaneboronate[b]
Propylene	76	71
Cyclopropane	17	18
Propane	1	1
Hexane	1	2
Ethane	1	2
Ethylene	5	7

[a] The aqueous solution was 1 *M* each in sodium butyrate and sodium hydroxide. [b] The aqueous solution was saturated with potassium propaneboronate (<0.8 *M*) and the pH was adjusted to 11.

The similarity of the products and the product distributions found for propaneboronate and butyrate obtains also in the anodic oxidations of butaneboronate and pentanoate (Table II). This further supports the

TABLE II
ANODIC OXIDATION OF POTASSIUM PENTANOATE AND SODIUM BUTANEBORONATE AT BRIGHT PLATINUM

	%	
Products	Potassium pentanoate[a]	Sodium butaneboronate[b]
1-Butene	56	60
cis-2-Butene	17	20
trans-2-Butene	27	20
n-Butane	Trace	Trace

[a] The aqueous solution was 1 *M* each in potassium pentanoate and potassium hydroxide. [b] This is from the work of A. A. Humffray and L. F. G. Williams, *Chem. Commun.*, 616 (1965). They say only that excess base was used in making up the solution. The results were interpreted in terms of a radical (Kolbe) mechanism.

postulate of a free cation in the alkaneboronate anodic oxidation, linking this reaction with deoxideation, deamination, and the Hofer–Moest reaction.[4,5] Tables I and II also suggest that the formal leaving groups, carbon dioxide and boric acid, have little effect on the behavior of the carbonium ion formed in anodic oxidation at platinum. A possible reason for this is that the radical is the carbonium ion precursor in both cases (eq 2).

$$\begin{array}{l} RCO_2^- \xrightarrow{-e^-} RCO_2\cdot \longrightarrow R\cdot + CO_2 \\ \qquad\qquad\qquad\qquad\quad \Big\downarrow{\scriptstyle -e^-} \\ \qquad\qquad\qquad\qquad\quad R^+ \longrightarrow \text{products} \\ RB(OH)_3^- \longrightarrow RB(OH)_3\cdot \longrightarrow R\cdot + B(OH)_3 \end{array} \quad (2)$$

In contrast to the results found at platinum, at a graphite anode the products and product distributions of the butyrate and propaneboronate anodic oxidations are not identical (Table III). It must be that at graphite the carbonium ion precursor is different in each

TABLE III

ANODIC OXIDATION OF POTASSIUM BUTYRATE AND POTASSIUM PROPANEBORONATE AT PYROLYTIC GRAPHITE

Products	% Potassium butyrate[a]	% Potassium propaneboronate[b]
Propylene	66	39
Cyclopropane	33	33
Ethylene	0	28

[a] The aqueous solution of 1 *M* potassium butyrate is at pH 7. Koehl was the first to obtain this result.[5] We confirm this and have shown also that the form of carbon used (porous carbon rods or either plane of pyrolytic graphite) does not affect the product ratios. [b] This was studied as a saturated aqueous solution of the acid and its potassium salt, 10:1. Some ethylene may be a product of β scission of the propyl cation; some may arise from oxidation of propanol, formed from the propaneboronic acid.[c] Since 28% ethylene is found after only 5-min reaction, ethylene is probably a primary product to the extent of at least 10–20%. Its yield increased with reaction time and with pH, while the cyclopropane to propylene ratio remained about constant. [c] A. G. Davies and B. P. Roberts, *J. Chem. Soc., B*, 17 (1967); T. G. Traylor and J. C. Ware, *J. Amer. Chem. Soc.*, 85, 3026 (1963).

case and makes its influence felt in the reactions of the carbonium ion. In addition, different rates of oxidation and desorption of the precursors on graphite may be responsible for the variation.[6] In any case, both cations exhibit the characteristic of the free cation, substantial production of cyclopropane.

The similarities in the alkaneboronate and alkanecarboxylate oxidations prompted the study of the anodic oxidation of alkyl halides. Propyl bromide was chosen because of the above-mentioned prominent difference between the free and the encumbered propyl cation. The reaction was run in methanol with sodium perchlorate as the electrolyte. The anode and cathode compartments were separated to prevent cathodic reduction of alkyl halide.[7] Table IV shows that the

TABLE IV

ANODIC OXIDATION OF PROPYL BROMIDE AT BRIGHT PLATINUM

Products	Propyl bromide,[a] %
Propylene	16
Cyclopropane	78
Propane	6

[a] The methanolic solution was 1 *M* each in propyl bromide and sodium perchlorate monohydrate. The anode and cathode compartments were separated by an agar bridge saturated with potassium chloride. It was not determined if the propylene would be destroyed by the perchlorate under the electrolysis conditions.

carbonium ion formed in this reaction can indeed be described as free. It is likely that the anodic oxidations of other alkyl halides also yield free carbonium ions.[8] A possible mechanism is shown in eq 3. Rough calcula-

$$\mathrm{PrBr} \xrightarrow{-e^-} (\mathrm{PrBr})^+ \longrightarrow \mathrm{Pr}^+ + \mathrm{Br}\cdot \qquad (3)$$

tions indicate that the separation in the gas phase of bromine atom from the propyl cation is ~30 kcal mol endothermic. This energy requirement could be ameliorated at the anode surface by adsorption and by charge–charge repulsion of $(\mathrm{PrBr})^+$ and the anode.

(6) A referee suggested this possibility.

(7) J. W. Sease, F. G. Burton, and S. L. Nickol, *J. Amer. Chem. Soc.*, **90**, 2595 (1968).

(8) L. L. Miller and A. K. Hoffman, *ibid.*, **89**, 593 (1967).

The anodic oxidation of 1-nitropropane was attempted in methanol with sodium perchlorate electrolyte. No products attributable to propyl cation intermediacy were detected. Barnes[9] has anodically oxidized *n*-propylamine at platinum in acetonitrile and has found propylene among the products. No mention is made of cyclopropane but it may not have been sought. A free propyl cation may be formed. Whatever the details of the Barnes reaction, our work shows that nitropropane is not a carbonium ion producing intermediate in the anodic oxidation of *n*-propylamine.

Experimental Section

Apparatus.—The cell used in the electrolyses has been described.[10] It was modified for the pyrolytic graphite reactions. In place of the platinum, two strips of graphite, $1/2 \times 4 \times 1/8$ in., were fixed in the rubber stopper by means of alligator clips inserted through the stopper. The graphite was purchased from High Temperature Materials, Inc., Boston, Mass. The unit for the anodic oxidation of propyl bromide was two cylinders, closed at the bottom, connected by a tube filled with potassium chloride saturated agar gel. The anode compartment of the unit was fitted with a stopper containing the anode, thermometer, and gas inlet and outlet tubes. A stainless steel cathode was put in the other cylinder.

Technique.—The anodic oxidations were typically run for 5 min at 25–35° at a current density of 0.1 A/cm. The gaseous products were swept into liquid nitrogen cooled traps. The material caught was analyzed by glpc. In addition to being identified by comparative retention times, the peaks were trapped as eluted and their ir and mass spectra were obtained.

Propaneboronic Acid.—This was prepared according to the method of Snyder, Kuck, and Johnson.[11]

Registry No.—Sodium butyrate, 156-54-7; potassium propaneboronate, 19581-69-2; potassium pentanoate, 19455-21-1; sodium butaneboronate, 19581-70-5; potassium butyrate, 589-39-9; propyl bromide, 106-94-5.

Acknowledgment.—We are grateful to the National Science Foundation for a graduate fellowship for J. T. K., and to the Air Force Office of Scientific Research and the Research Office of the U. S. Army for support of this work.

(9) K. K. Barnes, *Dissertation Abstr.*, 3805-B, (1967).

(10) P. H. Reichenbacher, M. Y.-C. Liu, and P. S. Skell, *J. Amer. Chem. Soc.*, **90**, 1816 (1968).

(11) H. R. Snyder, J. A. Kuck, and J. R. Johnson, *ibid.*, **60**, 105 (1938).

The Wolff Rearrangement of 1,3-Bisdiazo-2-decalones

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Our interest in the stereospecific synthesis of functionalized perhydroindans led us to an examination of the rearrangement of *cis*- and *trans*-1,3-bisdiazo-2-decalone with the aim of discovering (a) whether the ring contraction would be directionally selective, (b) whether the product composition would be dependent upon ring junction stereochemistry, and (c) whether the stereochemistry of the ring junction would be

retained. In addition, it was hoped that the results would shed some light on the mechanism of the Wolff rearrangement.

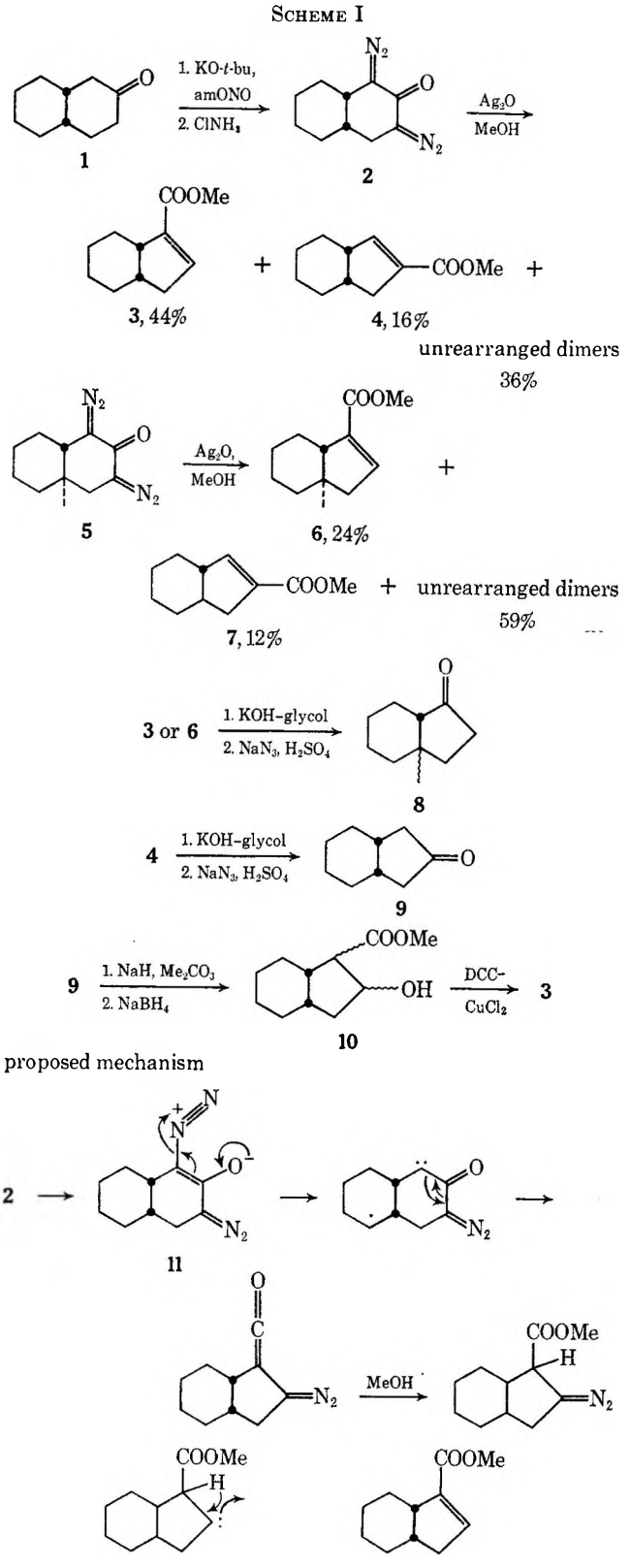
cis- and *trans*-bisdiazodecalones **2** and **5** were prepared by treatment of the ketones with amyl nitrite and potassium *t*-butoxide[1] and reaction of the dioximino ketones formed with chloramine.[2] The bisdiazo ketones, isolated in 25–40% yield, showed characteristic ir absorption at 2084, 2062, and 1580 cm^{-1} and strong ultraviolet absorption at 323 mμ (ε 25,000). Photolysis[3] of **2** in aqueous THF or in absolute methanol led to a complex mixture of at least 12 products. When the rearrangement was carried out by refluxing with silver oxide in absolute methanol, a 73% yield of crude product was obtained. Glpc analysis revealed that 64% of the product was composed of three monomeric compounds, present in yields of 4, 44, and 16%. The two major components were isolated by preparative glpc and proved to be the two unsaturated esters **3** and **4** (Scheme I). The remaining 36% of the product was composed of a mixture of three compounds of long retention time, which spectroscopic and mass spectral analysis indicated were unrearranged *dimeric* methoxydecalones; no effort was made to elucidate the detailed structures of these isomeric dimers.

Unequivocal structural assignment of **3** and **4** was made on the basis of the following data. Ester **3** was saponified with KOH–ethylene glycol and then subjected to Schmidt rearrangement[4] to give an equilibrium mixture (75:25)[5] of *cis*- and *trans*-perhydroindan-1-one **8**; no perhydroindan-2-one was detected. Similar degradation of **4** contaminated with a small amount of **3** afforded *cis*-perhydroindan-2-one **9** as the major product. Because of the equilibrating conditions of the Schmidt rearrangement, the ring-junction stereochemistry of **3** was confirmed by independent synthesis. *cis*-Perhydroindan-2-one[6] was treated with sodium hydride–dimethyl carbonate[7] and the resulting β-keto ester reduced with sodium borohydride to give hydroxy ester **10** in 77% yield. Dehydration with cupric chloride–DCC[8] afforded a 73% yield of an ester identical with **3** by glpc peak enhancement on two columns. Thus the *cis* stereochemistry was preserved in both of the unsaturated esters.

Silver oxide–methanol rearrangement of 1,3-bisdiazo-*trans*-2-decalone **5** led to an 89% yield of crude product in which the unrearranged methoxy ketone dimers predominated (59% of the total product). The monomeric products, obtained in 24 and 12% yields, respectively, were assigned structures **6** and **7** on the following basis. Although the basic spectral features of **6** and **7** were identical with those of **3** and **4** (see Experimental Section), glpc analysis revealed that all four compounds were indeed different. Schmidt degradation of **6** afforded the same mixture of stereoisomeric ketones **8** as that obtained from **3**; similar degration of **7** afforded a ketone different from **8** or **9** and thus was assumed to be *trans*-2-perhydroindanone.

The increased propensity for dimerization in the *trans*-fused system presumably results from the angle strain imposed on the adjacent six-membered ring in the transition state. When bond formation leads to a *cis*-fused perhydroindan, the angle strain can be relieved by the six-membered ring taking on a slightly twisted

SCHEME I



(1) H. Rapoport and J. B. Lavigne, *J. Amer. Chem. Soc.*, **75**, 5329 (1953).
(2) M. O. Forster, *J. Chem. Soc.*, **107**, 260 (1915).
(3) During the course of this work the photolysis of 1,6-bisdiazo-4-*t*-butylcyclohexanone was reported: R. Tasovac, M. Stefanović, and A. Stojiljković, *Tetrahedron Lett.*, 2729 (1967).
(4) E. W. Garbisch, Jr., and J. Wohllebe, *J. Org. Chem.*, **33**, 2157 (1968).
(5) H. O. House and G. H. Rasmusson, *ibid.*, **28**, 31 (1963).
(6) Prepared by rhodium–alumina reduction of 2-indanone; upon Wolff–Kishner reduction *cis*-perhydroindan was obtained, thus confirming that the ring junction was indeed *cis*.
(7) S. J. Rhoads, J. C. Gilbert, A. W. Decora, R. T. Garland, R. J. Spangler, and J. M. Urbigkit, *Tetrahedron*, **19**, 1625 (1963).
(8) E. J. Corey, N. H. Andersen, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Amer. Chem. Soc.*, **90**, 3245 (1968).

conformation. There is no possibility for strain relief in the *trans*-fused perhydroindane, however, and thus dimerization becomes energetically more favorable. This effect is also reflected in the fact that *cis*-perhydroindan-1-one is more stable than the *trans* form by 0.65 kcal/mol.[5]

The directional selectivity of the rearrangement is not so easily explained. It is possible that steric crowding accelerates the removal of the diazo group adjacent to the ring junction, thus leading to perferential formation of the carbene in the 1 position, although such crowding is not readily apparent from an examination of models. We feel that the best explanation of the results is provided by a transition state for ketocarbene formation in which the ketone exists largely in the enolic form, **11**, as in the mechanism outlined below. As nitrogen is expelled from the diazonium enolate, C-1 becomes less negative; the increase in the positive character at this position is favored by the inductive effect of the alkyl group attached to C-1. Thus the inductive effect promotes preferential loss of nitrogen from C-1, and the directional selectivity should be independent of ring-junction stereochemistry. This is confirmed by the similar product ratios obtained from the *cis* and the *trans* compounds. Therefore, it appears that the stabilization of increased positive character at the α carbon plays an important role in the mechanism and stereospecificity of the Wolff rearrangement.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer. Ultraviolet spectra were determined with a Carey 11 spectrophotometer. Nmr spectra were recorded on a Varian A-60 spectrometer in CCl_4 solutions using tetramethylsilane as an internal standard. The glpc analyses were obtained with an Aerograph 90-P3 gas chromatograph using a 10 ft × 0.25 in. column packed with 10% FFAP on Chromosorb W and with helium as the carrier gas.

1,3-Bisdiazo-*cis*-2-decalone (2).—To a solution of potassium *t*-butoxide (from 8.3 g of K, 0.21 mol) in 200 ml of dry *t*-butyl alcohol was added 12.8 g (0.084 mol) of *cis*-2-decalone[9] at 25°. Isoamyl nitrite (30 g, 0.26 mol) was then added dropwise, and the resulting solution was allowed to stand for 18 hr at 25°. Water (1 l.) was added, and the resulting solution was extracted with five 200-ml portions of ether. The aqueous layer was acidified with dilute HCl and extracted with three 100-ml portions of chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated, and the residue was taken up in 30 ml of hot methanol and poured into 250 ml of ether. The resulting precipitate was collected and dried to give 9.88 g (50%) of dioximino ketone: ν_{max} (Nujol) 3215, 1715, 1610, 1585 cm^{-1}; λ_{max}^{EtOH} 273 nm (ϵ 12,000).

The dioximino ketone (500 mg, 2.38 mmol) was dissolved in 9 ml of 2 *N* NaOH and 10 ml of concentrated ammonium hydroxide. Ether (100 ml) was added, and sodium hypochlorite (30 ml of 5% solution) was added dropwise with stirring over 2 hr. After stirring 18 hr at 25°, the ether layer was separated and the aqueous layer was extracted with three 50-ml portions of ether. The combined extracts were dried ($MgSO_4$) and evaporated to give 344 mg (69%) of **2** as a bright yellow oil: ν_{max} ($CHCl_3$) 2084, 2062, 1580 cm^{-1}; λ_{max}^{EtOH} 323 mμ (ϵ 25,000).

Rearrangement of 1,3-Bisdiazo-*cis*-2-decalone (2).—To a solution of **2** (1.19 g, 6.6 mmol) in 15 ml of refluxing absolute methanol was added 1 g of freshly prepared silver oxide in small portions over 2 hr. The mixture was refluxed for 12 hr, then filtered through Hy-Flo and evaporated to give 1.10 g of crude product. Distillation through a short-path column afforded 737 mg (73%) of yellow oil, bp 150–165° (bath temperature) (16 mm). Glpc analysis (120°) showed the presence of six products, three low-boiling products in **4**, 44, and 16% yields, and approximately equal amounts of three high-boiling products in 36% total yield. Preparative glpc afforded pure samples of **3** [44% yield, ν_{max} (neat) 1715 cm^{-1}; λ_{max} 227 mμ (ϵ 14,000); nmr δ 6.61 (t, 1), 3.62 (s, 3); molecular ion *m/e* 180. (*Anal.* Found: C, 73.2; H, 9.1)] and **4** [16% yield; ν_{max} (neat) 1720 cm^{-1}; λ_{max} 227 mμ (ϵ 10,000); nmr δ 6.61 (m, 1), 3.62 (s, 3); molecular in *m/e* 180 (*Anal.* Found: C, 73.2; H, 9.1)].

Schmidt Degradation of 3.—A solution of **3** (26.4 mg, 0.15 mmol) and 100 mg of potassium hydroxide in 2 ml of ethylene glycol was refluxed for 10 min. The solution was poured into 25 ml of water and extracted with two 5-ml portions of ether. The aqueous solution was acidified and extracted with three 5-ml portions of benzene. The extracts were concentrated to 2 ml, and 50 mg of sodium azide and 2 ml of concentrated H_2SO_4 were added. After heating at 45° for 30 min, the solution was poured into 20 ml of water and refluxed for an additional 30 min. The solution was extracted with three 5-ml portions of ether, and the extracts were dried ($MgSO_4$) and evaporated to give 14.0 mg of crude product. Glpc analysis indicated a 3:1 mixture of two compounds which were shown to be *cis* and *trans* **8** by peak enhancement with authentic samples.[6]

Schmidt Degradation of 4.—Reaction of 10.4 mg of **4** containing some **3** with KOH and then HN_3 as described above afforded 6.7 mg of product. Glpc showed the major product to be *cis*-2-perhydroindanone by peak enhancement with an authentic sample.[6]

Synthesis of Authentic 3.—A solution of *cis*-2-perhydroindanone[6] (2.0 g, 14.5 mmol) in 9.5 ml of dimethyl carbonate containing 5 drops of methanol was added dropwise to a stirred suspension of sodium hydride (3.0 g of 50% dispersion, freed of mineral oil by washing with petroleum ether) in 43 ml of dimethyl carbonate; stirring was then continued for 1 hr. The mixture was cooled to 0°, and a solution of 3 ml of glacial acetic acid in 25 ml of ether was added. Water (100 ml) was added, and the solution was extracted with three 50-ml portions of ether. The combined extracts were washed with sodium bicarbonate, dried ($MgSO_4$), and evaporated to give 2.60 g (92%) of product. The crude β-keto ester (2.60 g, 13.3 mmol) was dissolved in 150 ml of ethanol and 25 ml of water at 0°. Sodium borohydride (1.5 g) was added in portions to the cooled, stirred solution over 1 hr. The solution was stirred 1.5 hr at 25°, and most of the solvent was removed at reduced pressure. Ice was added, and the mixture was extracted with three 50-ml portions of ether. The combined extracts were dried ($MgSO_4$) and evaporated to give 2.20 g (84%) of hydroxy ester **10** as a mixture of diastereomers: ν_{max} (neat) 3400, 1730 cm^{-1}.

To a solution of hydroxy ester **10** (100 mg, 0.51 mmol) and N,N′-dicyclohexylcarbodiimide (110 mg, 0.53 mmol) in 25 ml of ether was added 50 mg of cuprous chloride;[8] the resulting mixture was stirred for 18 hr at 25°. The solution was filtered through a short column of silica gel to remove the urea; evaporation of the eluate afforded 67 mg (73%) of ester **3**. This product was identical with the major product from the Wolff rearrangement in spectral properties and by glpc peak enhancement on FFAP and SE-30 columns.

1,3-Bisdiazo-*trans*-2-decalone (5).—Bisdiazo ketone **5** was prepared from *trans*-2-decalone[10] in 25% yield as described for the *cis* compound **2**: ν_{max} (Nujol) 2080, 2062, 1580 cm^{-1}; λ_{max}^{EtOH} 324 mμ (ϵ 24,000).

Rearrangement of 1,3-Bisdiazo-*trans*-2-decalone (5).—To a solution of **5** (530 mg, 2.6 mmol) in 15 ml of refluxing absolute methanol was added 1 g of freshly prepared silver oxide in portions over 1 hr. After refluxing 2 hr more, the uv spectrum of an aliquot showed X2% of **5** remaining. The suspension was filtered through Hy-Flo and evaporated to give 435 mg of crude product. Glpc analysis showed the presence of two low-boiling products (12 and 24% yield) and two higher boiling products (59% total yield). Preparative glpc afforded pure samples of **6** [24% yield; ν_{max} (neat) 1720 cm^{-1}; λ_{max}^{EtOH} 227 mμ (ϵ 11,000); nmr δ 6.61 (t, 1), 3.62 (s, 3); molecular ion *m/e* 180] and **7** [12% yield, ν_{max} (neat) 1720 cm^{-1}; λ_{max}^{EtOH} 227 mμ (ϵ 10,000); nmr δ 6.61 (m, 1), 3.62 (s, 3); molecular ion *m/e* 180]. Both **6** and **7** were different from **3** and **4** on simultaneous injection glpc analysis.

Schmidt Degradation of 6 and 7.—Degradation was carried out on 20 mg of **6** and 15 mg of **7** exactly as described for **3**. The crude product (11 mg) from **6** upon glpc analysis proved to be a 75:25 mixture of *cis*- and *trans*-1-perhydroindanones **8**, identical with

(9) R. L. Augustine, *J. Org. Chem.*, **23**, 1853 (1958).

(10) E. E. van Tamelen and W. C. Proost, Jr., *J. Amer. Chem. Soc.*, **76**, 3632 (1954).

that obtained from **3**. Degradation of **7** afforded 7 mg of crude product which was similar but not identical with **8** or **9** on glpc analysis.

Registry No.—**2**, 19614-40-5; **5**, 19614-41-6.

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Tetramethyl Acetylenediphosphonate and Dimethyl Chloroacetylenephosphonate and Their Reactions with Cyclopentadiene, 1,3-Cyclohexadiene, and Diazomethane[1]

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Our previous work on Diels–Alder reactions of alkynyl derivatives of the group IVb elements, mainly of bis(trimethyltin)acetylene[1a-c] and bis(trimethylsilyl)acetylene,[1d] made an assessment of the Diels–Alder reactivity of acetylenes with group Vb organic substituents of interest to us. Especially noteworthy in our previous work was the formation of *m*-bis(trimethylsilyl)benzene as almost the sole product in the reaction of α-pyrone with bis(trimethylsilyl)acetylene,[1d] and it was especially of interest to investigate if a similar isomerization might occur in suitable Diels–alder reactions of phosphorus acetylenes of type $(RO)_2P(O)C{\equiv}CP(O)(OR)_2$.

The preparation of tetraethyl acetylenediphosphonate has been reported previously by Ionin and Petrov[3] (eq 1 and 2, R = Et). While some displacement re-

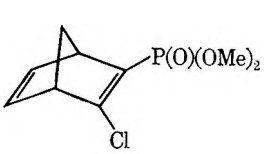
$$(RO)_3P + ClC{\equiv}CCl \xrightarrow[0°]{Et_2O} \underset{I}{(RO)_2P(O)C{\equiv}CCl} + RCl \quad (1)$$

$$(RO)_3P + (RO)_2P(O)C{\equiv}CCl \longrightarrow (RO)_2P(O)C{\equiv}\underset{II}{CP(O)(OR)_2} + RCl \quad (2)$$

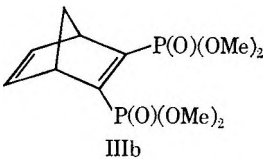
actions of the C—Cl bond of I (R = Et) were studied,[3,4] the reactivity of the C≡C bond in compounds such as I and II appears not to have been investigated. In the present study we have prepared tetramethyl acetylenediphosphonate by the Ionin–Petrov two-step procedure; in the first step $(MeO)_2P(O)C{\equiv}CCl$ was obtained in 88% yield and in the second step the $(MeO)_2P(O)C{\equiv}CP(O)(OMe)_2$ yield was 72%.

A brief study of the reactions of I and II (R = Me) showed that they readily undergo Diels–Alder reactions and 1,3 dipolar additions and thus organophosphorus-substituted acetylenes are potentially useful precursors for the introduction of organophosphorus substituents into diverse organic structures.

Reaction of cyclopentadiene with I and II (R = Me) gave the norbornadienephosphosphonates IIIa and IIIb

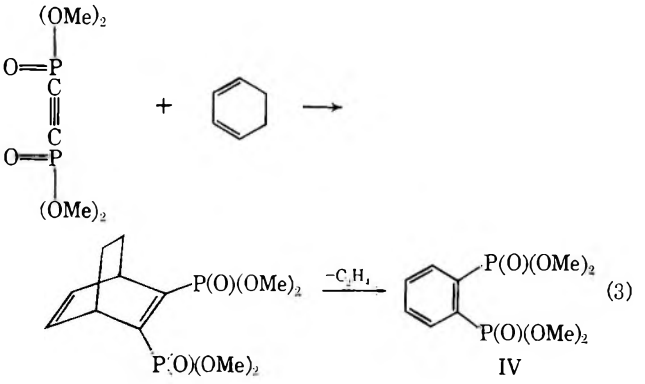


IIIa



IIIb

in good yield. Tetramethyl acetylenediphosphonate also was allowed to react with 1,3-cyclohexadiene since in the case of this diene it was expected that the initial bicyclic Diels–Alder adduct would undergo thermolysis with loss of the dimethylene bridge to form a benzene derivative.[5,6] Such thermolysis would be analogous to the loss of carbon dioxide from an acetylene–α-pyrone Diels–Alder adduct, and the structure of the benzene derivative formed would provide further useful information concerning the factors which are important in determining whether or not isomerization occurs in Diels–Alder reactions of this type. The reaction of II (R = Me) with 1,3-cyclohexadiene at 150° gave a phenylenediphosphonate in 93% yield (eq 3), and the melting point and spectral properties of this product were in complete agreement with those of the known[7] tetramethyl *o*-phenylenediphosphonate (IV). The ethylene

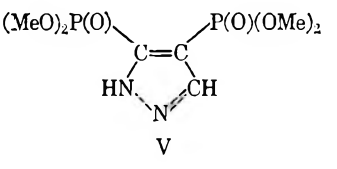


(3)

IV

evolved in the thermolytic decomposition of the initial adduct was identified by means of its conversion into 1,2-dibromoethane. The reaction of I (R = Me) with 1,3-cyclohexadiene similarly gave dimethyl *o*-chlorobenzenephosphonate, which also has been prepared previously.[7] Although the reaction of II (R = Me) with α-pyrone remains to be studied, it would appear that this acetylene reacts normally in Diels–Alder reactions of this type and thus bis(trimethylsilyl)acetylene remains the only acetylene which we have examined thus far which reacts anomalously.

The addition of a solution of diazomethane to II (R = Me) resulted in formation of the 2-pyrazoline V.



V

(1) Part V of a series of papers on "The Diels–Alder Reaction in Organometallic Chemistry." Parts I–IV are unnumbered and are listed below: (a) part I, D. Seyferth, C. Sarafidis, and A. B. Evnin, *J. Organometal. Chem.*, **2**, 417 (1965); (b) part II, A. B. Evnin and D. Seyferth, *J. Amer. Chem. Soc.*, **89**, 952 (1967); (c) part III, D. Seyferth and A. B. Evnin, *ibid.*, **89**, 1468 (1967); (d) part IV, D. Seyferth, D. R. Blank, and A. B. Evnin, *ibid.*, **89**, 4793 (1967).

(2) Postdoctoral Research Associate, 1967–1968.

(3) B. I. Ionin and A. A. Petrov, *Zh. Obshch. Khim.*, **35**, 1917 (1965).

(4) B. I. Ionin and A. A. Petrov, *ibid.*, **35**, 2255 (1965).

(5) K. Alder and H. Rickert, *Ann. Chem.*, **524**, 180 (1937).

(6) K. Alder and H. Rickert, *Ber.*, **70**, 1354 (1937).

(7) R. Obrycki and C. E. Griffin, *Tetrahedron Lett.*, 5049 (1966).

Experimental Section

Preparation of Dimethyl Chloroacetylenephosphonate.—Dichloroacetylene diethyl ether azeotrope was prepared by the procedure described in detail by Wotiz, *et al.*,[8] from 0.5 mol each of trichloroethylene and diethyl ether and distilled [bp 32° (760 mm)] into a 250-ml three-necked flask cooled to −78° and equipped with a magnetic stirring assembly, a gas inlet tube, and an exit tube leading to a bubbler. To the flask then was added under nitrogen 0.1 mol of trimethyl phosphite. The reaction mixture was warmed slowly to 0° and, after 1 hr, to room temperature. The evolution of a gas (methyl chloride) was observed. The reaction mixture was kept at room temperature overnight. Subsequently the unconverted dichloroacetylene and the ether were evaporated in a stream of dry nitrogen, the flask being warmed to 30–35°. A brown liquid residue (17.19 g) remained. Distillation gave 14.7 g of colorless liquid: bp 55° (2.2 mm); n^{25}D 1.4569; nmr spectrum, 3.71 ppm (d, J = 12.4 cps);[9] ir spectrum (neat liquid), 3000 (w), 2975 (m), 2850 (m), 2250 (sh), 2180 (vs), 2130 (w), 2060 (w), 1460 (s), 1280 (vs), 1185 (s), 1040 (vs), 950 (s), 840 (s), 795 (sh), 775 (s) cm^{-1}.

Anal. Calcd for $C_4H_6O_3ClP$: C, 28.51; H, 3.51; Cl, 21.05. Found: C, 28.27; H, 3.61; Cl, 21.15.

Preparation of Tetramethyl Acetylenediphosphonate.—Dimethyl chloroacetylenephosphonate (25 mmol) and 30 mmol of trimethyl phosphite were mixed at 0° in a reaction assembly as described in the previous experiment. The mixture was warmed slowly to 10–15° and stirred at this temperature for 15 hr. Evolution of a gas was noticed. Finally, the reaction mixture was heated at 30° for 1 hr. (Rapid heating from 0° to room temperature can result in an exothermic, uncontrollable reaction.) The brown liquid mixture was then heated at 1 mm while the external oil-bath temperature was raised slowly to 100°; 0.55 g of trimethyl phosphite distilled into the cooled trap, leaving 6.1 g of brown liquid. The latter was distilled to give 4.35 g (72%) of colorless liquid: n^{25}D 1.4476; bp 155–156° (1.5 mm), solidifying at 13–15°; nmr spectrum, 3.83 ppm (d, J = 12.3 cps); ir spectrum (liquid film), 2995 (w), 2950 (m), 2895 (sh), 2845 (m), 2160 (vw), 2020 (vw), 1890 (w), 1455 (s), 1290 (vs), 1185 (s), 1040 (vs), 845 (vs), 805 (sh), 795 (sh), 755 (m) cm^{-1}.

Anal. Calcd for $C_6H_{12}O_6P_2$: C, 29.76; H, 4.99. Found: C, 29.54; H, 4.98.

Diels–Alder Reactions.—The acetylene and the diene in equimolar quantities either were heated together without solvent under nitrogen with stirring using an oil bath heated to *ca.* 140–150° for 2–4 hr or, in the case of the tetramethyl acetylenediphosphonate–cyclopentadiene reaction, were heated in benzene solution for 10.5 hr. Distillation or, in the case of IV, crystallization gave the product.

Dimethyl 2-chloronorbornadiene-3-phosphonate (IIIa) was obtained in 64% yield: bp 85° (0.02 mm); n^{25}D 1.4996; nmr spectrum, 3.63 ppm (d, J = 11.2 cps), 2.2, 3.7, and 6.93 ppm (m, 2 H each).

Anal. Calcd for $C_9H_{12}O_3ClP$: C, 46.07; H, 5.16; Cl, 15.11. Found: C, 46.30; H, 5.12; Cl, 15.26.

Tetramethyl norbornadiene-2,3-diphosphonate (IIIb) was obtained in 72% yield: bp 137° (0.01 mm); n^{25}D 1.4947; nmr spectrum, 3.66 ppm (d, J = 11 cps), 2.0, 4.03, and 6.78 ppm (m, 2 H each).

Anal. Calcd for $C_{11}H_{18}O_6P_2$: C, 42.87; H, 5.88. Found: C, 42.65; H, 6.07.

Dimethyl o-chlorobenzenephosphonate was obtained in 22% yield: bp 87–88° (0.01 mm); n^{25}D 1.5209; nmr spectrum, 3.75 ppm (d, J = 12 cps), 7.22 (m), and 8.0 ppm (m).

Anal. Calcd for $C_8H_{10}O_3ClP$: C, 43.55; H, 4.57; Cl, 16.07. Found: C, 43.67; H, 4.86; Cl, 16.23.

Tetramethyl *o*-phenylenediphosphonate was obtained in 93.5% yield: mp 82–84° (from benzene–heptane) (lit.[7] mp 80–81° (the *meta* isomer was a high-boiling liquid; the *para* isomer melted at 100–101°);[7] nmr spectrum, 3.80 ppm (d, J = 11.8 cps), 7.62 (m), and 8.1 ppm (m).

Anal. Calcd for $C_{10}H_{16}O_6P_2$: C, 38.99; H, 5.48. Found: C, 39.15; H, 5.48.

Reaction of Tetramethyl Acetylenediphosphonate with Diazomethane.—To a stirred and cooled solution of the acetylene (10 mmol) in 20 ml of diethyl ether was added dropwise a solution of diazomethane in ether until the yellow color of the diazomethane no longer was discharged. A white crystalline solid formed immediately upon addition of the first drops of diazomethane solution. Filtration gave 2.80 g (95% yield) of white crystals, mp 130°. These were insoluble in ether, carbon tetrachloride, benzene, and hexane and soluble in chloroform, ethanol, and water. Recrystallization from chloroform–hexane gave pure material: mp 131.5°; white needles; nmr spectrum (in $CDCl_3$), 3.76 and 3.82 ppm (d, J = 11.8 cps), 8.25 ppm (s), and 11.9 ppm (s, broad); ir spectrum (Nujol), 3115 (s, broad), 2978 (m), 2940 (s), 2845 (m), 1560 (w), 1455 (s), 1374 (w), 1326 (w), 1240 (vs), 1040 (vs), 944 (m), 895 (w), 840 (s), cm^{-1}.

Anal. Calcd for $C_7H_{14}O_6N_2P_2$: C, 29.45; H, 4.97; N, 9.85. Found: C, 29.21; H, 5.00; N, 9.75.

Registry No.—I (R = Me), 19519-59-6; II (R = Me), 19519-58-5; IIIa, 19581-55-6; IIIb, 19519-61-0; V, 19519-63-2; cyclopentadiene, 542-92-7; 1,3-cyclohexadiene, 592-57-4; diazomethane, 334-88-3; dimethyl *o*-chlorobenzenephosphonate, 15104-43-5.

Acknowledgments.—The authors are grateful to the National Science Foundation (Grant GP 6466X) and the National Cancer Institute, U. S. Public Health Service (Research Grant CA 08278-03), for generous support of this work. We thank Professor C. E. Griffin for providing ir spectra of authentic IV and dimethyl *o*-chlorobenzenephosphonate.

(8) J. H. Wotiz, F. Huba and R. Vendley, *J. Org. Chem.*, **26**, 1626 (1961).

(9) Nmr spectra were measured using a Varian Associates T-60 nmr spectrometer in carbon tetrachloride solution. Chemical shifts are given in parts per million downfield from internal tetramethylsilane.

Nitrogen Inversion in N-Benzoylaziridines

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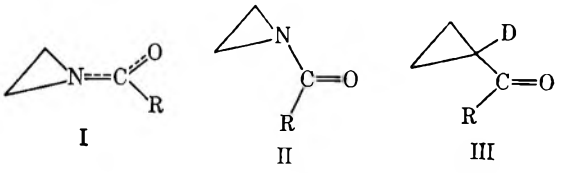
The molecular architecture of an N-acylaziridine is expected to be intermediate between two possible structures I and II. In form I, delocalization of the



I II III

a, R = CH_3O
b, R = $(CH_3)_2N$
c, R = CH_3
d, R = C_6H_5

nitrogen lone-pair electrons is significant and the atoms of the aziridine ring and the carbonyl group tend to lie in a common plane. This delocalization is minimal in structure II and the aziridine nitrogen is in a trihedral state. A competition between the tendency toward electron delocalization and the unfavorable effects of incorporation of an sp^2 nitrogen atom into a three-membered ring leads to a compromise structure between these two extremes.

Each of these limiting forms for an N-acylaziridine has distinctive kinetic features as regards either rotational isomerism about the nitrogen–acyl carbon bond or lone-pair inversion at the nitrogen atom. Structure I should exhibit a high barrier to rotation but, because

(1) Abstracted from the M.A. Thesis of G. R. B., University of California at Santa Barbara, Santa Barbara, Calif., Aug 1968.

the system is planar or nearly so, will have a low energy barrier to inversion. On the other hand, nitrogen inversion should be the dominant rate process for molecules close to structure II.

Anet and Osyany have studied several N-acylaziridines and have shown how it is possible to distinguish between these two kinetic processes by means of the spin-coupling pattern of the aziridine ring protons when the processes occur slowly on the nmr time scale.[2] These workers determined that when the substituent R was N,N-dimethylamino or methoxy—groups capable of strong resonance interaction with the carbonyl group—nitrogen inversion is the prevalent rate process. If this substituent is methyl, however, no change in the pmr spectrum was found down to −160°, a result consistent with a much smaller energy barrier to inversion than that found with the previously mentioned derivatives. These results are in line with the expected conjugative ability of N,N-dimethylamino or methoxy relative to methyl.

The conjugative ability of a phenyl group should be intermediate between that of the methyl group and the methoxy or dimethylamino groups; N-benzoylaziridine (Id) would thus be expected to have a lower barrier to inversion than Ia or Ib but a barrier higher than that for Ic. More importantly, the energy barrier to rotation about the carbon–nitrogen bond of the amide group may be large enough to produce additional effects in the pmr spectrum of this molecule. An X-ray crystallographic investigation of *p*-bromobenzoylaziridine shows that the nitrogen atom of this molecule is, in fact, strongly trihedral.[3] The angle between the plane of the ethylenimine ring and the nitrogen–carbonyl bond is 122°. From the magnitude of the carbon–nitrogen, carbon–oxygen, and carbon–carbon interatomic distances in the amide portion of the molecule, it was concluded that an appreciable resonance interaction is present in *p*-bromobenzoylazindine which increases the proclivity of this molecule for a structure closely resembling form II.[3] With the hope that we could obtain kinetic data for the inversion of nitrogen in N-benzoylaziridine, we have examined the pmr spectrum of this material as a function of temperature in a variety of solvents. The solvents used and the lowest temperature reached in each solvent are recorded in Table I. The aziridine ring protons appeared as a singlet and in no case were any changes beyond viscosity effects observed in these spectra as the temperature was decreased.

TABLE I

SOLVENTS USED IN N-BENZOYLAZIRIDINE EXPERIMENTS

Solvent	T,[a] °C	$\Delta\nu$,[b] ppm	$\Delta F^{\ddagger}$, kcal/mol
Acetone-d_6	−75	0.08	<11
50% acetone-d_6–50% toluene-d_8	−80	0.22	<10
Chloroform-d_1	−55	0.24	<11
Freon-11	−118	0.28	<8
Freon-22	−155	0.16	<6

[a] Lowest temperature that could be reached in the solvent before solubility or viscosity problems precluded further work. [b] Chemical shift difference for cyclopropyl phenyl ketone-d_1 in each solvent.

We have also prepared *p*-dimethylamino-, *p*-methoxy-, and *p*-nitrobenzoylaziridine and determined their pmr spectra in these solvents or various mixtures of these solvents, but with essentially the same results.

These observations are equally consistent with two interpretations. It may be that the dominant contributor to the ground state of these benzoylaziridines is structure I, in spite of the observation that *p*-bromobenzoylaziridine is nonplanar in the solid state. Alternatively, the nitrogen inversion process expected for structure II could be rapid at all temperatures. A comparison of the infrared spectra of the various aziridines in both a potassium bromide matrix and in chloroform solutions shows no consistent, pronounced shift of the carbonyl absorptions to lower frequency as might be expected if form I became more important in solution.[4] However, these vibrational frequencies in reality reflect molecular properties rather than properties of individual bonds so that changes in these quantities need not be related exclusively to variations in the hybridization of the amide nitrogen as the molecule is transferred from the solid state to the solution state.

If one presumes that these molecules are nonplanar, then the lowest temperature reached in these experiments must be above the coalescence temperature, as far as the kinetic dependence of the nmr spectra are concerned. If the chemical shift difference between the *syn* and the *anti* protons in the slowly inverting aziridine were available, it would be possible to estimate at least an upper limit for the free energy of activation for nitrogen inversion. Cyclopropyl phenyl ketone-d_1 (III) was chosen as a reasonable structural model for the noninverting aziridine and, therefore, we have obtained the approximate chemical shift difference between the *syn* and *anti* protons in this compound. (These spectra are of the AA′BB′ type and the chemical shift difference was taken as the frequency difference between the center of the two multiplets in the spectra.) These data are also recorded in Table I, along with the estimated upper limit for the free energy barriers to inversion of the aziridine in each of the solvents.

While we recognize the approximate nature of this procedure and the relative insensitivity of the calculated free energy barriers to the magnitude of $\Delta\nu$, our results suggest that the energy barrier to inversion in N-benzoylaziridine is less than 6 kcal/mol. This energy is less than the values of 10.3 and 7.6 kcal/mol found for *n*-(N′,N′-dimethylcarbamyl)aziridine (Ib) and N-carbomethoxyaziridine (Ia), respectively, as would be expected on the basis of the relative conjugative efficiencies of these groups, as discussed above. It also seems reasonable to infer that the barrier in the N-acetyl compound (Ic) is significantly lower than 6 kcal/mol.

Experimental Section

N-Benzoylaziridine was prepared according to the procedure of Goldberg and Kelly.[5]

N-(*p*-Dimethylaminobenzoyl)aziridine was prepared by a mixed anhydride method. Triethylamine (10 g, 0.099 mol) was added to a stirred solution of 7.5 g (0.046 mol) of *p*-dimethylaminobenzoic acid in 50 ml of dimethylformamide. The solution was cooled to 5° while 4.83 g (0.046 mol) of ethyl chloroformate was

(2) F. A. L. Anet and J. M. Osyany, *J. Amer. Chem. Soc.*, **89**, 353 (1967).
(3) R. P. Shihaeva, L. O. Atovmyan, and R. G. Kostyanoviskii, *Dokl. Akad. Nauk USSR*, **175** (3), 586 (1967).
(4) H. L. Spell, *Anal. Chem.*, **39**, 185 (1967).
(5) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1919 (1948).

added. After 3 hr, the triethylamine hydrochloride was filtered from the solution and the filtrate was added dropwise to a solution of 5 g (0.12 mol) of aziridine in 25 ml of dimethylformamide at 5° with stirring. The reaction mixture was stirred for an additional 4 hr and then poured into ice water. The resulting white solid (5.7 g, 67%) was recrystallized from ethanol–water and was found to melt over the range 98–101°. The mass spectrum exhibited a molecular ion at *m/e* 190 (relative abundance, 35) and fragments at *m/e* 149 and 42 (relative abundances 100 and 11, respectively) which are assigned to the ions $(CH_3)_2NC_6H_4CO^+$ and $C_2H_4N^+$. The pmr spectrum of a 10% solution of the material in deuteriochloroform showed a sharp singlet at 2.28 ppm (relative area 4), a singlet at 3.00 ppm (relative area 6), and an apparent quartet centered at 7.4 ppm (relative area 4), downfield from tetramethylsilane. Prominent infrared bands at 1670, 1625, 1360, 1190, and 820 cm^{-1} were observed for the compound in a KBr matrix while absorptions at 1690, 1625, 1370, 1172, and 840 cm^{-1} were found with a 1% chloroform solution. These infrared features are quite consistent with the proposed acylaziridine structure.[4]

N-(*p*-Methoxybenzoyl)aziridine was prepared by the reaction of aziridine with anisoyl chloride. A stirred solution of 5 g (0.12 mol) of aziridine and 100 ml (0.72 mol) of triethylamine was treated with 17.1 g (0.1 mol) of anisoyl chloride in anhydrous ether over the course of 15 min. The mixture was stirred for a few minutes after the addition of the acid chloride was completed and then poured into water. The ether layer was washed with water and cooled until the crystallization occurred. The white product (mp 76–77°) was obtained in 80% yield. The pmr spectrum of the material showed sharp singlets at 2.32 (area 4) and 3.32 ppm (area 3) and a quartet at 7.1 ppm relative to TMS. The mass spectrum consisted of a molecular ion at *m/e* 177 (relative abundance 100) and peaks at *m/e* 135, 107, and 42 (relative abundances 40, 40, and 40, respectively) which are assigned to the ions $CH_3OC_6H_4CO^+$, $CH_3OC_6H_4^+$, and $C_2H_4N^+$, respectively. The infrared spectrum evidenced absorption at 1680, 1650, 1360, 1250, and 850 cm^{-1} in a KBr matrix and absorption at 1650, 1590, 1350, and 845 cm^{-1} in chloroform solution.

N-(*p*-Nitrobenzoyl)aziridine was prepared in a manner analogous to that used for the methoxy-substituted compound except that the product was insoluble in ether and was isolated by filtration in 60% yield. After recrystallization from acetone–water the pale yellow material melted over the range 170–172°. The nuclear magnetic resonance spectrum of the compound exhibited a singlet at 2.48 (area 4) and a broad singlet at 8.28 ppm (area 4) downfield from TMS. The mass spectrum showed a molecular ion at *m/e* 192 (relative abundance 36) and peaks at *m/e* 150 and 42 (relative abundance 100 and 56) which are assigned to the ions $NO_2C_6H_4CO^+$ and $C_2H_4N^+$, respectively. The infrared spectrum in a KBr matrix consisted of bands at 1675, 1620, 1355, 1228, and 807 cm^{-1} while in chloroform solution absorptions at 1648, 1620, 1355, 1150, and 810 cm^{-1} were noted. The pmr, ir, and mass spectral data were in complete accord with the assigned structure.

Cyclopropyl phenyl ketone-d_1 was prepared by dissolution of cyclopropyl phenyl ketone (Aldrich Chemical Co.) in a 2 *M* solution of NaOD in deuterium oxide. An equivalent volume of dioxane was added to help solubility and the mixture was heated under reflux for 2 or 3 days. The mixture was poured into water and extracted with ether. The ether extracts were washed with water, dried over sodium sulfate, and concentrated *in vacuo*. The residue was vacuum distilled to afford a product which showed essentially complete incorporation of deuterium into the position α to the carbonyl group, as determined by pmr spectroscopy.

The nuclear magnetic resonance spectra were taken with a JEOL C60-H spectrometer at 60 MHz and/or a Varian Associates HA-100 instrument at 100 MHz. Samples were 4–6% solute. Spectra of the cyclopropyl phenyl ketone-d_1 were recorded at 100 MHz with decoupling of the deuterium nucleus by means of an NMR Specialties, Inc., HD-60A spin decoupler. The standard variable-temperature accessory for each spectrometer was used; temperatures were determined with a Digitec Model 560 digital thermocouple and are believed to be accurate to at least 1°.

Registry No.—N-Benzoylaziridine, 7646-66-4; N-(*p*-dimethylaminobenzoyl)aziridine, 19614-27-8; N-(*p*-methoxybenzoyl)aziridine, 15269-50-8; N-(*p*-nitrobenzoyl)aziridine, 19614-29-0; IIId, 19614-30-3.

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Proton Nuclear Magnetic Resonance, Infrared, and Electronic Spectral Properties of the Cyanide Ion–1,3,5-Trinitrobenzene σ Complex

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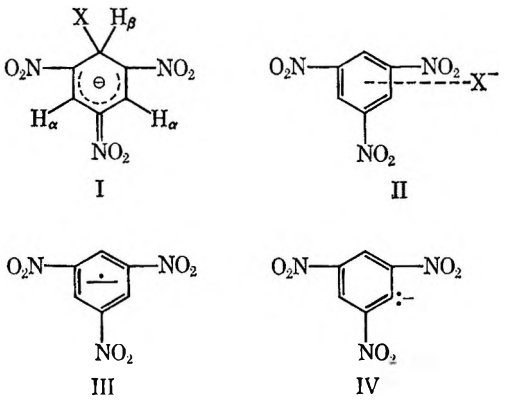
In recent years the ^1H nuclear magnetic resonance (nmr), infrared, and visible absorption spectra characteristic of the interactions of 1,3,5-trinitrobenzene and a variety of anions have been used to support the formulation of the resulting anionic species as σ complexes (I) rather than π complexes (II), radical anions (III), or aryl carbanions (IV).[1]



I II III IV

X = OH, OCH_3, OC_2H_5, SO_3^-, CN, CH_2COCH_3, CH_3NH, and $C_5H_{10}N$

The spectra have been obtained, however, under quite different experimental conditions: nmr data from solutions approximately 0.50–1.0 *M* in both anion and nitro compound;[2-5] visible absorption data[6-8] from solutions whose concentration in either component may vary from 10^{-5} to 10^{-3} *M;* and infrared data, with one exception,[9] from the solids precipitated from concentrated solutions containing the two components.[10-13] As a result, there is some question whether the spectroscopic data refers to the same species in all cases.

We have now succeeded in obtaining nmr, infrared, and visible absorption data for the 1,3,5-trinitroben-

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(2) M. R. Crampton and V. Gold, *Chem. Commun.*, 256 (1965).
(3) M. R. Crampton and V. Gold, *J. Chem. Soc., B*, 893 (1966).
(4) K. L. Servis, *J. Amer. Chem. Soc.*, **87**, 5495 (1965).
(5) R. Foster, C. A. Fyfe, P. H. Emslie, and M. I. Foreman, *Tetrahedron*, **23**, 227 (1967).
(6) A. R. Norris, *Can. J. Chem.*, **45**, 175 (1967).
(7) V. Gold and C. H. Rochester, *J. Chem. Soc.*, 1692 (1964).
(8) R. Foster and R. K. Mackie, *Tetrahedron*, **16**, 119 (1961).
(9) A. R. Norris, *Can. J. Chem.*, **45**, 2703 (1967).
(10) R. Foster and D. Ll. Hammick, *J. Chem. Soc.*, 2153 (1954).
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(13) L. K. Dyall, *ibid.*, 5160 (1960).

zene–cyanide ion adduct in solutions of approximately the same concentration and here report some of our observations.

At −30°, deuteriochloroform solutions initially 0.39 *M* in 1,3,5-trinitrobenzene (TNB) and 0.35 *M* in tetraphenylarsonium cyanide (TPAC) possess, in addition to the multiplet in the 7.80-ppm region (external tetramethylsilane = 0.0 ppm) due to the tetraphenylarsonium ion (TPA^+), absorptions at 8.42 and 5.48 ppm (relative intensity 2:1). These resonance absorptions have been assigned previously to the H_α and H_β protons of the 1:1 σ complex I (X = CN).[14] The resonance absorption at 9.36 ppm which is characteristic of uncomplexed TNB in this system[14] is not observed in this case.

The infrared spectra (0.10-mm path length cells at −32°) of chloroform and deuteriochloroform solutions initially 0.39 *M* in TNB and 0.35 *M* in TPAC show absorptions due to TPA^+ [1490 (m), 1440 (m), 1080 (m), 995 (m), and 685 cm^{-1} (m)], uncomplexed TNB [3100 (vw), 1550–1555 (vw), and 1345 cm^{-1} (vw)], and new or *enhanced* absorptions at *1615* (m), 1495 (m), 1410–1400 (vw), 1235 (vs), 1190 (vs), 1050 (s), and *928* cm^{-1} (m). Possible new absorption bands in the 700–800-cm^{-1} region are not detected owing to strong solvent absorption in this region. The presence of very weak infrared absorptions at 3100, 1550, and 1345 cm^{-1} is in full accord with the absence of nmr absorption at 9.36 ppm.

Separate experiments establish that the new absorption bands at 1495, 1235, 1190, and 1050 cm^{-1} are characteristic of a 1,3,5-trinitrobenzene–cyanide ion complex of 1:1 stoichiometry and enable effective molar extinction coefficients to be obtained for each of these peaks.[15] Since the results of nmr spectroscopy suggest the predominant species in solution is σ complex I (X = CN), the infrared absorption bands at 1495, 1235, 1190, and 1050 cm^{-1} can be taken to be characteristic of this complex.

Deuteriochloroform solutions initially 0.042 *M* in TNB and 0.043 *M* in TPAC display, at −32°, infrared absorption bands similar to those observed in the more concentrated solutions. By employing the observed absorbance at 1235 cm^{-1} and the effective molar extinction coefficient of the 1235-cm^{-1} peak, the concentration of the σ complex is estimated to be 0.028 *M*.

The visible absorption spectrum (0.012-mm path length cell at −32°) of a deuteriochloroform solution initially 0.042 *M* in TNB and 0.043 *M* in TPAC possesses absorption maxima at 448 and 561 mμ with a ratio of absorbances at these two wavelengths of 1.81. This absorption pattern has been shown previously to be characteristic of a 1:1 1,3,5-trinitrobenzene–cyanide ion complex.[9] Employing the reported molar extinction coefficient of the 561-mμ peak in chloroform (ϵ 2.25×10^4 M^{-1} cm^{-1} at 25.3°)[9] the concentration of complex in the solution is calculated to be 0.030 *M*. This value is in good agreement with the calculated concentration of the complex obtained on the basis of infrared studies.

In conclusion we believe the major anionic species in chloroform and deuteriochloroform solutions containing TNB and TPAC in the concentration range 0.5–10^{-4} *M* is a σ complex of 1:1 stoichiometry. It is characterized by nmr resonance absorptions at 8.42 and 5.48 ppm (relative intensity 2:1), and infrared absorptions at 1495 (m), 1410–1400 (w), 1235 (s), 1190 (s), and 1050 cm^{-1} (m), and visible absorptions at 448 and 561 mμ (ϵ 4.05×10^4 and 2.25×10^4 M^{-1} cm^{-1}, respectively, at 25.3°). All of these absorptions may be used to obtain quantitative information on the extent of complex formation under given reaction conditions.

Simultaneous measurements of this type are now being extended to the 1-Y-2,4,6-trinitrobenzene–cyanide ion interactions.

Registry No.—I, 19614-50-7.

(14) E. Buncel, A. R. Norris and W. Proudlock, *Can. J. Chem.*, **46**, 2759 (1968).

(15) A. R. Norris, unpublished results.

Reactions of *t*-Butyl Hypohalites with Carbanions and Alkoxides[1]

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Hydrogen peroxide and its organic derivatives react rapidly with a variety of nucleophiles,[3] and, as an example, *t*-butyl peroxy esters react with Grignard reagents by nucleophilic displacement on oxygen to give *t*-butyl ethers in satisfactory yields.[4] With *t*-butyl hypohalites, nucleophilic displacement might occur on either halogen or oxygen, and in the latter case carbanionoid reagents would again yield ethers. We have now investigated the reaction of *t*-butyl hypochlorite with a number of organometallic compounds, Table I, and find that, not surprisingly, reaction on halogen is in fact the predominant, if not exclusive, path; thus the reaction, if informative, is of little synthetic interest.

TABLE I
REACTIONS OF *t*-BUTYL HYPOCHLORITE WITH ORGANOMETALLIC REAGENTS[a]

Reagent	Products
RLi (from RCl)	RCl
RLi (from RBr)	RCl, RBr
RMgCl (from RLi)	RCl
RMgBr	RCl (50%), RBr (25%), RO-*t*-Bu (trace)
R_2Zn (from RMgBr)	RCl, RBr, RO-*t*-Bu (0.5%)
R_2Cd (from RMgBr)	RCl, RBr, RO-*t*-Bu (1%)
R_2Hg	RCl, acetone, *t*-butyl alcohol[b]
R_4Sn	RCl[c]

[a] R = phenyl. [b] On irradiation, little or no reaction in dark. [c] After 14 days, very slow reaction.

The reaction of *t*-butyl hypohalites with the *t*-butoxide anion is more interesting. Here displacement of halogen is simply an identity reaction regenerating

(1) Taken from the Ph.D. dissertation of J. Kjellgren, Columbia University, 1966. Support of this work by the National Science Foundation is gratefully acknowledged.

(2) National Science Foundation Fellow, 1962–1964; Union Carbide Corp. Fellow, 1964–1965.

(3) J. T. Edwards, "Peroxide Reaction Mechanisms," John Wiley & Sons, Inc., New York, N. Y., 1962, Chapter 5.

(4) S. O. Lawesson and N. C. Yang, *J. Amer. Chem. Soc.*, **81**, 4230 (1959).

starting materials, but displacement on oxygen should yield di-*t*-butyl peroxide (eq 1). In actual fact, the

$$(CH_3)_3CO^- + (CH_3)_3COCl \longrightarrow (CH_3)_3COOC(CH_3)_3 + Cl^- \quad (1)$$

reaction takes quite a different course. Slow addition of *t*-butyl hypochlorite to potassium *t*-butoxide in *t*-butyl alcohol at 25° gives an immediate exothermic reaction with precipitation of KCl, and the reaction continues until roughly 3 equiv of hypochlorite have been added. Rapid exothermic reaction also occurs with a suspension of *t*-butoxide in chlorobenzene at −30°. Products (using 1:1 mole ratios of reactants) in various solvents are listed in Table II. Higher temperatures or too rapid hypochlorite addition leads

TABLE II
REACTION OF *t*-BUTYL HYPOCHLORITE WITH POTASSIUM *t*-BUTOXIDE

Conditions (temp, °C)	Products (%)[a]
Chlorobenzene (−30) or *t*-butyl alcohol (25)	*t*-Butyl alcohol (140–150), isobutylene oxide (40–50), CH_3Cl (3), CCl_4 (1–3), methyl-*t*-butyl ether (1), isobutylene (1)
Toluene (−30)	Same + benzyl chloride (36)
Toluene (−30) + O_2	Same + benzyl chloride (17)
Cyclohexane	Same + cyclohexyl chloride

[a] Yields calculated on hypochlorite.

to decreased yields, some acetone, and tarry by-products. No di-*t*-butyl peroxide is formed (although it is stable and can be recovered from the reaction mixture if deliberately added). Instead, isobutylene oxide and *t*-butyl alcohol are the major products (mass balances at −20° in chlorobenzene are 90–95% for *t*-butyl groups, 77–98% for chlorine).

Quite similar results, but lower yields, are obtained using chlorine, *t*-butyl hypobromite, or bromine in place of hypochlorite, with methyl bromide replacing methyl chloride in the latter two cases. With the halogens, hypohalites are presumably produced *in situ via* the displacement (eq 2). The chief clue to what is

$$RO^- + X_2 \longrightarrow ROX + X^- \quad (2)$$

going on is the finding that toluene and cyclohexane are both chlorinated during the reaction, obvious results of a radical chain process.

Further, it is evidently a *t*-butoxy radical chain, since hypochlorite and hypobromite give similar results, and competitive experiments using *t*-butyl hypochlorite with cyclohexane and toluene give relative reactivities of 4.1–4.4, within the range observed with *t*-butoxy radicals, but much lower than the chlorine atom value.[5]

In the absence of added hydrocarbon, the most reactive substrates available would be *t*-butyl alcohol or (perhaps better) *t*-butoxide; thus presumably isobutylene chlorohydrin is first produced[6] and then converted into epoxide by the *t*-butoxide. We have shown the latter reaction to be quantitative under our reaction conditions.

(5) C. Walling and J. McGuinness, *J. Amer. Chem. Soc.*, in press.
(6) C. Walling and M. J. Mintz, *ibid.*, **89**, 1515 (1967).

Although this sequence accounts satisfactorily for the major and most of the minor products the nature of the redox reaction by which the radicals are initially produced remains obscure,[7] as do the exact details of a number of other "spontaneous" radical-forming processes observed in the hypochlorite chemistry.[6,8] In contrast to chlorine and bromine, iodine added to *t*-butoxide solutions leads to no violent spontaneous reaction, and the solution retains its oxidizing power unchanged. With 2 mol of butoxide/1 mol of I_2, the iodine color is almost entirely discharged and a tan precipitate forms, which on drying appears to be a mixture of potassium iodide and iodate. The reaction was not examined further, but it is interesting to note that, while Akhbar and Barton[9] have proposed the formation of alkyl hypoidites by either the reaction of mercuric oxide, iodine, and an alcohol or from *t*-butoxide and iodine, and several investigators have used the former combination as a radical-iodinating agent,[10] *t*-alkyl hypoiodites have never, in fact, been isolated and identified as such.[11]

Experimental Section

Organometallic reactions were carried out in general by adding an equivalent of *t*-butyl hypochlorite to benzene solutions of the appropriate reagent under N_2, and products were analyzed by gas liquid partition chromatography (glpc).

Reactions with *t*-butoxide were carried out by slow addition of the hypochlorite, or other reagent, to vigorously stirred solutions or suspensions of potassium *t*-butoxide with cooling. Products were determined by glpc and identified by retention time on two or more columns. The precipitate from the *t*-butoxide–iodine reaction gave a copious precipitate of AgI with $AgNO_3$. The presence of KIO_3 was demonstrated by ir spectra (KBr pellet) on a sample dried at 140°. Elemental analysis indicated approximately 6.4:1 KI-KIO_3.

Registry No.—*t*-Butyl hypochlorite, 507-40-4; potassium *t*-butoxide, 865-47-4.

(7) A possible redox reaction, $ROCl + RO^- \rightarrow 2RO\cdot + Cl^-$, is energetically very implausible since both of the steps, $ROCl \rightarrow RO\cdot + Cl\cdot$ and $Cl\cdot + RO^- \rightarrow Cl^- + RO\cdot$, should be endothermic.
(8) C. Walling, L. Heaton, and D. D. Tanner, *ibid.*, **87**, 1715 (1963).
(9) M. Akhtar and D. H. R. Barton, *ibid.*, **86**, 1528 (1964).
(10) K. Heusler and J. Kalvoda, *Angew. Chem.*, **76**, 518 (1964).
(11) Recently D. D. Tanner and G. C. Gidley [*J. Amer. Chem. Soc.*, **90**, 808 (1968)] have reported that treatment of *t*-butyl hypochlorite with HgI_2 also yields an iodinating agent, but it appears more complex than a simple hypoiodite.

Alkoxy Radicals in Lead Tetraacetate Oxidations[1]

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The role of free radicals as transient intermediates is well established in a number of reactions of lead tetraacetate, including the alkylation of aromatics,[3] the

(1) Taken from the Ph.D. dissertation of J. Kjellgren, Columbia University, 1966. Support of this work by the National Science Foundation is gratefully acknowledged.
(2) National Science Foundation Fellow, 1962–1964; Union Carbide Corp. Fellow, 1964–1965.
(3) L. F. Fieser, R. C. Clapp, and W. H. Daudt, *J. Amer. Chem. Soc.*, **64**, 2052 (1942).

oxidative decarboxylation of carboxylic acids,[4] and the conversion of long-chain alcohols into tetrahydrofurans.[5] In particular, the last process has been formulated[6] as involving an exchange to yield a Pb^{IV} alkoxide (eq 1), and homolytic scission (eq 2) followed

$$ROH + Pb(OAc)_4 \rightleftharpoons ROPb(OAc)_3 + HOAc \quad (1)$$

$$ROPb(OAc)_3 \longrightarrow RO\cdot + Pb(OAc)_3 \quad (2)$$

by intramolecular hydrogen abstraction, and oxidation of the resulting carbon radical to the tetrahydrofuran by Pb^{III} or Pb^{IV}.

Such a sequence suggests the possibility of carrying out an induced oxidation of a hydrocarbon using a short-chain alcohol and lead tetraacetate, involving bimolecular hydrogen abstraction *via* an intermediate alkoxy radical, *i.e.*, reactions 1 and 2 followed by reactions 3 and 4 or 4a.

$$RO\cdot + R'H \longrightarrow ROH + R'\cdot \quad (3)$$

$$R'\cdot + Pb(OAc)_3 \longrightarrow R'OAc + Pb(OAc)_2 \quad (4)$$

$$\text{or } R'\cdot + Pb(OAc)_4 \longrightarrow R'OAc + Pb(OAc)_3 \quad (4a)$$

To see whether this is in fact the case, we have examined the effect of *t*-butyl alcohol on the reaction of lead tetraacetate with representative hydrocarbons by shaking the acetate with hydrocarbon in sealed, degassed tubes at 85°, with and without the alcohol. *t*-Butyl alcohol was chosen because the reactions of *t*-butoxy radicals are well characterized[7] and because it is not itself subject to easy oxidation. Unfortunately, it also appears to undergo exchange reactions with the acetate much more sluggishly than primary and secondary alcohols, although some acceleration of tetraacetate decomposition was observed.[8] Thus with cyclohexane or toluene 0–30% unreacted tetraacetate remained after 6 days at 85° in the presence of *t*-butyl alcohol, compared with 60–65% in its absence.

Our rather qualitative results are summarized in Table I. With cyclohexane and toluene, *t*-butyl alcohol increases the yield of cyclohexyl acetate and benzyl acetate, respectively, at least 10-fold, and they become the major products of attack on the hydrocarbon. With benzene the yield of toluene is also increased, perhaps in part *via* methyl radicals arising from β scission of *t*-butoxy radicals to acetone and methyl. In addition, reactions in the presence of alcohol showed increased yields of CO_2, methane, and methyl acetate plus *t*-butyl acetate (approximately 60% of substrate acetate) and a small amount of acetone from the alcohol.

TABLE I

EFFECT OF *t*-BUTYL ALCOHOL ON LEAD TETRAACETATE OXIDATIONS

Substrate	Alcohol	Products (yield)[a]
Cyclohexane	No	Cyclohexyl acetate (8)
Cyclohexane	Yes	Cyclohexyl acetate (100), cyclohexene (5), benzene (1)
Toluene	No	Benzyl acetate (10)
Toluene	Yes	Benzyl acetate (100), xylenes (2), bibenzyl (1), benzaldehyde (0.5)
Benzene	No	Toluene (50)
Benzene	Yes	Toluene (100)

[a] Yields relative to major product in presence of alcohol; see Experimental Section.

Alcohol-derived acetates are common by-products of other lead tetraacetate–alcohol reactions, and higher yields of other products may reflect rapid decomposition of intermediate Pb^{III} products, *e.g.*, eq 5.

$$Pb(OAc)_3 \rightarrow Pb(OAc)_2 + CH_3COO\cdot \longrightarrow CH_3\cdot + CO_2 \quad (5)$$

Although our results are certainly consistent with our reaction scheme, we have also attempted to obtain further evidence for *t*-butoxy radical participation *via* competitive relative reactivity measurements, chiefly with cyclohexane–ethylbenzene mixtures. Here we were unsuccessful. Toward *t*-butoxy radicals from *t*-butyl hypochlorite, relative reactivities are 2.4.[7] With lead tetraacetate, we obtained inconsistent values ranging from 0.9 to 2.2. In view of our previous discussion we believe that the inconsistency arises because attack on hydrocarbon involves both *t*-butoxy and methyl radicals, so that the results observed are actually a composite of the two reactions.

Experimental Section

Lead tetraacetate was commercial material; purity by titration[9] was 90–95%.

Oxidations were carried out in sealed, degassed tubes, using equivalent quantities of alcohol and tetraacetate plus excess hydrocarbon and shaking in a thermostat at 85°, usually for 6 days. Products were analyzed by gas liquid partition chromatography and were usually identified by actual isolation. Because of the heterogeneous mixture of reaction products, only relative yields could be determined easily. In addition to products reported in the text, bicyclohexyl, cyclohexanol, cyclohexanone, and cyclohexyl *t*-butyl ether were shown to be absent in cyclohexane reactions; thus, cyclohexyl acetate was plainly the major product. Similarly with toluene benzyl alcohol, benzene and benzyl *t*-butyl ether were absent, although possible more complex products[10] were not examined.

Competitive experiments were carried out similarly using less hydrocarbon diluted with *o*-dichlorobenzene, and relative reactivities were determined by hydrocarbon consumption.[7]

Registry No.—Lead tetraacetate, 546-67-8.

(4) J. K. Kochi, *J. Amer. Chem. Soc.*, **87**, 3609 (1965).

(5) G. Cainelli, M. Mihailovic, D. Arigoni, and O. Jager, *Helv. Chim. Acta*, **42**, 1124 (1959).

(6) M. Mihailovic, Z. Cekovic, and D. Jeremic, *Tetrahedron*, **21**, 2813 (1965).

(7) C. Walling, *Pure Appl. Chem.*, **15**, 69 (1967).

(8) Attempts to use methyl alcohol simply led to its rapid oxidation with little or no attack on hydrocarbon.

(9) O. Dimroth and R. Schweizer, *Ber.*, **56**, 1375 (1923).

(10) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **90**, 1082 (1968).

An Electrochemical Reduction of Unactivated Carbon–Carbon Double Bonds

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Unactivated double bonds are known to be difficult to reduce electrochemically,[1] although Sternberg, *et al.*,[2]

(1) F. D. Popp and H. P. Schultz, *Chem. Rev.*, **62**, 19 (1962).

(2) H. W. Sternberg, R. E. Markby, I. Wender, and D. M. Mohilner, *J. Amer. Chem. Soc.*, **89**, 186 (1967); H. W. Sternberg in the Synthetic and Mechanistic Aspects of Electroorganic Chemistry Symposium at the U. S. Army Research Office, Durham, N. C., Oct 14–16, 1968.

have recently described a procedure where solvated electrons were suggested to be the reducing agents. In addition Burke, *et al.*,[3] have shown that ethylene could be reduced by electrochemically generated hydrogen at a platinum wire electrode. With the development of fuel cell electrodes with their huge surface areas, electrochemical reductions of unactivated olefins on a preparative scale appeared possible.

Experimental Section

The cell and circuitry have been described previously.[4] The working electrode was a type LAA-25 (American Cyanamid Co., Commercial Products Division, Wayne, N. J.) having an active geometrical area of 20.3 cm^2. It consisted of 25 mg of platinum black/cm^2 and 25 wt % Teflon pressed together on a tantalum screen. A porous Teflon coating was applied to the gas side of the electrode to prevent electrolyte leakage into the gas space which was $^1/_{16}$ in. in depth over the active area of the working electrode. The reactant, whether propene, Matheson 99.7% research grade, or hexene-1, Phillips 99% pure grade, in a helium carrier was continuously introduced into the gas space through the top port. The reactant and product exited through the bottom port and were vented to the atmosphere after passing through a gas-sampling valve of a gas chromatograph or were trapped for injection into a gas chromatograph (Perkin-Elmer 154-D or Hewlett-Packard 5750). Potentials were measured against the dynamic hydrogen electrode, dhe,[5] in which hydrogen is generated *in situ* electrochemically. This reference electrode was typically 40 mV cathodic to the normal hydrogen electrode.

Results

Using propene as the reactant and 85% H_3PO_4 at 100° as the electrolyte, greater than 99% conversion of propene into propane was observed when the reactant flowed over the working electrode at a rate of 0.02 mol/hr or 9 sec/cc. The potential difference between the working electrode and the dhe was found not to be important as long as it was cathodic to 0.03 V. There was no rapid decrease in conversion with time as, after 7 continuous hr under the above conditions, greater than 99% conversion was still being obtained.

In addition to H_3PO_4, other electrolytes may be used. NaOH (1 *M*) at 60° gave a conversion of 97% at a flow rate of 19 sec/cc; 1 *M* $NaHCO_3$ also gave a 97% conversion of propene at 60° but at a flow rate of 40 sec/cc. Increases in flow rate at high conversions should be made possible for all electrolytes by baffles in the gas space to increase contact of reactants with catalyst and/or by using a larger working electrode.

Identical results could be obtained without potential control of the working electrode. In this experiment, four 1.5-V batteries were connected in series between the working and counter electrodes, and the potential difference between the reference and working electrodes was read off an electrometer. (No reference electrode or electrometer is necessary for reduction, but hydrogen must be present at the working electrode.) The working electrode could be cleansed of any adsorbed impurities by connecting the positive terminal of the battery to the working electrode and the negative terminal to the counter electrode. The working electrode surface was oxidized as the potential rose to 1.7 V *vs.* dhe. After a few minutes, the battery terminals were reversed, and the potential fell to −0.02 V *vs.* dhe. On passing propene over the working electrode at a flow of 9 sec/cc, essentially quantitative conversion of propene into propane was again observed.

Hexene-1 could also be easily hydrogenated. Hexene-1 was placed in a small reactor through which helium flowed so as to carry the olefin over the working electrode. The effluent from the gas space was condensed and analyzed by gas chromatography. At a flow rate of 0.02 mol/hr, 98% of the hexene-1 was converted into hexane. In this experiment, 85% H_3PO_4 at 100° was the electrolyte.

Work is in progress on the mechanism of this reaction.

(3) L. D. Burke, C. Kemball, and F. A. Lewis, *Trans. Faraday Soc.*, **60**, 913 (1964).

(4) H. J. Barger, Jr., and M. L. Savitz, *J. Electrochem. Soc.*, **115**, 686 (1968).

(5) J. Giner, *ibid.*, **111**, 376 (1964).

The Chemistry of 1-Lithio-2-chloroperfluorocycloalkenes[1]

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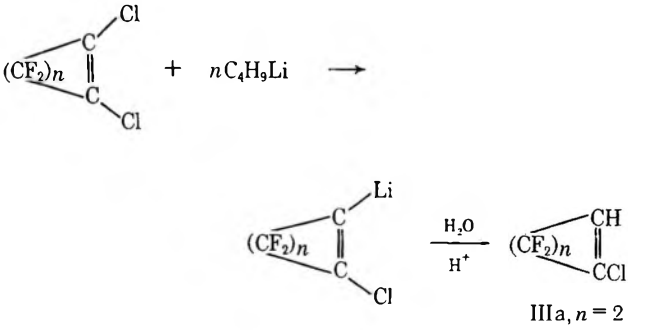
Although vinyllithium reagents derived from linear polyfluoro olefins have been the center of recent attention,[2-5] the analogous lithium derivatives of alicyclic perfluoro olefins have little chemical precedent[6] outside of our previously reported preliminary work.[7]

In this paper, we wish to report the facile preparation of the homologs of one particular series of these lithio derivatives [1 - lithio - 2 - chlorotetrafluorocyclobutene (IIa), 1-lithio-2-chlorohexafluorocyclopentene (IIb), 1-lithio-2-chlorooctafluorocyclohexene (IIc)] and to demonstrate the utility of these reagents as intermediates in the synthesis of heretofore inaccessible or difficultly accessible substituted alicyclic polyfluoro olefins.

These lithio reagents (II) were prepared by the action of *n*-butylithium on the readily available 1,2-



IIIa, $n = 2$
b, $n = 3$
c, $n = 4$

(1) This paper represents part of the Ph.D. thesis of B. T. Nakatá submitted to the Graduate School, University of Colorado, Boulder, Colo., 1968.

(2) P. Tarrant, P. Johncock, and J. Savory, *J. Org. Chem.*, **28**, 839 (1963).

(3) F. Drakesmith, O. J. Stewart, and P. Tarrant, *ibid.*, **33**, 280 (1968).

(4) F. G. Drakesmith, R. D. Richardson, O. J. Stewart, and P. Tarrant, *ibid.*, **33**, 286 (1968).

(5) F. G. Drakesmith, O. J. Stewart, and P. Tarrant, *ibid.*, **33**, 472 (1968).

(6) S. F. Campbell, R. Stephens, and J. C. Tatlow, *Chem. Commun.*, 151 (1967).

(7) (a) J. D. Park and B. T. Nakatá, Abstracts, 154th Meeting of the American Chemical Society, Chicago, Ill., 1967, p K-12; (b) J. D. Park, C. Bertino, and B. T. Nakatá, Abstracts, 156th Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, p Fluo-22.

TABLE I

SUBSTITUTED 2-CHLOROPERFLUOROCYCLOALKENES PREPARED FOR THIS STUDY

0.05 mol — 0.06 mol ≡ 19.5 ml of 2.57 *M* in hexane — 0.06 mol

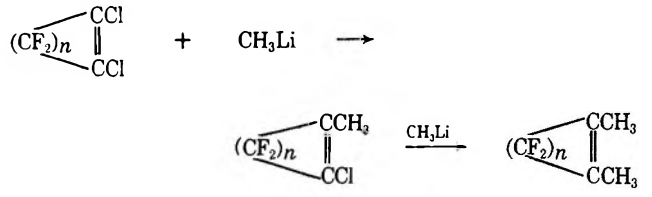
Ia = 9.75 g
b = 12.7 g
c = 14.8 g

Product	*n*	Reagent	A	Yield, g	Theory, %	Mp or bp (mm), °C	n_D, t, °C	Calcd,[h] % C	H	Cl	F	Found, % C	H	Cl	F	Neut equiv Calcd	Found	Proton nmr, τ	Ir, cm⁻¹
IIIa[a]	2	H_3O+	–H	9.3	74	54 (628)	1.3496[25]											3.33 (multiplet)	C=C, 1596
IIIb[b]	3	H_3O+	–H	7.46	71	73 (630)	1.3232[20]											3.50 (multiplet)	C=C, 1640
IIIc[c]	4	H_3O+	–H	10.5	81	90 (627)													C=C 1660
IVa	2	CO_2	–COOH	7.96	78	93–94	1.8									204.5	203.7		C=C, 1640; C=O, 1735
IVb	3	CO_2	–COOH	10.6	83	64.5–65.5	1.9	p*K*	28.31	0.39	13.93	44.79	28.09	0.3	13.71	44.70	254.6	256.0		C=O, 1730; C=C, 1640
IVc	4	CO_2	–COOH	10.3	67	55.5	2.0		27.61	0.33	11.64	49.91	27.67	0.43	11.85	49.66	304.5	303.6		C=C, 1640; C=O, 1740
Va	2	CH_2O	–CH_2OH	6.46	68	153 (625)	1.402[20]		31.52	1.58	18.61	39.89	31.65	1.60	18.46	39.74			5.52 (multiplet); 5.46 (singlet)	—OH, 3400; C=C, 1660
Vb	3	CH_2O	–CH_2OH	7.48	65	158 (628)	1.3928[20]		29.96	1.26	14.74	47.39	30.11	1.36	15.02	47.03			5.43 (singlet)	C—C, 1660; —OH, 3400
Vc	4	CH_2O	–CH_2OH	12.0	82	42.5–43.5			28.94	1.04	12.20	52.31	28.66	1.01	12.29	52.37				—OH, 3300; C=C, 1655
VIa[d]	2	Br_2	–Br	7.78	65	81 (630)	1.3966[25]												C=C, 1600
VIb[e]	3	Br_2	–Br	10.3	71	101 (629)	1.3890[25]												C=C, 1610
VIc	4	Br_2	–Br	10.5	62	122 (630)	1.3901[27]		21.2		10.4	44.7	21.01		10.59	44.9				C=C, 1620
VIIa[d]	2	I_2	–I	9.58	67	110 (630)	1.4420[25]												C=C, 1580
VIIb[f]	3	I_2	–I	9.74	58	128 (628)	1.4268[28]												C=C, 1600
VIIc[g]	4	I_2	–I	14.7	76	144 (632)	1.4218[26]												C=C, 1605

[a] J. D. Park, L. H. Wilson, and J. R. Lacher, *J. Org. Chem.*, **28**, 1008 (1963). [b] D. J. Burton and R. L. Johnson, *J. Amer. Chem. Soc.*, **86**, 5361 (1964). [c] D. E. M. Evans, W. J. Feast, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 4828 (1963). [d] R. Sullivan, J. R. Lacher, and J. D. Park, *J. Org. Chem.*, **29**, 3667 (1964). [e] J. D. Park and R. J. McMurtry, *ibid.*, **32**, 2399 (1967). [f] J. D. Park, R. J. McMurtry, and R. Sullivan, *ibid.*, **33**, 33 (1968). [g] O. Furuta, Ph.D. Thesis, University of Colorado, 1968. [h] Br, 23.18 (calcd 23.2).

dichloro compounds, 1,2-dichlorotetrafluorocyclobutene (Ia), 1,2-dichlorohexafluorocyclopentene (Ib), and 1,2-dichlorooctafluorocyclohexene (Ic).

This is a radical departure from our previously reported method of preparing the same lithio derivatives[7] which necessitated the reaction of CH_3Li on the iodohalocycloalkenes. Under similar conditions CH_3Li reacts with Ia, b, and c to yield methyl-substituted products.



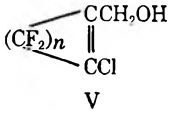
The preparation of II can be conveniently carried out by the dropwise addition of *n*-butyllithium in hexane solution (1 equiv) to a stirred solution of the 1,2-dichloro olefin in ether under a nitrogen blanket and held at −70° by means of a Dry Ice–acetone bath. Under these conditions, an extremely rapid and facile metal–halogen exchange occurs, giving rise to solutions of IIa, b, and c. The extent of the exchange may be determined by hydrolyses of these solutions II with aqueous acid measuring the amount of 1-hydro-2-chloropolyfluoro olefin III produced. In each instance, the yields of the hydro derivatives were in excess of 60%.

To demonstrate the synthetic utility of these polyfluorolithio derivatives, we prepared a number of previously inaccessible compounds through treatment of solutions of II at −70° with a variety of reagents.

Accordingly, carbonation of II with either Dry Ice or gaseous carbon dioxide offered the corresponding 2-chloropolyfluorocycloalkene-1-carboxylic acid IV in good yield (see Table I, p 1491).

The pK's of these acids were determined in aqueous solution and are shown in Table I. Because of the admitted somewhat crude nature of these determinations, we hesitate to attach much significance to the apparent variation of pK values with ring size and would only comment at the moment that these compounds are extremely strong organic acids.

The treatment of solutions of IIa, b, and c, at −70°, with formaldehyde gave the corresponding carbinols, V.

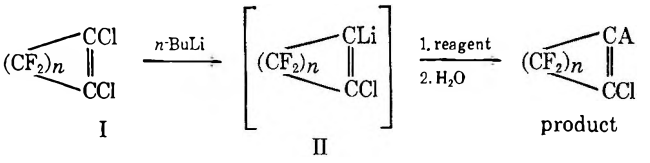


V

The halogens, bromine and iodine, combined with anions IIa, b, and c at −70° to yield the corresponding mixed dihalofluoro olefins VIa, b, and c and VIIa, b, and c listed in Table I. These syntheses of the various 1-halo-2-chloro derivatives are much easier than those previously reported in the literature.

Experimental Section

General Procedure.—To a precooled (−70°) stirred solution of 0.05 mol of 1,2-dichloroperfluorocycloalkene in 100 ml of anhydrous ether was added 0.05 mol of *n*-butyllithium in hexane. The mixture was maintained at −70° for 1 hr with stirring. The resulting dark, reddish violet solution of 1-lithio-2-chloroperfluorocycloalkene was subsequently treated with 0.06 mol of reagent. The reaction mixture was allowed to come to room temperature and hydrolyzed with water. The aqueous phase was extracted twice with two 25-ml portions of ether and the combined organic phase and ether extracts were dried over anhydrous magnesium sulfate. Distillation of this material then yielded the product.



When the above reaction was carried out with CH_3Li under similar conditions no lithiochloroperfluorocycloalkenes were obtained. Thus with 1,2-dichloro-hexafluorocyclopentene, 1-methyl-2-chlorohexafluorocyclopentene, bp 98° (626 mm) [lit.[8] bp 97.5° (621 mm)], was obtained.

Table I is a compilation of the various reactions carried out along with the properties and analyses of the various products isolated. The literature references are given when the products were previously prepared by other routes.

Acknowledgments.—The authors wish to express their appreciation to the 3M, St. Paul, Minn., and to the U. S. Army Natick Laboratories, Natick, Mass., for their partial support of this work.

Registry No.—IIIa, 695-44-3; IIIb, 3761-95-3; IIIc, 777-96-8; IVa, 19614-54-1; IVb, 19640-45-0; IVc, 19614-55-2; Va, 2898-26-2; Vb, 2890-35-9; Vc, 19640-46-1; VIa, 697-07-4; VIb, 13169-17-0; VIc, 19614-59-6; VIIa, 697-10-9; VIIb, 14627-45-3; VIIc, 19614-62-1.

(8) R. J. McMurtry, unpublished work (University of Colorado, 1966).

Dechlorinative Coupling of *gem*-Dichlorides by Sodium Selenide

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There are a few publications on the reaction of alkyl halides with sodium selenide. Alkyl halides react with sodium selenide to give symmetrical selenides.[1] Cyclic selenides are made from polymethylene dibromides and sodium selenide.[2] However, the reaction of vicinal alkyl dihalide with sodium selenide results in the formation of the dechlorinated product, *i.e.*, the alkene instead of alkyl selenide.[3,4]

We wish now to report another interesting reaction of dechlorinative coupling of alkyl *gem*-dichlorides by sodium selenide. Thus sodium selenide effects dechlorination of dichlorodiphenylmethane to give tetra-

(1) L. Brandsma and H. Wijes, *Rec. Trav. Chim. Pays-Bas*, **82**, 68 (1963).
(2) G. T. Morgan and F. H. Burstall, *J. Chem. Soc.*, 1096, 1497, 2197 (1929); 1497 (1930).
(3) M. Prince, B. W. Bremer, and W. Brenner, *J. Org. Chem.*, **31**, 4292 (1966).
(4) M. Prince and B. W. Bremer, *ibid.*, **32**, 1655 (1967).

phenylethylene in good yield in accord with the equation[5]

$$2(C_6H_5)_2CCl_2 + 2Na_2Se \longrightarrow (C_6H_5)_2C{=}C(C_6H_5)_2 + 4NaCl + 2Se$$

The reaction was conducted with excess sodium selenide in dioxane at the refluxing temperature, 101°, for 24 hr under nitrogen atmosphere.

The formation of the condensed olefin may have involved a carbene intermediate. However, treatment of dichlorodiphenylmethane with sodium selenide in the presence of cyclohexene did not produce the expected carbene–cyclohexene addition product, 7,7-diphenylnorcarane.

The latter reaction was carried out at 80° in the presence of a large excess of cyclohexene. Under these conditions (lower reaction temperature and lower dielectric constant of the medium), dichlorotetraphenylethane was the main product. When the dichlorotetraphenylethane was further treated with sodium selenide in dioxane, tetraphenylethylene was isolated quantitatively. Furthermore, when chlorodiphenylmethane was treated with sodium selenide in dioxane, tetraphenylethane was obtained. Therefore, the dechlorinative coupling reaction may involve two consecutive steps, namely, the intermolecular dechlorination and the intramolecular dechlorination.

$$2(C_6H_5)_2CCl_2 + Na_2Se \longrightarrow (C_6H_5)_2C(Cl)\text{—}C(Cl)(C_6H_5)_2 + 2NaCl + Se$$

$$(C_6H_5)_2C(Cl)\text{—}C(Cl)(C_6H_5)_2 + Na_2Se \longrightarrow (C_6H_5)_2C{=}C(C_6H_5)_2 + 2NaCl + Se$$

The reaction also was carried out with methyl methacrylate as a solvent at 100° for 1 hr. Dichlorotetraphenylethane was isolated but poly(methyl methacrylate), which would indicate a free-radical intermediate, was not obtained.

A similar reaction was observed with other *gem*-dichlorides. Benzotrichloride with sodium selenide produced *trans*-α,α'-dichlorostilbene. Benzal chloride gave *trans*-stilbene, but in rather poor yield (10%). However, from the reaction of 1,1-dichlorobutane with sodium selenide, the dechlorinative coupling product, octene was not obtained. Methylene chloride gave, instead of ethylene, various cyclic poly(selenomethylenes.[5] Therefore, in order to effect dechlorinative coupling of *gem*-dichlorides, the carbon bonded with the two chlorines must be substituted by at least one, and preferably two, groups such as phenyl.

Experimental Section

The chloride compounds were obtained from commercial sources and purified by distillation or recrystallization. Sodium selenide, a purified grade (>95% pure), was obtained from City Chemical Co., New York, N. Y., and was used as the powder (<100 mesh) without further purification. The products obtained were identified by infrared and mixture melting point measurements with authentic compounds. Melting points were uncorrected. All the reactions were carried out under an atmosphere of nitrogen. Dioxane was distilled over calcium hydride and stored with sodium wire.

A representative experimental procedure is as follows. Dichlorodiphenylmethane (2.4 g, 0.010 mol) in 40 ml of dried dioxane was gradually added to a rapidly stirred suspension (in 40 ml of dioxane) of sodium selenide (4.3 g, 0.035 mol). The reaction was carried out at the refluxing temperature for 24 hr. The solid materials were removed by filtration and the dioxane was distilled off. The yellow solid obtained was recrystallized from a mixture of benzene and ethyl alcohol and gave 1.0 g (60% yield) of pure tetraphenylethylene, mp 215° (lit. mp 220–222,[7] 220°[8]). When an equivalent quantity of sodium selenide was used, the yield was poor (20–30%) and a large amount of unreacted chloride was recovered. The reason for the low yield is not clear at this time, but it may have been due to the heterogeneity of the reaction system. A search for a suitable solvent is currently being made.

The reaction of dichlorodiphenylmethane (9.5 g, 0.040 mol) with sodium selenide (11.0 g, 0.090 mol) in 80 ml of dioxane was carried out in the presence of cyclohexene (8.4 g, 0.090 mol) at 80° for 20 hr. Recrystallization of the product, from carbon tetrachloride, gave 6.0 g (yield 75%) of pure dichlorotetraphenylethane, mp 183° dec (lit.[9] mp 182–184° dec). The reaction in methyl methacrylate at 100° for 1 hr also gave dichlorotetraphenylethane (60%) yield). The reaction of chlorodiphenylmethane (7.1 g, 0.020 mol) with sodium selenide (4.3 g, 0.035 mol) in dioxane gave 4.4 g (yield 70%) of tetraphenylethane, mp 209–211° (lit.[10] mp 207–208°).

Treatment of dichlorotetraphenylethane (1.0 g, 0.0025 mol) with sodium selenide (1.0 g, 0.0080 mol) yielded tetraphenylethylene (0.60 g, yield 80%, after recrystallization).

trans-α,α'-Dichlorostilbene, mp 145° (lit.[11] mp 143–145°), 3.5 g, 52% yield, was obtained from the reaction of benzotrichloride (4.5 g, 0.022 mol) with sodium selenide (10 g, 0.065 mol). The reaction of benzal chloride (3.2 g, 0.020 mol) with sodium selenide (5.9 g, 0.05 mol) gave, upon vacuum distillation of the product, 1.8 g (10% yield) of *trans*-stilbene, mp 120° (lit.[12] mp 124°). The distillation residue contained selenium compounds. Structures have not as yet been established. 1,1-Dichlorobutane (2.3 g, 0.025 mol) was also treated with sodium selenide (7.0 g, 0.056 mol) in dioxane. Gas chromatographic analysis did not show any octene in the reaction product. A dark selenium-containing liquid material was also obtained.

Acknowledgment.—The authors gratefully acknowledge the financial support of the Selenium–Tellurium Development Association, Inc.

(5) A similar dechlorinative coupling reaction was reported with gem-dihalides by iron pentacarbonyl: C. Eugene Coffey, *J. Amer. Chem. Soc.*, **83**, 1623 (1961).

(6) M. Russo, L. Mortillaro, L. Credali, and C. DeChecchi, *J. Polym. Sci.*, **4**, 248 (1966).

(7) C.-H. Wang and S. G. Cohen, *J. Org. Chem.*, **26**, 3301 (1961).

(8) H. Gusten and L. Horner, *Angew. Chem.*, **74**, 586 (1962).

(9) T. L. Jacobs and D. M. Fenster, *J. Org. Chem.*, **30**, 1808 (1965).

(10) L. L. Alexander and R. C. Fuson, *J. Amer. Chem. Soc.*, **58**, 1745 (1936).

(11) Y. Ogata and H. Nakamura, *J. Org. Chem.*, **21**, 1170 (1956).

(12) O. H. Wheeler and H. N. Battle DuPabon, *ibid.*, **30**, 1473 (1965).

The Oxidation of Ethylbenzene with Aqueous Sodium Dichromate

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Received October 25, 1968

Aqueous sodium dichromate has been used by Friedman, Fishel, and Shechter[1] to oxidize alkylated aromatic compounds to the corresponding carboxylic acids in high yields. The procedure is particularly useful with polynuclear aromatic compounds since the side chain can be oxidized without the occurrence of extensive nuclear degradation. For example, 2-methyl-

(1) L. Friedman, D. L. Fishel, and H. Shechter, *J. Org. Chem.*, **30**, 1453 (1965).

TABLE I

OXIDATION WITH AQUEOUS SODIUM DICHROMATE

Expt no.	Reductant	Reaction time, hr	Temp, °C	Recovd material (%)
1	Ethylbenzene	1.0	246	Acetophenone (48) Benzoic acid (11) Ethylbenzene (41)
2	Ethylbenzene[a]	1.0	254	Acetophenone (27) Benzoic acid (6) Ethylbenzene (67)
3	Ethylbenzene	2.8	254	Acetophenone (54) Benzoic acid (17) Ethylbenzene (28)
4	Ethylbenzene[b]	0.5	256	Acetophenone (45) Benzoic acid (15) Ethylbenzene (40)
5	Ethylbenzene	1.0	258	Acetophenone (47) Benzoic acid (11) Ethylbenzene (42)
6	Ethylbenzene	1.0	270	Acetophenone (47) Benzoic acid (22) Ethylbenzene (31)
7	Ethylbenzene[c]	1.0	275	Acetophenone (30) Benzoic acid (38) Ethylbenzene (32)
8	Ethylbenzene	0.5	275	Acetophenone (52) Benzoic acid (23) Ethylbenzene (25)
9	Ethylbenzene[d]	2.0	250	Acetophenone (68) Benzoic acid (21) Ethylbenzene (11)
10	Ethylbenzene[e]	2.0	275	Acetophenone (6) Ethylbenzene (94)
11	Ethylbenzene[f]	1.0	248	Acetophenone (45) Benzoic acid (11) Ethylbenzene (44)
12	Ethylbenzene[f]	1.0	275	Acetophenone (40) Benzoic acid (21) Ethylbenzene (39)
13	Ethylbenzene[g]	1.0	259	Acetophenone (44) Benzoic acid (20) Ethylbenzene (36)
14	Ethylbenzene[h]	1.0	252	Acetophenone (34) Benzoic acid (7) Ethylbenzene (59)
15	Ethylbenzene[i]	1.0	249	Acetophenone (58) Benzoic acid (7) Ethylbenzene (35)
16	Phenylacetic acid	2.8	250	Benzoic acid (100)
17	Equimolar amounts of ethylbenzene and phenylacetic acid	1.0	270	Acetophenone (10) Benzoic acid (52) Ethylbenzene (33) Phenylacetic acid (4) Benzaldehyde (1)
18	Equimolar amounts of acetophenone and phenylacetic acid	1.0	274	Acetophenone (44) Benzoic acid (52) Phenylacetic acid (2) Benzaldehyde (1)
19	2-Methylnaphthalene[j]	2.0	250	2-Naphthoic acid (100)
20	*n*-Propylbenzene	1.0	195	Propiophenone (4) Benzoic acid (8) *n*-Propylbenzene (88) 1-Phenyl-1,2-propanedione (trace)

[a] A 2 molar excess of ethylbenzene was used. [b] Initial pressure was increased to 90 psi by use of CO_2 gas and a 0.2 molar excess of ethylbenzene was used. [c] The solution was buffered at about pH 7 using NaH_2PO_4 and Na_2HPO_4. [d] The solution contained 6.4 *M* NH_4OH and a 2 molar excess of dichromate was used. [e] The solution contained 1.3 *M* NaOH and a 2 molar excess of dichromate was used. [f] The solution was agitated by shaking rather than stirring. [g] The solution was not agitated. [h] The solution contained 2 g of sulfur/700 ml. [i] The solution contained 2 g of V_2O_5/700 ml. [j] A 1.5 molar excess of dichromate was used.

naphthalene is converted cleanly into 2-naphthoic acid with aqueous dichromate at 250°, whereas use of most other oxidants results in ring degradation and formation of a considerable amount of 2-methylnaphthoquinone. Even more remarkable is the report by Reitsema and Allphin[2] that the oxidation of ethylbenzene by sodium dichromate at 275° for 1 hr leads to the formation of phenylacetic acid in almost quantitative yields. Similarly these authors report that *n*-propylbenzene, isopropylbenzene, and *n*-butylbenzene can be converted into 3-phenylpropionic acid, 2-phenylpropionic acid, and 4-phenylbutyric acid, respectively.

In the interval between the time of publication of their work and the present it has been assumed that all of these reactions are of a general nature and review articles have presented them in this light.[3,4] However, in an attempt to repeat some of these experiments we have observed that the reactions described by Friedman and coworkers could be easily duplicated, but, to date, after a large number of trials we have not been able to obtain the products reported by Reitsema and Allphin for the oxidation of longer chain arenes.

(2) R. H. Reitsema and N. L. Allphin, *J. Org. Chem.*, **27**, 27 (1962).

(3) K. B. Wiberg in "Oxidation in Organic Chemistry," part A, K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, pp 90–92.

(4) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 1061. (These authors note that the reported oxidation of ethylbenzene to phenylacetic acid has not been confirmed.)

Experimental Section

The apparatus used for the oxidations was a Parr 4501 stirrer-type, high-temperature hydrogenator of 2-l. capacity equipped with a thermocouple to monitor the temperature of the solution. Typically 0.175 mol of $Na_2Cr_2O_7 \cdot 2H_2O$ in 700 ml of water was placed in the reactor and 0.175 mol of ethylbenzene was added. The solution was brought to the required temperature rapidly with vigorous stirring and the reaction was allowed to continue for the desired time. After cooling, the resulting basic solution was extracted with ether to isolate nonacidic organic products and filtered to remove chromium(III) oxide. This precipitate was boiled in water to dislodge any remaining organic products and refiltered. The combined filtrates were acidified and any products which precipitated were collected by filtration. Finally, any residual products which remained in solution were isolated by ether extraction. The products were identified by comparison with authentic materials through melting and boiling points, ir and nmr spectroscopy, and the use of gas–liquid partition chromatography. Yields were determined gravimetrically for solid products and *via* the use of gas–liquid partition chromatography

for liquid products. The total amount of material recovered by this method was quite high (73–94%).

Results and Discussion

Several attempts were made to find the proper conditions for the conversion of ethylbenzene to phenylacetic acid. In some twenty-four different experiments the temperature was varied from 126 to 282°, the time of reaction was varied from 0.5 to 12 hr, the ratio of oxidant to reductant was varied from 2:1 to 1:2, and the pH was varied from 5 to 11. However, in every experiment the only isolable products obtained were acetophenone and benzoic acid. In general, long reaction times, high temperatures, low pH, and an excess of oxidant tended to favor the production of benzoic acid, while less vigorous conditions decreased the amount of reaction and tended to make acetophenone the main product. Some typical results are presented in Table I, no. 1–10. (Friedman and coworkers[5] have also been unable to reproduce the results reported by Reitsema and Allphin.[2]) Similarly, the only products obtained from an oxidation of *n*-propylbenzene were propiophenone, 1-phenyl-1,2-propanedione, and benzoic acid; no detectable amount of 3-phenylpropionic acid was formed (Table I, no. 20). On the other hand 2-methylnaphthalene was readily converted into 2-naphthoic acid as reported by Friedman and coworkers[1] (Table I, no. 19).

Furthermore the results of expt 17 and 18 indicate that phenylacetic acid is more readily oxidized than either ethylbenzene or acetophenone. Hence it can be concluded that under these conditions phenylacetic acid *could not* accumulate.

A possible explanation for our failure to obtain any appreciable amount of phenylacetic acid may be that a specific catalyst was present in the reactor used by Reitsema and Allphin.[6] In a very cursory investigation of this possibility we carried out the reaction in the presence of catalytic amounts of sulfur and vanadium pentoxide, but were unable to detect any major change in the product composition (Table I, no. 14 and 15). However, the existence of a specific catalyst for the formation of phenylacetic acid cannot be completely ruled out. In any case it is apparent that the applications of this reaction are not so general as was once supposed.

Registry No.—Ethylbenzene, 100-41-4; sodium dichromate, 10588-01-9.

Acknowledgment.—The authors are grateful to Professor L. Friedman and Dr. R. H. Reitsema for some helpful correspondence during the course of this work. They are also pleased to acknowledge financial assistance from the National Research Council of Canada and one of us (U. A. S.) gratefully acknowledges the receipt of the Goodfellow Scholarship for 1968.

(5) L. Friedman, personal communication, 1968. See also footnote 17 on p 1455 of ref 1.

(6) In a private communication Dr. Reitsema has informed us that their reactor, although superficially clean, had been used for Willgerodt reactions as well as numerous other experiments and that they used the same reactor for all of their experiments.

The Reaction of Silver Nitrate with Vinyl Bromides

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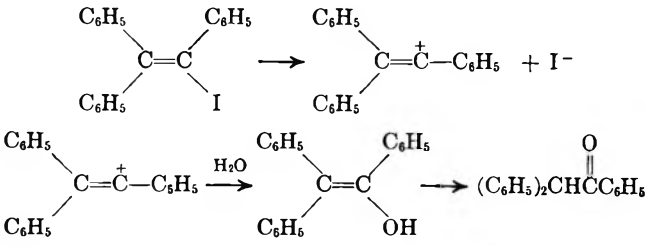
In earlier work, triarylvinyl halides were shown to solvolyze in aqueous dimethylformamide to yield halide ion and benzhydryl ketones *via* an SN1 mechanism.[2] Our work showed that the intermediate vinyl



cations exhibited a high degree of selectivity, implying that they are not more reactive than alkyl cations. Thus we have attributed the substitutional lethargy of vinyl halides to ground-state stabilization rather than to the instability of vinyl cations.

As a continuation of these studies, we sought to prepare vinyl cations that would not be stabilized by an α-aryl group. Such unstabilized vinyl cations have been implicated in the nitrosyl chloride deamination of 1,1-diphenyl-2-aminoethylene,[3] the decomposition of nitroso oxazolidones,[4] and the acid-catalyzed decomposition of vinyl triazenes.[5] The reaction of vinyl halides with silver ion suggested itself as a more general and mechanistically less complicated reaction. While the unreactivity of vinyl halides toward refluxing alcoholic silver nitrate has been noted in numerous organic texts,[6] a literature search substantiated Peterson's conclusion[7] that no definitive study of the reaction of vinyl halides with silver nitrate has appeared in the literature.

Although it is less reactive than alkyl halides with silver nitrate, β-bromostyrene afforded a quantitative yield of silver bromide within 30 min at 100° in 80% aqueous acetonitrile. Quantitative precipitations of silver bromide were also obtained with 1,1-diphenyl-2-bromoethylene and 1-bromo-2-phenylpropene within 2 hr at 130°. Triphenyliodoethylene gave an 80% yield of silver iodide after 24 hr at 130°.

The organic product isolated in all but one[8] case was the corresponding vinyl nitro compound. If a

(1) National Aeronautics and Space Administration Trainee, 1967–1969.

(2) L. L. Miller and D. A. Kaufman, *J. Amer. Chem. Soc.*, **90**, 7282 (1968).

(3) D. Y. Curtin, J. A. Kampmeier, and B. R. O'Connor, *ibid.*, **87**, 863 (1965).

(4) M. S. Newman and A. E. Weinberg, *ibid.*, **78**, 4654 (1956).

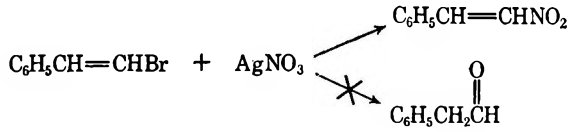
(5) W. M. Jones and F. W. Miller, *ibid.*, **89**, 1960 (1967).

(6) See, for example, R. T. Morrison and R. N. Boyd, "Organic Chemistry," 2nd ed, Allyn and Bacon, Inc., Boston, Mass., 1966, p 828; and J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p 321.

(7) P. E. Peterson and J. E. Duddey, *J. Amer. Chem. Soc.*, **85**, 2865 (1963).

(8) See Experimental Section regarding the explosion which occurred when 2-methylbromopropene was heated with silver nitrate.

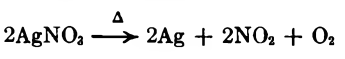
vinyl cation were involved in these reactions, one would expect to obtain a carbonyl product by analogy with our earlier work.[2] The formation of nitro compounds



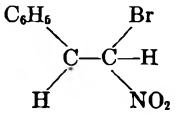
and no carbonyl products, therefore, suggested that silver assisted heterolytic cleavage was not involved in this reaction. Two further observations appear to vitiate the possible intermediacy of vinyl cations: (1) 1,1-diphenyl-2-bromoethylene gave 1,1-diphenyl-2-nitroethylene and not the rearranged product, 1,2-diphenyl-1-nitroethylene, expected for carbonium ion participation;[3-5] (2) triphenylbromoethylene reacted much more slowly with silver ion than did any of the other halides. The α-aryl group present in the triphenyl compound should have stabilized an intermediate carbonium ion and led to a rate enhancement, not deceleration.

Addition–elimination mechanisms with various nitrogen oxide species as addends were then considered. Nitrite ion was eliminated as an intermediate on the basis of the reaction of β-bromostyrene with sodium nitrite. After a reaction time of 2.5 hr at 130°, nmr did show approximately 20% consumption of the starting material and the appearance of a corresponding amount of β-nitrostyrene. However, during this reaction time β-bromostyrene is allowed to react quantitatively with silver nitrate. Thus nitrite ion cannot be a reacting intermediate. Similarly, nitrate was eliminated since heating with β-bromostyrene for 2 hr at 130° gave only starting material. Finally, nitronium ion involvement was rendered unlikely by our inability to trap it with anisole.

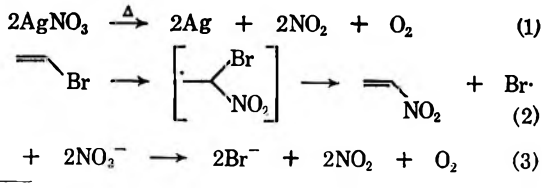
The participation of nitrogen dioxide as the nitrating species seems quite plausible. Silver nitrate is known to decompose with heat according to the following equation[9] and a brown irritating gas was produced in



our reaction tubes when excess silver nitrate was used. The ability of NO_2 to serve as a vinyl nitrating agent was shown by Stevens,[10] who prepared β-nitrostyrene by passing NO_2 through an ethereal solution of β-bromostyrene. It was proposed that products arise *via* the following radical intermediate.



Equations 1–3 are consistent with both our experimental work and the above reactions.



(9) T. Moeller, "Qualitative Analysis," 1st ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1958, p 255.

(10) T. E. Stevens, *J. Org. Chem.*, **25**, 1658 (1960).

It is possible that reaction 1 is necessary only to initiate a radical chain and that the main source of NO_2 is from eq 3. In agreement with this possibility, silver ion was found to react catalytically. As was previously noted, sodium nitrate did not react with β-bromostyrene. In the presence of catalytic amounts of silver nitrate, however, sodium nitrate produced much more β-nitrostyrene than could be accounted for by the stoichiometric amount of silver ion. The catalytic effect could also be explained by replacing eq 1 with a more complex set of reactions involving hydroxyl radicals. Participation of acetonitrile in the radical chain is an additional complicating possibility.

As a conclusion to our investigation, silver fluoroborate was substituted for silver nitrate in an attempt to avoid the complicating addition-type reaction found with silver nitrate. However, reaction of β-bromostyrene with silver fluoroborate for 6 hr at 130° and for 24 hr at 100° showed no silver bromide formation. It seems apparent, therefore, that, although silver nitrate does give a silver bromide precipitate with vinyl bromides, this sort of reaction is not a useful route to vinyl cations.

Experimental Section

1,1-Diphenyl-2-bromoethylene was prepared according to the method of Elderfield[11] with a 70% yield of recrystallized product. Recrystallization was successful using Skellysolve H after attempts with methanol had failed. The nmr spectrum showed singlets at τ 3.32 (1 H), 2.84 (5 H), and 2.72 (5 H).

1,1,2-Triphenylbromoethylene was prepared according to the method of Koelsch[12] in 96% yield with mp 116° (lit.[12] mp 114–115.5°).

1,1,2-Triphenyliodoethylene was prepared according to the method of Koelsch[12] *via* addition of iodine to the Grignard of the corresponding bromide in 78% yield, mp 126–128° (lit.[12] mp 125–126°).

1-Bromo-2-phenylpropene was prepared by dehydrobromination of the dibromide through refluxing with 40% alcoholic KOH for 10 hr. The product was purified by vacuum distillation [81–84° (3.5–4.0 mm)] with a 75% yield. The dibromide was obtained by slow addition of Br_2 to an ethereal solution of α-methylstyrene.

β-Nitrostyrene was prepared by the method of Worrall[13] in which nitromethane was condensed with benzaldehyde in the presence of sodium hydroxide. The intermediate carbinol was dehydrated by dropwise addition to dilute hydrochloric acid. Recrystallization from Skellysolve gave yellow needles, mp 55.5–57° (lit.[13] mp 56–58°).

Cleavage Reactions (General).—All reactions of the vinyl halides with silver nitrate were carried out in 80% aqueous acetonitrile in heavy-walled sealed tubes at 130–135° unless otherwise noted. Aqueous ethanol was rejected as a solvent system for blank runs with silver nitrate gave considerable amounts of elemental silver when heated at 130° for periods of 2 hr or longer. A small molar excess of the intended nitrating agent was used. Reaction work-up consisted of filtering off the silver bromide precipitate when present and then concentrating the solution on the rotary evaporator to remove sufficient acetonitrile so as to render the solution extractable with ether. The combined ether layers were extracted with aqueous sodium carbonate to remove any acidic products. The ether layer was then dried and concentrated to yield a crude product which was purified by either recrystallization or column chromatography.

β-Bromostyrene with Silver Nitrate.—Quantitative reaction occurred within 2 hr at 130° as judged by recovery of the theoretical amount of silver bromide and by the complete disappearance of starting material *via* nmr. β-Nitrostyrene and benzoic acid were isolated as products in a ratio of 9:1, the benzoic

(11) R. C. Elderfield and T. P. King, *J. Amer. Chem. Soc.*, **76**, 5436 (1954).

(12) C. F. Koelsch, *ibid.*, **54**, 2045 (1932).

(13) D. E. Worrall, *Org. Syn.*, **9**, 66 (1929).

acid probably being an oxidation product of the initially formed nitro compound. Subsequent reactions showed that quantitative reaction could be achieved at 100° within 30 min and that 10% reaction was reached after 30 min at 80°. At these shorter times, β-nitrostyrene was the only reaction product found. Identification of β-nitrostyrene was made through comparison of spectra and melting points with an independently prepared sample.

1,1-Diphenyl-2-bromoethylene with Silver Nitrate.—Quantitative reaction was shown after 5 hr at 130°. The weight of crude product obtained represented quantitative conversion into 1,1-diphenyl-2-nitroethylene. The crude product was recrystallized from Skellysolve H to give yellow needles, mp 86–88° (lit.[14] mp 86–88°), which gave an nmr spectrum which was essentially identical with that of the crude product and as expected for the nitro olefin. Elemental analysis gave results expected for the nitro compound.

1-Bromo-2-phenylpropene with Silver Nitrate.—Complete reaction was reached after 2 hr at 130°. The crude product was initially purified by vacuum distillation [90–100° (0.5–0.75 mm)]. Final purification was achieved through chromatography on silica gel. The 2-phenyl-1-nitropropene was eluted with Skellysolve H. Minimum yield was 75%. The ir spectrum showed prominent peaks at 6.38, 6.61, and 7.46 μ;[15] mass spectrum *m/e* 163 (P, 9%), 129 (P − 34, 33%), 117 (P − 46, 36%), 116 (P − 47, 37%), 115 (P − 48, 100%), 91 (P − 72, 78%), 77 (P − 86, 73%).

Triphenylbromoethylene with Silver Nitrate.—Only a trace of silver bromide was seen after heating for 6 hr at 130°. Reaction work-up yielded only unreacted starting material.

Triphenyliodoethylene with Silver Nitrate.—After 24 hr at 130°, 80% reaction was reached. The crude product obtained in 75% yield was purified by chromatographing over silica gel. Triphenylnitroethylene was eluted with 20% benzene–Skellysolve H. Recrystallization from Skellysolve yielded yellow needles with mp 176–178° (lit.[16,17] mp 175–176°); mass spectrum *m/e* 301 (P − 48%), 255 (P − 46, 100%), 253 (P − 48, 33%), 178 (P − 123, 22%).

1-Bromo-2-methylpropene.—The reaction of this vinyl bromide with silver nitrate resulted in a rather violent explosion approximately 10 min after the sealed tube was immersed in the oil bath at 130°. The magnitude of the explosion appeared to be too large to be accounted for by simple increased vapor pressure of the solvent system. A preliminary run with small amounts (~250 mg) of the halide gave no explosion and a silver bromide precipitate formed. The explosion occurred when larger amounts (3.0 g) of halide were used for product study.

Registry No.—Silver nitrate, 7761-88-8; 2-phenyl-1-nitropropene, 15795-70-7.

(14) R. Anschutz and A. Hilbert, *Ber.*, **54**, 1854 (1921).
(15) J. F. Brown, Jr., *J. Amer. Chem. Soc.*, **77**, 6341 (1955).
(16) E. A. Shilov, *J. Russ. Phys. Chim. Soc.*, **62**, 95 (1930).
(17) L. Hellerman and R. Garner, *J. Amer. Chem. Soc.*, **57**, 139 (1935).

The Hydrogen-Bonding Basicity of Aryl Alkyl Ketones

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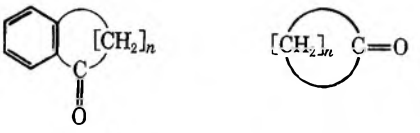
We wish to report the results of experiments which define systems for the study of conjugation effects on the hydrogen-bonding propensity of aryl alkyl ketones,[2,3] and to propose a tentative interpretation of these effects.

(1) To whom inquiries should be addressed.
(2) We have terminated research in this area and invite interested researchers to pursue a more complete investigation.
(3) There have been numerous studies of hydrogen bonding between ketones and phenols; yet for several reasons conclusions based on many such investigations must now be considered tentative. T. D. Epley and R. S. Drago [*J. Amer. Chem. Soc.*, **89**, 5770 (1967)] have published a succinct review of the problems involved.

Bellamy and Pace[4] have observed that benzaldehyde and acetaldehyde appear to be hydrogen-bonding bases of comparable strength, and that acetone is a slightly better hydrogen-bonding base than acetophenone. From data pertaining to these and other compounds they were led to the conclusion that conjugation has little effect on the hydrogen-bonding propensity, and that it sometimes produces inexplicable disparities.[4]

It seemed to us that intuitively one would expect that resonance interaction with an aryl group would increase the hydrogen-bonding basicity of a carbonyl group, and we envisaged a system in which the extent of orbital overlap with an aryl group might be controlled without drastically changing the nature of the carbonyl group in other respects.

Hydrogen-bonding basicities were determined for a series of benzocyclanones (**1–4**) and for a corresponding series of cyclanones (**5–8**). The difference ($\Delta\nu_{OH}$)



1, $n=2$
2, $n=3$
3, $n=4$
4, $n=5$

5, $n=4$
6, $n=5$
7, $n=6$
8, $n=7$

between the O—H stretching frequency of phenol alone in carbon tetrachloride and that of phenol in carbon tetrachloride containing a benzocyclanone or cyclanone was assumed to be proportional to the strength of the C=O···HOC_6H_5 hydrogen bond.[3] The magnitude of the spectral shift was observed to decrease with increasing ring size in the benzocyclanone series, but increased with increasing ring size in the cyclanone series.[5] The data are summarized in Table I.

TABLE I
HYDROGEN-BONDING AND ULTRAVIOLET SPECTRAL DATA FOR BENZOCYCLANONES AND CYCLANONES

Benzocyclanone	$\Delta\nu_{OH}$, cm^{-1}	λ_{max}, cm^{-1} [a]	ϵ_{max} [a]	Cyclanone	$\Delta\nu_{OH}$, cm^{-1}
1	224	41,900	12,720	5	208
2	215	41,200	11,450	6	209
3	211	41,600	9,000	7	217
4	201	41,100	6,500	8	228

[a] See ref 10.

In an effort to rationalize the behavior of the benzocyclanones a working hypothesis concerning the factors that contribute most significantly to the hydrogen-bonding basicity was adopted. The relative basicity of a benzocyclanone was considered to be dependent upon (1) influences that are an intrinsic function of the ring size of the cyclanone portion, and (2) some factor which is a function of the degree of conjugation

(4) L. J. Bellamy and R. J. Pace, *Spectrochim. Acta*, **19**, 1831 (1963).
(5) The same trend for cyclanones has been observed by others[6] using CH_3OD as a hydrogen-bonding acid. Lactones and cyclic ethers were also studied. The reported trend for ethers[6] was not observed when measurements of ΔH for hydrogen-bond formation were made,[7] but the accuracy of similar enthalpy measurements has been questioned.[3]
(6) M. Tamres and S. Searles, Jr., *J. Amer. Chem. Soc.*, **81**, 2100 (1959).
(7) R. West, D. L. Powell, M. K. T. Lee, and L. S. Whatley, *ibid.*, **86**, 3227 (1964).

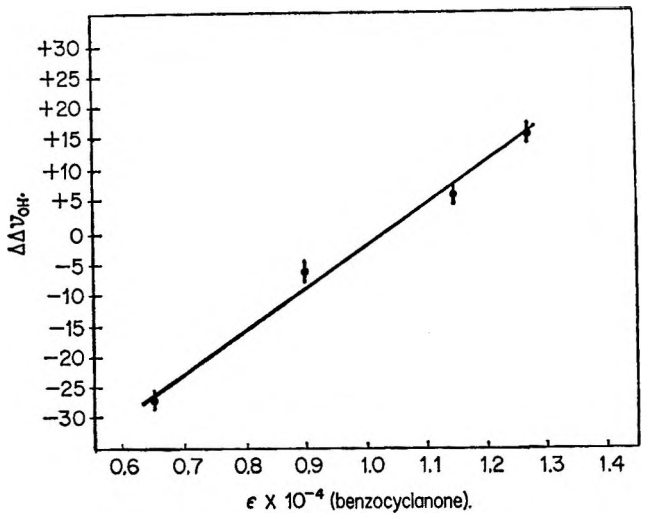


Figure 1.—A plot of the difference between the hydrogen-bonding propensity of a benzocyclanone and the corresponding cyclanone *vs.* the extinction coefficient of the intramolecular charge-transfer band of the benzocyclanone.

between the aryl and carbonyl moieties. The behavior of the cyclanones was assumed to reflect the ring-size effect. The $\Delta\nu_{OH}$ for each cyclanone was therefore subtracted from that for the corresponding benzocyclanone in an effort to correct for ring-size factors. The adjusted values ($\Delta\Delta\nu_{OH}$) were then examined to see if they could be correlated with the degree of conjugation in the benzocyclanones.

The molar absorptivity (ϵ) of the intramolecular charge-transfer band[8] of each benzocyclanone was taken as a measure of the extent of orbital overlap between the aromatic ring and the carbonyl group. The magnitude of ϵ is related to the average deviation of these groups from coplanarity.[9] For a benzocyclanone such as 1-indanone, effective overlap is reflected in the large value of ϵ, whereas in benzocyclooctanone overlap is diminished as a result of the conformational strain that would be associated with the coplanar conformation, and this diminution is reflected in a smaller ϵ (Table I).

Figure 1 is a plot of $\Delta\Delta\nu_{OH}$ *vs.* ϵ, and it is apparent that a good linear relationship exists.[13] This suggests that as the average interplanar angle of the carbonyl and aryl groups in a benzocyclanone increases, resonance interaction subsides and the influence of the electron-withdrawing inductive effect of the aryl group becomes evident.

This effect of aryl rotational conformation on H-bonding propensity does not seem to have been considered in previous studies. Although it is a relatively minor influence, it is obvious that it could contribute to the unexplained disparities noted by Bellamy.[4] Obviously, if one selected data for a particular benzocyclanone–cyclanone pair he could support opposite conclusions regarding the effect of the aryl group on $\Delta\nu_{OH}$.

We believe the conjugation effect also contributes to the hydrogen-bonding trends observed for certain other ketones. For example, Table II shows the decrease in $\Delta\nu_{OH}$ observed for phenol with two series of phenones. In both series the intrinsic steric and electronic effects of R as well as its influence on the coplanarity of the phenyl and carbonyl groups could affect the magnitude of the hydrogen-bonding shift. However, hydrogen-bonding shifts for a related series of ketones (Table III) in which the phenyl group has been replaced by methyl do not show so great a sensitivity to the nature of R. This may indicate that the decrease in $\Delta\nu_{OH}$ observed for the phenones as R increases in size is partially the result of the phenyl group being forced out of coplanarity with the carbonyl.

TABLE II

HYDROGEN-BONDING SHIFTS FOR PhCOR

R	Registry no.	$\Delta\nu_{OH}$, cm^{-1}
CH_3	98-86-2	194
CH_2CH_3	93-55-0	164
$CH(CH_3)_2$	611-70-1	166
$C(CH_3)_3$	938-16-9	150
CH_2Ph	451-40-1	138
$CH(Ph)_2$	1733-63-7	126
$C(Ph)_3$	466-37-5	109

TABLE III

HYDROGEN-BONDING SHIFTS FOR CH_3COR

R	Registry no.	$\Delta\nu_{OH}$, cm^{-1}
CH_3	67-64-1	202
CH_2CH_3	78-93-3	191
$CH(CH_3)_2$	563-80-4	188
$C(CH_3)_3$	75-97-8	188
$C(Ph)_3$	795-36-8	156

Experimental Section

Ketones.—All ketones used were either redistilled or recrystallized commercial products or were prepared by standard literature procedures. The purities of all except the trityl compounds were shown to be at least 99% as indicated by vapor phase chromatography. The trityl compounds melted over less than a 2° range and gave one spot when subjected to thin layer chromatography.

Infrared spectra were obtained on a Perkin-Elmer Model 421 grating spectrophotometer using 1-cm cells. Spectra of carbon tetrachloride solutions of phenol (0.01 *M*) plus a ketone (0.1 *M*) *vs.* a reference solution of the ketone (0.1 *M*) alone in carbon tetrachloride yielded ν_{OH} values with an estimated accuracy of ± 3 cm^{-1}.

Registry No.—**1**, 83-33-0; **2**, 529-34-0; **3**, 826-73-3; **4**, 829-14-1; **5**, 120-92-3; **6**, 108-94-1; **7**, 502-42-1; **8**, 502-49-8.

Acknowledgment.—Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

(8) S. Nagakura and J. Tanaka, *J. Chem. Phys.*, **22**, 236 (1954); S. Nagakura, *ibid.*, **23**, 1441 (1955).

(9) Assuming a cosine-squared relationship, angles of twist between the plane of the carbonyl group and that of the aryl group have been calculated.[10,11] However, the justification for such calculations has been questioned.[12]

(10) G. D. Heddon and W. Brown, *J. Amer. Chem. Soc.*, **75**, 3744 (1953).

(11) E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955).

(12) N. L. Allinger and E. S. Jones, *J. Org. Chem.*, **30**, 2165 (1965).

(13) A good linear relationship is also obtained if one plots $\Delta\nu_{OH}$ benzocyclanone *vs.* ϵ, and this result suggests identical conclusions. The linear relationship observed between $\Delta\Delta\nu_{OH}$ and ϵ does not necessarily confirm that the same ring size influences are operative in both cyclanones and benzocyclanones.

Lithium Aluminum Hydride Reduction of Phenacyl Halides. An Aryl Rearrangement Pathway[1]

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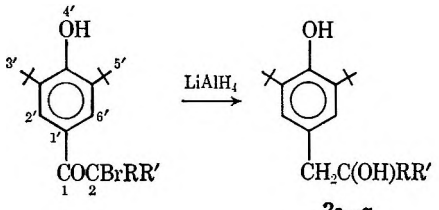
The reduction of phenacyl halides with $LiAlH_4$ has been the subject of a number of previous studies. The earlier work showed these reactions to proceed normally and to yield 1-aryl-1-ethanols[2-4] and 1-aryl-2-halo-1-ethanols.[4] The formation of the former products was favored by an excess of $LiAlH_4$. More recently, it was reported that the reduction of a series of 2-substituted 2-bromo-4'-hydroxy-3',5'-di-*t*-butylacetophenones (**1a-g**) with excess $LiAlH_4$ proceeded abnormally (eq 1).[5]

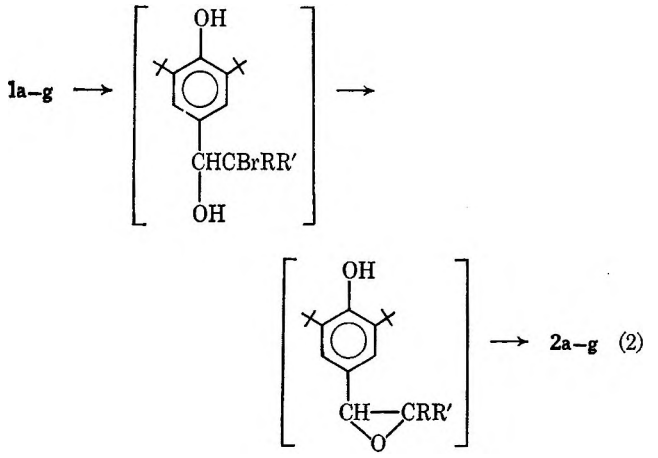


(1)

1a–g **2a–g**

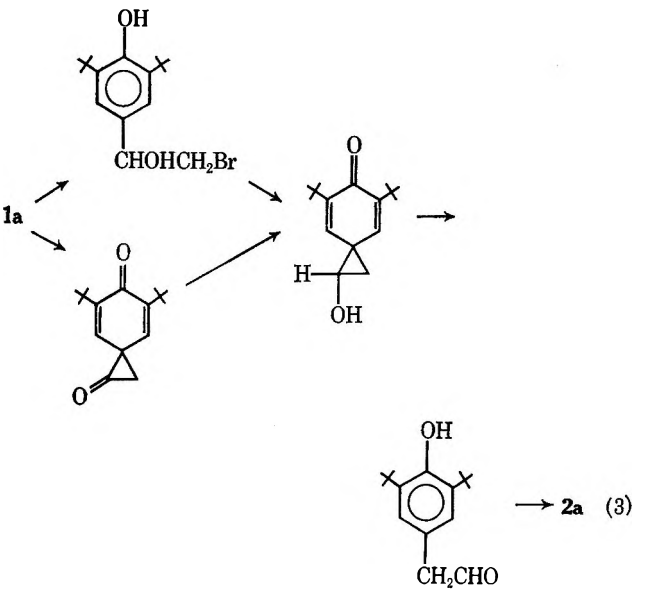
R, R': **a**, H, H; **b**, H, CH_3; **c**, H, C_2H_5; **d**, H, *n*-Pr; **e**, H, *i*-Pr; **f**, H, C_6H_5; **g**, CH_3, CH_3

The products, 1-substituted 2-(4-hydroxy-3,5-di-*t*-butylphenyl)ethanols (**2a-g**), were suggested to arise by way of a hydride attack on an epoxide intermediate (eq 2).[6]



(2)

We recently reported our findings of a study of the reduction of 2-bromo-4'-hydroxy-3',5'-di-*t*-butylacetophenone (**1a**) with $LiAlD_4$.[7] The product of this reaction, 1,-1-dideuterio-2-(4-hydroxy-3,5-di-*t*-butylphenyl)ethanol (**3**), is inconsistent with the reaction pathway previously postulated (eq 2).[5] To explain the formation of **3**, we suggested an aryl rearrangement pathway (eq 3).[6,8] For the substituted phenacyl bromides previously studied,[5] this mechanism predicts the formation of 2-substituted 2-(4-hydroxy-3,5-di-*t*-butylphenyl)ethanols (**4**) rather than the previously suggested products (**2b-g**).



(3)

It was not apparent to us why the presence of substituents at C_2 of **1** should cause a change in mechanism, from eq 3 to eq 2. We, therefore, decided to reinvestigate the earlier work. Bromides **1b**, **1c**, **1f**, and **1g** were synthesized from the corresponding 2-substituted acetophenones[9] by reaction with cupric bromide in ethyl acetate–chloroform.[10] In each case, the structure of the bromide was established by elemental analysis and nmr spectroscopy (Table I). The bromides were reduced with excess $LiAlH_4$. In each case, nmr spectroscopy of the crude reaction product (chemical shift of the methylene group and a triplet for the aliphatic OH proton in DMSO-d_6) indicated the product to be a 2-substituted 2-(4-hydroxy-3,5-di-*t*-butylphenyl)-ethanol (**4**) (Table II) in essentially pure form, rather than a 1-substituted 2-(4-hydroxy-3,5-di-*t*-butylphenyl)-ethanol (**2**) as previously reported.[5] We conclude that the reduction of 2-bromo-4'-hydroxy-3',5'-di-*t*-butylacetophenones (**1**) with $LiAlH_4$ proceeds by way of an

(1) Support of this work by the National Science Foundation (GP 6404), The City University of New York, and The General Faculty Research Committee of The City College of New York is gratefully acknowledged.

(2) S. W. Chaiken and W. G. Brown, *J. Amer. Chem. Soc.*, **71**, 122 (1949).

(3) L. W. Trevoy and W. G. Brown, *ibid.*, **71**, 1675 (1949).

(4) R. E. Lutz, R. L. Wayland, Jr., and H. G. France, *ibid.*, **72**, 5511 (1950).

(5) V. V. Ershov, A. A. Volod'kin, and N. V. Portnykh, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1632 (1966); A. A. Volod'kin, N. V. Portnykh, and V. V. Ershov, *ibid.*, 1352 (1967).

(6) For simplicity of representation, the various alkoxide ions present throughout the reaction scheme are shown as neutral hydroxyl groups.

(7) L. H. Schwartz and R. V. Flor, *Chem. Commun.*, 1129 (1968).

(8) The alternate routes shown in eq 3 cannot be distinguished by this work. Efforts to distinguish between these pathways are in progress.

(9) N. V. Portnykh, A. A. Volod'kin, and V. V. Ershov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2181 (1966).

(10) L. C. King and C. K. Ostrum, *J. Org. Chem.*, **29**, 3459 (1964).

TABLE I

PHYSICAL PROPERTIES AND YIELDS OF 2-BROMO-4′-HYDROXY-3′,5′-DI-*t*-BUTYLACETOPHENONES (1)

R, R′	% yield	Mp, °C	Found, % C	Found, % H	Found, % Br	Calcd, % C	Calcd, % H	Calcd, % Br	Nmr,[a] δ 2′,6′-ArH	3′,5′-*t*-Bu	4′-OH	R	R′
H, CH_3	57	133–134	59.85	7.37	23.54	59.83	7.38	23.41	8.00	1.50	5.86	5.33 (q)[b]	1.89 (d)[b]
H, C_2H_5	80	126–127	60.84	7.63	22.49	60.85	7.66	22.49	7.99	1.50	5.86	5.10 (t)[b]	2.22 (p)[b] (CH_2) 1.08 (t)[b] (CH_3)
H, C_6H_5	83	119–120	65.37	6.79	19.94	65.51	6.75	19.81	7.94	1.43	5.80	6.40	7.24–7.74 (m)
CH_3, CH_3	82	141–142	61.00	7.73	22.48	60.85	7.66	22.49	8.21	1.48	5.76	2.07	2.07

[a] Unless otherwise specified, all absorptions are singlets: d, doublet; t, triplet; q, quartet; p, quintet; m, multiplet. In each case, integration was consistent with the proposed assignment. [b] J = 7 cps.

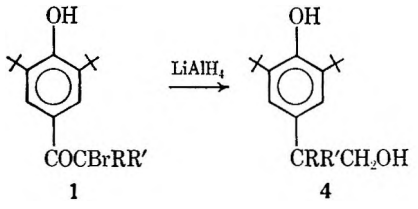
TABLE II

CHARACTERIZATION OF 2-SUBSTITUTED 2-(4-HYDROXY-3,5-DI-*t*-BUTYLPHENYL)ETHANOLS (4)

R, R′	Mp, °C	Found, % C	Found, % H	Calcd, % C	Calcd, % H	Nmr,[a,b] δ ArH	*t*-Bu	ArOH	CH_2	ROH	RO*H*[c]	R	R′
H, CH_3	93.2–94.5	77.11	10.80	77.23	10.67	7.06	1.45	5.13	3.66 (d)[d]	1.62	4.54 (t)[e]	2.85 (s)[d]	1.28 (d)[d]
H, C_2H_5	86.0–86.5	77.73	10.92	77.65	10.86	7.01	1.45	5.11	3.71 (d)[d]	1.52	4.46 (t)[e]	2.59 (p)[d]	1.76 (m) (CH_2) 0.85 (t)[d] (CH_3)
H, C_6H_5	107–108	80.70	9.13	80.94	9.26	7.10	1.42	5.11	4.11	1.58	4.70 (t)[f]	4.11	7.31
CH_3, CH_3	149.8–150.3	77.85	10.82	77.65	10.86	7.24	1.47	5.14	3.57	1.47	4.54 (t)[e]	1.32	1.32

[a] Unless otherwise specified, all absorptions are singlets: d, doublet; t, triplet; p, quintet; s, sextet; m, multiplet. In each case, integration was consistent with the proposed assignment. [b] For comparison, 2-(4-hydroxy-3,5-di-*t*-butylphenyl)ethanol (R, R′ = H, H) has the following absorptions: 7.05 (ArH), 1.45 (*t*-Bu), 5.11 (ArOH), 1.77 (ROH), 3.82 (t)[d] (CH_2O), 2.78 (t)[d] ($ArCH_2$). [c] Spectrum taken in DMSO-d_6. [d] J = 7 cps. [e] J = 5.5 cps. [f] J = 5.0 cps.

aryl rearrangement pathway (eq 4) and is independent of the substitution at C_2.[11]



1 4 (4)

Experimental Section

Melting points are corrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Unless otherwise specified, nmr spectra were determined in $CDCl_3$ solution using a Varian Associates A-60 spectrometer. Chemical shifts (δ) are reported in parts per million relative to tetramethylsilane as zero.

2-Bromo-4′-hydroxy-3′,5′-di-*t*-butylacetophenones (1).—The acetophenone (0.29 mol), cupric bromide (0.67 mol) (the preparation of **1b** is best accomplished with 0.58 mol), 330 ml of ethyl acetate, and 220 ml of chloroform were heated at reflux, with stirring, for 1.25 hr (the preparation of **1g** required 1.75-hr heating time). The cooled reaction mixture was filtered and the solvent was removed by evaporation. The dark residue was dissolved in excess $CHCl_3$–hexane and repeatedly treated with charcoal until a light colored solution was obtained. Recrystallization from hexane or $CHCl_3$–hexane yielded the product **1** (Table I).

Reduction with $LiAlH_4$.—To 0.020 mol of the phenacyl bromide (**1**) in 200 ml of anhydrous ether, cooled to 0°, was rapidly added 0.045 mol of powdered $LiAlH_4$ with vigorous stirring. The reaction mixture was heated at reflux for 3 hr with vigorous stirring. Addition of 30 ml of H_2O and 100 ml of 10% H_2SO_4, followed by drying and evaporation of the ether layer, yielded the crude product in essentially quantitative yield. In each case, nmr spectroscopy indicated the crude product to be essentially pure. Crystallization was effected from hexane to yield the pure product **4** (Table II).

(11) Preliminary results by R. V. Flor indicate that the substituents at C_3' and C_5' have a profound effect on the course of the reaction.

Registry No.—Lithium aluminium hydride, 1302-30-3; **1b**, 17055-13-9; **1c**, 17055-14-0; **1f**, 17055-17-3; **1g**, 17055-18-4; **4b**, 19510-15-7; **4c**, 19598-29-9; **4f**, 19598-30-2; **4g**, 19598-31-3.

Acknowledgment.—We thank Mr. Sidney Liebgold for his kind assistance.

The Reaction of Iodobenzene and Nickel Carbonyl in the Presence of Olefins

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In the course of our study of the reactions of organo transition metal complexes with unsaturated compounds, we observed that organo transition metal complexes derived from the reaction of transition metal carbonyls with organolithiums or active halides are reactive toward acetylenes and/or olefins.[1-3]

Bauld[4] reported that nickel carbonyl reacted with iodobenzene at 50–60° to form benzoylnickel carbonylate, $C_6H_5CoNi(CO)_nI$, as an intermediate complex, and its thermal decomposition or alcoholysis gave benzil or esters of benzoic acid, respectively.

On the other hand, acetylene insertion between the acyl and metal carbonyl groups in acyl metal carbonyls

(1) Y. Sawa, I. Hashimoto, M. Ryang, and S. Tsutsumi, *J. Org. Chem.*, **33**, 2159 (1968).

(2) S. Fukuoka, M. Ryang, and S. Tsutsumi, *ibid.*, **33**, 2959 (1968).

(3) (a) I. Rhee, M. Ryang, and S. Tsutsumi, *J. Organometal. Chem.*, **9**, 369 (1967); (b) I. Rhee, N. Mizuta, M. Ryang, and S. Tsutsumi, *Bull. Chem. Soc. Jap.*, **41**, 1417 (1968).

(4) N. L. Bauld, *Tetrahedron Lett.*, 1841 (1963).

has been reported by several groups of workers in recent years,[1,5,6] but examples of olefin insertion into an acyl metal bond are limited only butadiene insertion with acylcobalt carbonyls and intramolecular olefin insertion in ω-alkenoylcobalt carbonyls.[7,8] Benzoylnickel carbonylate is too unstable to be isolated,[4] but seems to be reactive to olefins because of the relatively positive character of the metal atom compared with the case of acylcobalt carbonyls and lithium acylnickel carbonylates. We studied the reaction of iodobenzene with nickel carbonyl in the presence of olefins such as styrene, acrylonitrile, and ethyl acrylate and obtained some interesting results.

The reaction was carried out in tetrahydrofuran or in benzene at 50–60° for 100 hr in an argon atmosphere. Slight evolution of carbon monoxide was observed in the course of the reaction. The products obtained are listed in Table I.

TABLE I

THE REACTION OF IODOBENZENE WITH NICKEL CARBONYL IN THE PRESENCE OF OLEFINS

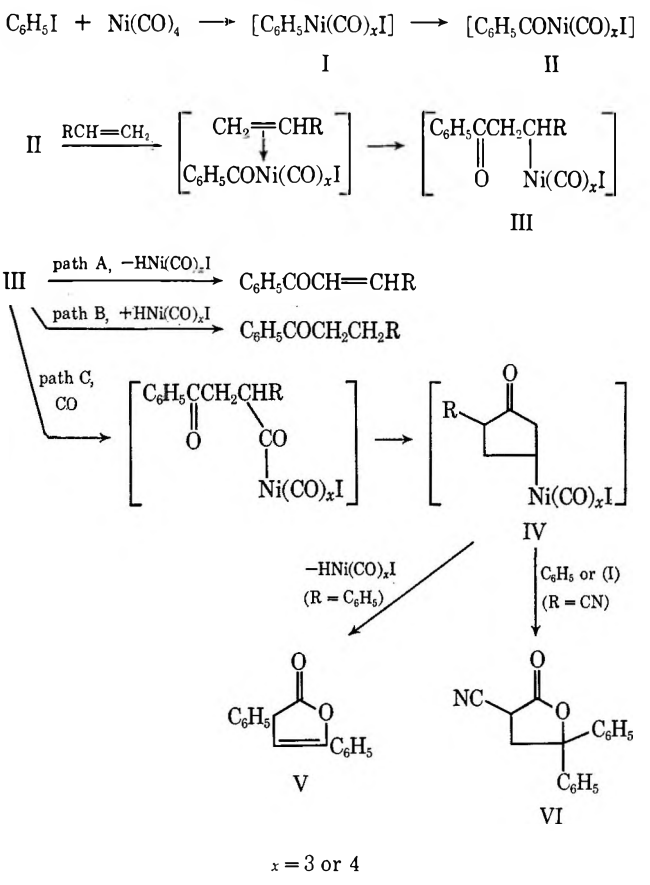
Olefin	Solvent	Products identified (yield %[a])
$CH_2=CHC_6H_5$	THF[b]	$C_6H_5COCH=CHC_6H_5$ (5)
		$C_6H_5CH=CHC_6H_5$ (4)
		Lactone V (19)
$CH_2=CHC_6H_5$	Benzene	$C_6H_5COCH=CHC_6H_5$ (1)
		$C_6H_5COCH_2CH_2C_6H_5$ (43)
		Lactone V (25)
$CH_2=CHCN$	Benzene	$C_6H_5COCH=CHCN$[c] (1)
		$C_6H_5COCH_2CH_2CN$ (29)
		Lactone VI (30)
$CH_2=CHCOOC_2H_5$	Benzene	$C_6H_5COCH_2CH_2COOC_2H_5$[d] (24)

[a] Based on iodobenzene consumed. [b] Considerable amounts of benzoic acid esters were formed by the cleavage of the tetrahydrofuran (THF) ring. This kind of side reaction was observed in another system. For example, see E. Yoshisato and S. Tsutsumi, *J. Org. Chem.*, **33**, 869 (1968). [c] See Experimental Section. [d] Identified as 3-benzoylpropionic acid.

The above results can be explained by a stepwise insertion mechanism as shown in Scheme I; herein the coordination number of carbon monoxide is not certain because of the possibility of carbon monoxide exchange reaction in solution.

As shown in Table I, the reactions of styrene were considerably influenced by the solvent. In tetrahydrofuran solution, the products isolated were all unsaturated compounds but in benzene saturated compounds were obtained mainly. The latter might be produced by the reduction of III by the nickel hydride complex shown by path B. Although there is no certain evidence for a nickel hydride complex, this result suggests that the coordinating ability of the solvent, on which the stability of the eliminated hydride complex depends, plays an important role for the product distribution. This mechanism is in agreement with the fact that, when the reaction (in benzene solution) was carried out in the presence of an appropriate base such as dicyclohexylethylamine, only unsaturated benzalacetophenone was obtained in 19% yield and no saturated benzylacetophenone was detected. In this case the eliminated nickel hydride complex (path A) might be

SCHEME I



$x = 3$ or 4

stabilized as a stable salt such as $[BH]^+ [Ni(CO)_xI]^-$ (B = base), which would no longer have the reducing ability of III by path B.

While the final structures of lactones depend on individual olefins, their formation is considered to proceed *via* path C, *i.e.*, insertion of a second carbonyl group in carbon nickel bond in III followed by cyclization to form the complex IV, from which unsaturated or saturated lactone is produced by the elimination of the nickel hydride complex or the cleavage of carbon nickel bond by iodobenzene or I, respectively. Although the formation of lactones from acetylenes and acyl metal carbonyls were reported,[1,5,6] the present results are the first examples of the formation of lactones from olefins. This is, at least in part, due to the high ability of nickel, compared with other metals, to absorb or exchange carbon monoxide in solution.[9] Another carbon monoxide absorbed is considered to occupy the coordinately unsaturated site caused by the insertion of second carbonyl group in III and allows the formation of lactones. In the case of acetylenes, the resulting double bond may take this role forming the relatively stable π-lactenyl metal complexes.[5] Thus lactones can be prepared more easily without absorption of carbon monoxide.

When butadiene or cyclohexene was used as the olefin, these olefins were recovered unreacted. In the case of 1-octene, infrared (ir) spectroscopy showed the

(5) R. F. Heck, *J. Amer. Chem. Soc.*, **86**, 2819 (1964).
(6) L. Cassar and G. P. Chiusoli, *Tetrahedron Lett.*, 3295 (1965).
(7) R. F. Heck, *J. Amer. Chem. Soc.*, **85**, 3381 (1963).
(8) R. F. Heck, *ibid.*, **85**, 3116 (1963).

(9) Thus nickel carbonyl can be prepared from the reaction of carbon monoxide at atmospheric pressure with nickel halide in the presence of a reducing agent and catalysts in aqueous solution. For the rate of exchange reaction of various metal carbonyls with carbon monoxide in solution, see D. F. Keeley and R. E. Johnson, *J. Inorg. Nucl. Chem.*, **11**, 33 (1959); F. Basalo and A. Wojicki, *J. Amer. Chem. Soc.*, **83**, 520 (1961).

presence of lactones among the products; however, these could not be isolated in pure form owing to the easy rearrangement during the column chromatography and recrystallization. Further investigation concerning the mechanism and application of this reaction is being undertaken.

Experimental Section[10]

Commercially available iodobenzene was treated with concentrated sulfuric acid, washed with water, and then distilled. Nickel carbonyl was prepared by the procedure of Chiusoli and Mondelli.[11] Styrene and ethyl acrylate were distilled under reduced pressure before use. Tetrahydrofuran was refluxed with sodium and benzophenone until the solution turned blue and was then distilled. All solvents were saturated with argon before use.

The Reaction of Iodobenzene with Nickel Carbonyl in the Presence of Styrene. A. In Tetrahydrofuran.—A mixture of 10.2 g (0.05 mol) of iodobenzene, 8.5 g (0.05 mol) of nickel carbonyl, and 5.2 g (0.05 mol) of styrene in 50 ml of tetrahydrofuran was stirred at 50–60° for 100 hr under an atmosphere of argon. The reaction mixture was filtered to remove nickel iodide deposited during the reaction. The filtrate was distilled under reduced pressure to give the following fractions: fraction 1, bp 140–190° (0.5 mm), 2.5 g; fraction 2, bp 190–230° (0.5 mm), 2.3 g; and 1.0 g of polymeric residue. The ir spectrum of fraction 1 showed that this fraction consisted mainly of esters of benzoic acid, which were probably formed from the cleavage of tetrahydrofuran. Chromatography of fraction 1 on silica gel using petroleum benzine (bp 70–80°) as an eluent gave 0.4 g of white crystals and 0.5 g of pale yellow crystals. The former was recrystallized from ethanol to give white needles, mp 124°, and was found to be *trans*-stilbene by mixture melting point with an authentic sample. The latter was also recrystallized from ethanol to give pale yellow needles, mp 56°, and was identified as benzalacetophenone by mixture melting point with an authentic sample. Fraction 2 crystallized on standing and these crystals were recrystallized from ethanol to give 1.5 g of white crystals, mp 109°. This compound was shown to be 2,4-diphenyl-$\Delta^{3,4}$-crotolactone (V) (lit.[12] mp 109–110°) by the following data. The ir spectrum showed a carbonyl band at 1760 cm^{-1} and the nmr spectrum in $CDCl_3$ showed signals at τ 4.10 (one proton) and at 2.2–2.8 (ten aromatic protons and one olefinic proton).

Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.34; H, 5.12; mol wt, 236. Found: C, 80.98; H, 5.17; mol wt (in benzene), 240.

B. In Benzene.—A mixture of 10.2 g (0.05 mol) of iodobenzene, 8.5 g (0.05 mol) of nickel carbonyl, and 5.2 g (0.05 mol) of styrene in 50 ml of benzene was treated in a similar manner to that described above. From the reaction mixture 4.8 g of iodobenzene was recovered and vacuum distillation gave two fractions: fraction 1, bp 130–160° (1 mm), 2.7 g; and fraction 2, bp 190–230° (1 mm), 2.5 g. Chromatography of fraction 1 gave a small amount (<0.1 g) of benzalacetophenone and 2.5 of benzylacetophenone, mp 72–73° (lit. mp 73°), and no depression resulted on admixture with an authentic sample. Fraction 2 was triturated in petroleum ether (bp 50–60°) and 1.4 g of 2,4-diphenyl-$\Delta^{3,4}$-crotolactone (V) was obtained.

C. In the Presence of Amine.—An equimolar mixture (0.05 mol) of iodobenzene, nickel carbonyl, styrene, and dicyclohexylethylamine in 50 ml of benzene was treated as described above. Distillation at reduced pressure gave a fraction of bp 130–150° (0.7 mm), 2.4 g. Chromatography of this fraction gave 2.0 g of benzalacetophenone; no benzylacetophenone was detected.

The Reaction of Iodobenzene and Nickel Carbonyl in the Presence of Acrylonitrile.—A mixture of 10.2 g (0.05 mol) of iodobenzene, 8.5 g (0.05 mol) of nickel carbonyl, and 5.3 g (0.1 mol) of acrylonitrile in 50 ml of benzene was treated as described above. Distillation at reduced pressure gave two fractions: fraction 1, bp 135–170° (1 mm), 2.7 g; and fraction 2, bp 185–240° (1 mm), 2.5 g. Fraction 1, which crystallized on standing, was recrystallized from ethanol to give 2.3 g of white needles, mp 70°. This compound was identified as 3-benzoylpropionitrile as follows. The ir spectrum showed a nitrile band at 2270 and a carbonyl band at 1680 cm^{-1}. The nmr spectrum showed a triplet at τ 7.27 (two protons), a triplet at 6.67 (two protons), and a broad band at 2.0–2.8 (five protons).

Anal. Calcd for $C_{10}H_9ON$: C, 75.45; H, 5.70; N, 8.80; mol wt, 159. Found: C, 75.71; H, 5.88; N, 8.54; mol wt (in N,N-dimethylformamide), 159.

The ir spectrum of fraction 1 showed also weak bands at 2250, 1675, and 1610 cm^{-1}, indicating the presence of small amounts of unsaturated 3-benzoylacrylonitrile. Fraction 2, which crystallized on standing, was recrystallized from benzene and petroleum benzine (bp 70–80°) to give 1.8 g of white crystals, mp 123–124°. This compound showed in its ir spectrum a nitrile band at 2270 and a carbonyl band at 1742 cm^{-1} but showed no bands characteristic for ester group. The nmr spectrum in $CDCl_3$ showed a doublet at τ 6.70 (two protons), a triplet at 4.15 (one proton), and a broad band at 2.0–3.0 (ten protons).

Anal. Calcd for $C_{17}H_{13}O_2N$: C, 77.55; H, 4.98; N, 5.32; mol wt, 263. Found: C, 77.84; H, 5.03; N, 5.13; mol wt (in N,N-dimethylformamide), 265.

Thus this material was assigned the structure of 4,4-diphenyl-2-cyanobutylolactone (VI).

The Reaction of Iodobenzene with Nickel Carbonyl in the Presence of Ethyl Acetate.—A mixture of 10.2 g (0.05 mol) of iodobenzene, 8.5 g (0.05 mol) of nickel carbonyl, and 5.0 g (0.05 mol) of ethyl acrylate was treated as described above. The fraction, bp 100–160° (1.5 mm), 3.5 g, was hydrolyzed by KOH in diethylene glycol to give 2.5 g of white leaflets. These crystals, recrystallized from ethanol and water, mp 116°, was identified as 3-benzoylpropionic acid by mixture melting point with an authentic sample.

Registry No.—Iodobenzene, 591-50-4; nickel carbonyl, 13463-39-3; 3-benzoylpropionitrile, 5343-98-6; 4,4-diphenyl-2-cyanobutylolactone, 19598-21-1.

(10) Nmr spectra were taken with a Model JNM-G-60 spectrometer (Japan Electron Optics Laboratory Co.). Infrared spectra were taken with a Shimazu IR-27C spectrometer. Molecular weights were determined in benzene or in N,N-dimethylformamide by using a Mechrolab vapor pressure osmometer. Melting points and boiling points are uncorrected.

(11) G. P. Chiusoli and G. Mondelli, *Chem. Ind.* (Milan), **43**, 259 (1961).

(12) A. Anshütz and W. F. Montfort, *Ann.*, **284**, 5 (1895).

Preparation and Spectral Characteristics of Some Allyltins. Nature of Allyltin Interactions

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In the course of our kinetic study of acid cleavage reaction,[1] we have observed a red shift in the uv spectrum of allyltin compounds compared with that of vinyl derivatives.

A red shift is observed in the spectrum of allylmercuric iodide, too.[2] This suggests an interaction between the allyl group and the metal atom. Spectral data for a series of $R_3M(CH_2)_nCH{=}CH_2$ compounds (in which M = C, Si, Ge, Sn; R = alkyl or halogen, and n = 1 or 2) have been reported.[3] The results show that the red shift increases with the atomic weight of M. It was proposed that these shifts result from an interaction between the σ C–M bond and the allylic double bond.

As a means of probing further into the cause of this red shift, we have prepared, and examined some spec-

(1) H. G. Kuivila and J. A. Verdone, *Tetrahedron Lett.*, 119 (1964).

(2) M. M. Kreevoy, P. J. Steinwand, and T. S. Straub, *J. Org. Chem.*, **31**, 4291 (1966).

(3) V. A. Petukhov, V. F. Mironov, and P. P. Shorygin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2203 (1964).

TABLE I
NMR SPECTRAL DATA OF ALLYLTIN COMPOUNDS[a]

Compound	Registry no.	δ, ppm SnCH₃	δ, ppm SnCH₂–		J, cps ¹¹⁹SnCH₃	J, cps ¹¹⁷SnCH₃	J, cps SnCH₂–	
$(CH_2{=}CHCH_2)_4Sn$	7393-43-3		8.04	8.18			63.0	63.1
$(CH_2{=}CHCH_2)_3RSn$								
R = CH_3	19713-79-2	9.90	8.08	8.21	50.9	48.6	63.9	64.5
R = C_6H_5	19713-80-5		7.87	8.03			65.8	66.1
R = n-C_3F_7			7.73	7.88			69.4	70.2
$(CH_2{=}CHCH_2)_2R_2Sn$								
R = CH_3	19434-15-2	9.89	8.11	8.27	52.0	49.8	65.3	65.8
R = C_6H_5	10074-32-5		7.72	7.85			68.3	68.6
R = C_2F_5			7.47	7.60			75.7	77.5
$(CH_2{=}CHCH_2)R_3Sn$								
R = CH_3	762-73-2	9.90	8.18	8.31	53.1	51.0	66.0	65.5
R = C_6H_5	76-63-1		7.53	7.67			75.6	75.6

[a] Spectra were obtained at 60 Mc by a Varian Associates A-60A spectrometer using 20% carbon tetrachloride solution.

tral characteristics of, a series of allyltins in which the electronegativity of the groups on the tin atom is varied.

Results and Discussion

Absorption spectra of the compounds were measured in n-hexane and acetonitrile in order to test the effect of solvent polarity. In each case, a strong band was observed in the 190–220-mμ region. The locations of the maxima and extinction coefficients are given in Table I.

In general, the greater the number of allyl groups attached to tin, the lower is the stability. This may be the cause, in some cases, for the lower extinction coefficients than expected in some of the compounds.

The presence of a strong band in the 190–220-mμ region with an extinction coefficient around 10,000 per allyl group requires comment. Thus the values for allyltri-n-propyltin, diallyldi-n-propyltin, and triallyl-n-propyltin show values of 1.1×10^4, 1.80×10^4, and 2.88×10^4, respectively. Clearly, these intense absorptions are due to the combination of the allylic group and the metal atom. The red shift resulting upon change from the nonpolar solvent n-hexane to the more polar acetonitrile suggests that an electron polarization already present in the ground state is increased in the excited state. One possible interaction in the ground state is a π–π interaction between the two chromophores through space as suggested for allylmercuric iodide.[2] The other is a hyperconjugation-like interaction, I–II, between the σ C–Sn bond

$$\underset{\text{I}}{CH_2{=}CHCH_2SnR_3} \;\updownarrow\; \underset{\text{II}}{\bar{C}H_2CH{=}CH_2\overset{+}{S}nR_3 \longleftrightarrow CH_2{=}CH\bar{C}H_2\overset{+}{S}nR_3}$$

and the allylic double bond, as has been suggested for allyl compounds of the group IVB metals[3] and for α,β-unsaturated sulfides.[4] On the basis of our data we tend to suggest the latter possibility. If the tin atom functions as an electron π acceptor, substitution of alkyl groups by perfluoroalkyl groups should result in a red shift due to a decrease in electron density at the tin atom. As a matter of fact, the observed effect is in the opposite direction, the blue shift being about 10 mμ in the perfluoroalkyl derivatives. On the other hand, perfluoroalkyl groups should strengthen the σ allyl carbon–tin bond with the result that the hyperconjugation-like interaction would be smaller than in alkyl derivatives, and a blue shift should be observed. This is the case. Thus the red shifts observed in a series of allyltin compounds may be expressed in terms of an interaction between the σ allyl–tin bond and the allyl group (I–II) in the ground state. This also accounts for the high reactivity toward electrophilic attack.

Other spectral characteristics lend support to this type of formulation. Substitution of perfluoroalkyl for alkyl causes a 10-cm^{-1} shift to higher wavelength $\nu_{C=C}$. If the double bond were functioning as a donor into vacant d orbitals of the tin atom, the opposite effect should be observed. The increase of $\nu_{Sn-C(allyl)}$ and J_{SnCH_2-} in perfluoroalkyl derivatives seem to suggest the strengthening of the σ allyl carbon–tin bond.

Experimental Section

Materials.—Six new allyltin compounds have been prepared along with ten other known analogs. Typical procedures are described for the preparation of diallylbis(pentafluoroethyl)tin and triallylpentafluoroethyltin. All preparative work was done in an atmosphere of argon.

Diallylbis(pentafluoroethyl)tin and Triallylpentafluoroethyltin.—Anhydrous ether was obtained by refluxing commercial ether over $LiAlH_4$ under the atmosphere of argon. Pentafluoroethyl iodide (0.28 mol, 46.0 g) was placed in 400 ml of anhydrous ether in a 1-l. three-necked flask with a mechanical stirrer and two pressure-equalized dropping funnels which were immersed in a Dry Ice–acetone cooling bath. Methyllithium (0.17 mol, 108 ml of 1.6 M solution in ether) was added to pentafluoroethyl iodide over a period of 10 min. The reaction mixture was stirred for 5 min, and then allyltin bromides mixture[5] was added. The reaction mixture was again stirred for 4 hr during which time the temperature was allowed to rise up to that of the room. It was concentrated, filtered, and the filtrate was distilled under reduced pressure. The distillate was fractionally distilled over a column (height of 15 cm; packed with Heli-Pack stainless steel, 0.05 × 0.100 × 0.100 in.) to give diallylbis(pentafluoroethyl)tin [bp 48° (3.1 mm); ir (neat) 1631 ($\nu_{C=C}$), 909 (γ_{C-H}), 500 cm^{-1} ($\nu_{Sn-(allyl)}$); nmr (CCl_4) 7.47, 7.60 ppm ($SnCH_2$–), J = 75.7, 77.5 cps ($SnCH_2$–) (*Anal.* Calcd for $C_{10}F_{10}H_{10}Sn$: C, 27.37; F, 43.20; H, 2.30. Found: C, 27.77; F, 43.25; H, 2.64)] and triallylpentafluoroethyltin [bp 58° (2.4 mm) (*Anal.* Calcd for $C_{11}F_5H_{15}Sn$: C, 36.61; H, 4.19; Sn, 32.89. Found: C, 36.54; H, 4.10; Sn, 32.8)].

(4) H. P. Koch, *J. Chem. Soc.*, 387 (1949).

(5) The direct synthesis of diallyltin dibromide by Shishido and Takeda [*J. Org. Chem.*, **26**, (1961)] resulted in the mixture of diallyltin dibromide and triallyltin bromide.

Triallylheptafluoro-*n*-propyltin was prepared similarly: bp 64–68° (2.7 mm); ir (neat) 1630 ($\nu_{C=C}$), 896 (γ_{C-H}), 497 cm^{-1} ($\nu_{Sn-C(allyl)}$); nmr (CCl_4) 7.73, 7.88 ppm ($SnCH_2$–), J = 69.4, 70.2 cps ($SnCH_2$–). *Anal.* Calcd for $C_{12}H_7F_{15}Sn$: C, 35.07; F, 32.36; H, 3.68; Sn, 28.88. Found: C, 36.09; F, 31.45; H, 3.85; Sn, 27.8.

Alkyl derivatives were prepared from alkyltin chlorides and allylmagnesium halides. New compounds are as follows: triallylmethyltin [bp 100–101° (23 mm); ir (neat) 1620 ($\nu_{C=C}$), 880 (γ_{C-H}), 486 cm^{-1} ($\nu_{Sn-C(allyl)}$); nmr (CCl_4) 9.90 ($SnCH_3$), 8.08, 8.21 ppm ($SnCH_2$–), J = 48.6 ($^{117}SnCH_3$), 50.9 ($^{119}SnCH_3$), 63.9, 64.5 cps ($SnCH_2$–) (*Anal.* Calcd for $C_{10}H_{18}Sn$: C, 46.72; H, 7.06; Sn, 46.21. Found: C, 46.97; H, 7.25; Sn, 46.5)]; triallylethyltin [bp 60–61 (0.6 mm); ir (neat) 1621 ($\nu_{C=C}$), 881 (γ_{C-H}), 487 cm^{-1} ($\nu_{Sn-C(allyl)}$) (*Anal.* Calcd for $C_{11}H_{20}Sn$: C, 48.75; H, 7.44; Sn, 43.80. Found: C, 48.52; H, 7.37; Sn, 44.0)]; triallyl-*n*-propyltin [bp 51–52 (0.2 mm); ir (neat) 1623 ($\nu_{C=C}$), 882 (γ_{C-H}), 487 cm^{-1} ($\nu_{Sn-C(allyl)}$) (*Anal.* Calcd for $C_{12}H_{22}Sn$: C, 50.57; H, 7.78; Sn, 41.65. Found: C, 50.85; H, 7.94; Sn, 42.0)].

Other spectral data are as follows: triallyl-*n*-propyltin [ir (neat) 1623 ($\nu_{C=C}$), 882 (γ_{C-H}), 487 cm^{-1} ($\nu_{Sn-C(allyl)}$)]; diallyldiethyltin [ir (neat) 1621 ($\nu_{C=C}$), 879 (γ_{C-H}), 488 cm^{-1} ($\nu_{Sn-C(allyl)}$)]; diallyldimethyltin [ir (neat) 1622 ($\nu_{C=C}$), 882 (γ_{C-H}), 488 cm^{-1} ($\nu_{Sn-C(allyl)}$); nmr (CCl_4) 9.89 ($SnCH_3$), 8.11, 8.27 ppm ($SnCH_2$–), J = 49.8 ($^{117}SnCH_3$), 52.0 ($^{119}SnCH_3$), 65.3, 65.8 cps ($SnCH_2$–)].

Measurements of Electronic Absorption Spectra.—The solvents were all spectrograde and were used, as supplied, without further purification. The solutions were made under argon, and concentrations were such as to give optical densities between 0.3 and 0.7 at the maximum. The spectra were obtained with a Cary 14 spectrophotometer, using 1-mm cells.

Registry No.—Diallylbis(pentafluoroethyltin), 19647-32-6; triallylpentafluoroethyltin, 19713-76-9; triallylheptafluoro-*n*-propyltin, 19647-33-7; triallylethyltin, 19713-77-0.

The Reaction of Dimethylmethylchromium Carbenoids with Olefins

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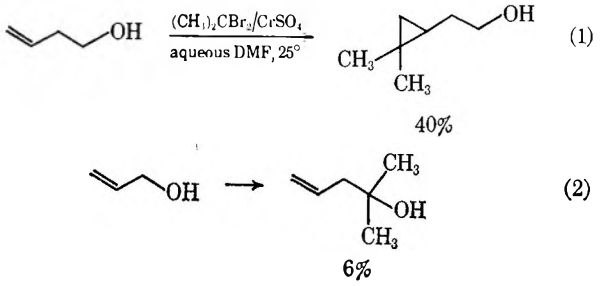
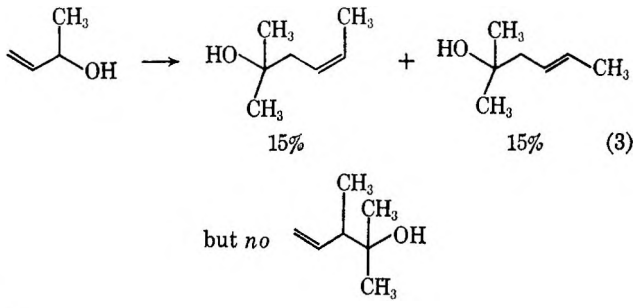
The general chemistry of the reduction of geminal halides and polyhalomethanes with chromous sulfate has been outlined.[1] An important feature of these reactions is the generation of a unique dialkylcarbenoid entity that does have the capacity to react with water and olefins in addition to being reduced and undergoing rearrangement. Adduct formation[2] was typified by eq 1 and 2.

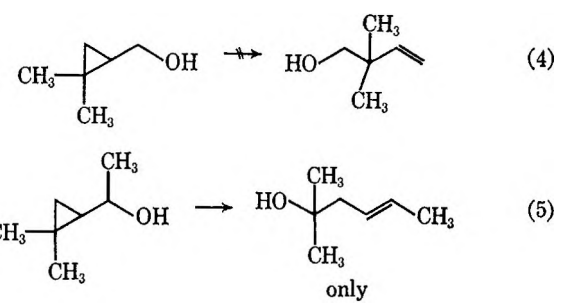


This Note corrects the suggestion that cyclopropanes are intermediates in reactions with allylic alcohols and eliminates a direct C–O insertion.[3]

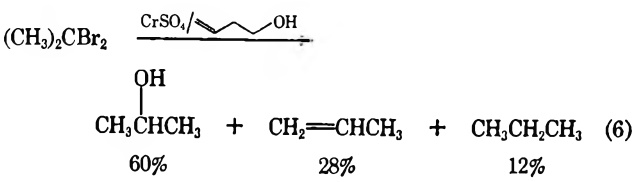
We have confirmed the results of the reactions with 3-buten-1-ol (eq 1) and allyl alcohol (eq 2). However, reaction with 3-buten-2-ol (eq 3) and an examination



of the possible rearrangement of the potential cyclopropane intermediates (under reaction and work-up conditions, eq 4 and 5 are revealing. Moreover, re-

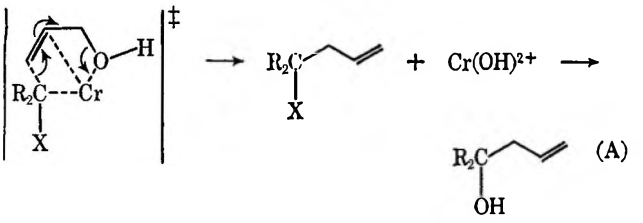


action 1 at −5° yields *no* olefinic trapping product[4] (eq 6). The ratio of isopropyl alcohol to propylene



and propane produced is constant throughout the run. The over-all kinetics at this temperature (Figure 1) are in accord with the initial buildup of $(CH_3)_2C(Br)$-Cr^{2+}.

Taken together the data suggest a transition state for olefin insertions that resembles that written for addition by haloalkyllithiums (eq A).[5] In the absence



(1) C. E. Castro and W. C. Kray, *J. Amer. Chem. Soc.*, **88**, 4447 (1966).

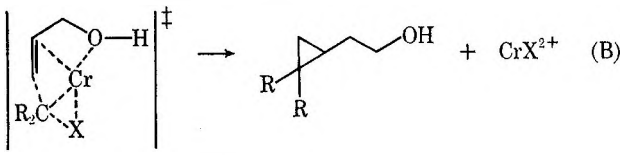
(2) For clarity only adducts are depicted. All yields are based on Cr(II) consumption. Unreacted olefin can be recovered.

(3) C–O insertion by a Cu(II) complex of carbethoxycarbene has been reported: H. Nozaki, S. Moruta, H. Takaya, and R. Noyori, *Tetrahedron Lett.*, **43**, 5239 (1966).

(4) Comparative yields at room temperature in the absence of olefin are propane (2%), propylene (21%), and isopropyl alcohol (76%).

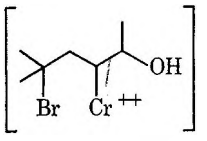
(5) G. L. Closs and J. J. Coyle, *J. Amer. Chem. Soc.*, **87**, 4274 (1965).

of a neighboring leaving group like hydroxyl in the allylic alcohols, bromide is lost in incipient 1,3 fashion (X = halogen, eq B). That is to say, in an extreme



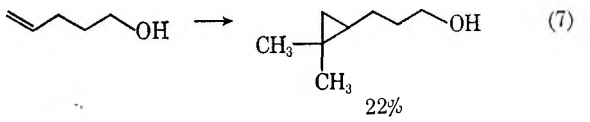
(B)

form, a transient ion like



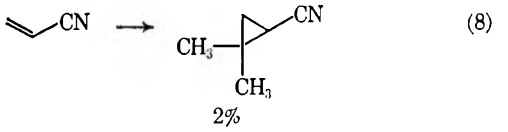
could be considered to eliminate preferentially Cr-(OH)$^{2+}$ rather than undergo 1,3 elimination of Cr-Br^{2+} when it has that option.

Attack of a "free" bromoalkyl radical upon an olefin followed by scavenging with Cr(II) could result in the same products. However, both 3-butenol (eq 1) and 4-pentenol (eq 7) are better "traps" than acrylonitrile



(7)

(eq 8) for the carbenoid. These alcohols would appear to coordinate with the metal ion more favorably for the addition of an adjoining ligand.



(8)

Allyl amine a more strongly bonding ligand, when employed in these reactions, completely suppresses isopropyl alcohol formation. The products from isopropylidene bromide are propane (41%) and propylene (59%). This result is in keeping with the heightened reductive capacity of amine complexes of Cr(II).[6] We are not continuing this investigation.

Experimental Section

Preparation, transfer, storage, and analysis of chromous sulfate was accomplished as previously described. All purchased and prepared starting substances and reference samples had physical constants and infrared spectra that checked the literature. Liquids gas chromatographed as one peak. 1-Cyano-2,2-dimethylcyclopropane was obtained from 2,2-dimethyl-1,3-dihydroxypropane in two steps.[7] In contrast to literature reports, and under a variety of conditions, treatment of lithium dimethylcyclopropylcarboxylate with methyllithium in ether yielded dimethylcyclopropyldimethylcarbinol in addition to dimethylcyclopropyl methyl ketone. Dimethylcyclopropylmethylcarbinol was prepared from the carefully fractionated ketone by lithium aluminum hydride reduction.[8]

Trapping Experiments.—Reactions and product analysis were carried out as previously described.

With 3-Hydroxybutene-1.—To a solution composed of the olefin, 50 g, 50 ml of dimethylformamide, and 9.77 g of 2,2-dibromopropane (0.0484 mol) was slowly added 162.2 ml of 0.97 *M* $CrSO_4$ solution at room temperature. The reaction was allowed to stir at room temperature under nitrogen for 24 hr. At this time 0.141 mol of Cr(II) was consumed. In addition to propane (2.5%), propylene (14%), and isopropyl alcohol (53%), 1.91 g of a fraction of *cis*- and *trans*-1,1-dimethyl-1-hydroxy-3-pentene in equal amounts was obtained. The isomer mixture had bp 68–69° (45 mm), n^{24}D 1.4337. *Anal.* Calcd for $C_7H_{14}O$: C, 73.63; H, 12.4; Found: C, 73.39; H, 12.18. The olefinic pair was cleanly separated from the isomer 2,3-dimethyl-2-hydroxy-4-pentene. The latter alcohol (8.5 min) emerged before the *cis*-*trans* pair (12.5 and 11 min, respectively) on a 3-ft DC-710 column at 70°. Pure factions of the *cis* and the *trans* isomers were trapped from a 10-ft 15% DC-710 on firebrick column at 110°. The discerning infrared features were (cm^{-1}) *cis* 680 (strong), 765, 775, 953 and 974 (medium), 1650 (weak); *trans* 960 (s), 1660 (w). Otherwise the spectra were identical. The nmr spectra accord with the structures and are similar. Gas chromatographic analysis of the isomer pair before distillation placed the yield at 30%.

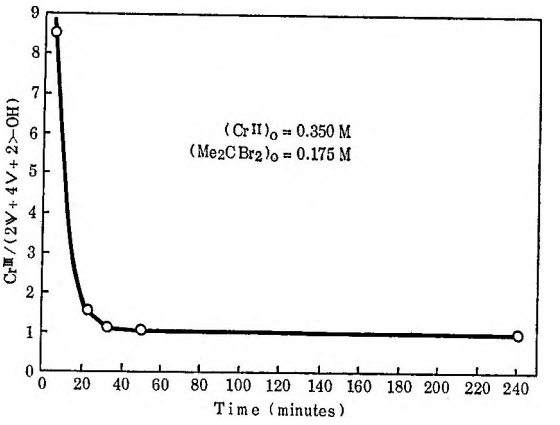


Figure 1.—The relative rates of production of Cr(III) and organic products from the reaction of isopropylidene bromide at −5° in the presence of 3-buten-1-ol.

5-Hydroxypentene-1.—Under identical conditions with this olefin, propane (1%), propylene (17), and isopropyl alcohol (59%) were produced. In addition, the other major substance detected was γ-dimethylcyclopropylpropanol. The substance was isolated by trapping the corresponding peak from gas chromatography. *Anal.* Calcd for $C_5H_{10}O$: C, 74.98; H, 12.60. Found: C, 74.48; H, 12.48. The substance had n^{24}D 1.4391; ir (cm^{-1}) 3300, 2965 (sh), 2919, 2850 (sh), 1432, 1369, 1050, 1010 all strong; nmr (ppm) δ 0.1 s (1 H), 0.42 d(?) (2 H), 1.02 s (6 H), 1.54 m (4 H), 2.25 s (1 H), 3.688 t (2 H).

Acrylonitrile.—In addition to propane (trace), propylene (12%), isopropyl alcohol (35%), and propionitrile (50%),[9] a small amount of dimethylcyclopropylacetonitrile (~2%) was obtained. The substance was identical with authentic materials (*vide supra*) in all respects.

Rearrangement of Dimethylcyclopropylmethylcarbinol.—The carbinol (0.5 g), 3 ml of DMF, 2.7 g of chromic sulfate, and 10 ml of 0.55 *M* chromous sulfate solution were stirred for 24 hr under nitrogen (pH ~2.6) at 25°. The solution was extracted with ether, washed with sodium bicarbonate and water, and dried over sodium sulfate. The concentrated ethereal solution was analyzed by gas chromatography on a 10-ft 20% DC-710 column. The product coemerged only with the *trans*-olefinic alcohol at all temperatures. No trace of the *cis* material could be detected. At 98° the emergence times are dimethylcyclopropylmethylcarbinol (37 min), *trans*-2-methyl-2-hydroxy-4-hexene (40 min), and *cis*-2-methyl-2-hydroxy-4-hexene (45 min). The infrared and nmr spectrum were identical with the *trans* isomer obtained from 3-hydroxybutene-1. An acid-catalyzed rearrangement with DMF (2 ml), water (10 ml), and concentrated H_2SO_4 (0.3 ml) yielded the same result. No isomerizations occurred on the column. Under reaction conditions dimethylcyclopropylcarbinol was unchanged.

(6) J. K. Kochi and D. M. Singleton, *J. Amer. Chem. Soc.*, **90**, 1582 (1968).
(7) E. R. Nelson, M. Maienthal, L. A. Lane, and A. A. Benderly, *ibid.*, **79**, 3467 (1957).
(8) M. Julia, S. Julia, and J. S. Du Chaffant, *Bull. Soc. Chim. Fr.*, 1736 (1960).
(9) This yield is based on Cr(II) consumption. The reduction of this olefin has been described: C. E. Castro, R. D. Stephens, and S. Moje', *J. Amer. Chem. Soc.*, **88**, 4964 (1966).

Registry No.—*cis*-1,1-Dimethyl-1-hydroxy-3-pentene 19639-96-4; *trans*-1,1-dimethyl-1-hydroxy-3-pentene, 19639-97-5; 5-hydroxypentene-1, 821-09-0.

Acknowledgment.—The authors are indebted to the National Science Foundation for generous support. We are grateful to Professor W. Robert Moore for suspecting the rearrangement of dimethylcyclopropylcarbinol under our reaction conditions.

Aluminum Chloride Catalyzed Arylation of Ferrocene with Hydrazines

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The phenylation of aromatic hydrocarbons with diazonium salts proceeds by electrophilic substitution in the case of haloborates,[1] or radical substitution in the case of chlorides.[1,2] In the latter instance, the presence of aluminum chloride changes the character of the reaction to that of electrophilic substitution,[3] and it would appear that, in common with the former, phenyl cation ($C_6H_5^+$) is generated *via* loss of molecular nitrogen by an SN1 mechanism.

We report a new arylation process in which nitrogen is displaced from the aromatic ring very likely by a concerted displacement mechanism in aluminum chloride catalyzed reactions of arylhydrazines with ferrocene. This appears at the same time to be not only the first indisputable example of the arylation of ferrocene by an ionic mechanism, but also the first arylation of the neutral species.

Beckwith and Leydon[4] have convincingly demonstrated that arylation of ferrocene with diazonium salts (and N-nitrosoacetanilide) proceeds by free-radical attack on ferricinium ion,[5] rather than ionic substitution of the neutral species.[6] Thus

$$FcH + ArN_2^+ \longrightarrow FcH^+ + ArN_2\cdot$$

$$ArN_2\cdot \longrightarrow Ar\cdot + N_2$$

$$FcH^+ + Ar\cdot \longrightarrow [FcArH]^+ \longrightarrow FcAr + H^+$$

This mechanism, besides explaining why ferrocene (FcH) is unaffected by radicals or aryldiazonium salts under experimental conditions precluding the formation of ferricinium ion, explains why diazonium salts do not react with ferricinium ion in the absence of free ferrocene.

We have verified that in contrast to the behavior of aromatic hydrocarbons,[1] ferrocene reacts with *o*-tolyldiazonium fluoroborate[7] by radical rather than electrophilic substitution. Complete inhibition was obtained when the reaction was conducted in the presence of an excess of powdered zinc to preclude the formation of ferricinium ion.

In the present work (Table I), *o*- and *p*-tolyl-, *p*-bromophenyl-, and α-naphthylferrocenes were obtained as sole monoarylated products of the reactions of the corresponding hydrazines in *n*-heptane, establishing the ring carbon atom formerly connected to hydrazine nitrogen as the point of attachment of the ferrocene moiety. A reaction with zinc present to reduce any ferricinium ion formed, but otherwise identical with that producing phenylferrocene in 34% yield (Table I), gave the product in 29% yield. This served to establish that attack of aryl radical on ferricinium ion, generated as follows, is not part of the reaction mechanism.[8]

$$FcH + \overset{\delta+}{Ar}NHNH_2\cdot\overset{\delta-}{AlCl_3} \longrightarrow FcH^+ + Ar\cdot + H_2NNHAlCl_3^-$$

TABLE I

ARYLATION OF FERROCENE (FcH) WITH HYDRAZINES[a]

Ar in $ArNHNH_2$	Molar ratio, FcH: $ArNHNH_2$: $AlCl_3$	Product (yield, %[b])	Recovd FcH, %
C_6H_5	1:1:1	C_6H_5Fc (4)	77
C_6H_5	1:1:2	C_6H_5Fc (20)	66
C_6H_5	1:2:2	C_6H_5Fc (36)	56
C_6H_5	1:2:3	C_6H_5Fc (34)[c,d]	52
C_6H_5 (HCl)[e]	1:2:3	C_6H_5Fc (23)	54
o-$CH_3C_6H_4$	1:2:3	o-$CH_3C_6H_4Fc$ (14)	52
p-$CH_3C_6H_4$(HCl)[e]	1:2:3	p-$CH_3C_6H_4Fc$ (7)	33
p-BrC_6H_4	1:2:3	p-BrC_6H_4Fc (19)[f]	46
α-$C_{10}H_7$	1:2:3	α-$C_{10}H_7Fc$ (16)	60

[a] Solvent: *n*-heptane. [b] Based on starting ferrocene. [c] In the presence of powdered zinc, the yield was 29%. [d] 1,1′-Diphenylferrocene (<1%) was also obtained. A reaction in *n*-octane gave 2% of this compound besides 26% of C_6H_5Fc. [e] The hydrazine was employed as the hydrochloride. [f] Also isolated was 1,1′-bis(*p*-bromophenyl)ferrocene (1%).

The results are consistent with an ionic mechanism involving direct displacement by ferrocene on the benzene ring, with simultaneous removal of hydrazide ion by aluminum chloride. Thus

$$FcH + \overset{\delta+}{Ar}NHNH_2\cdot\overset{\delta-}{AlCl_3} \longrightarrow [FcArH]^+[H_2NNHAlCl_3]^- \longrightarrow FcAr + H_2NNHAlCl_2 + HCl \text{ (by-product)}$$

Alkylated ferrocenes were not produced in attempted reactions of methyl- or *t*-butylhydrazines, raising the interesting question of whether or not the attack of ferrocene on aryl may initially involve the ring π system of each.[9,10] The displacement of hydrazide ion from arylhydrazines may be grossly related to Friedel–

(1) G. A. Olah and W. S. Tolgyesi, *J. Org. Chem.*, **26**, 2053 (1961), and references cited therein.

(2) The free-radical nature of the Gomberg-Bachman reaction, in which the arylating agent is a diazonium salt and base, is well recognized [C. Rüchardt and E. Merz, *Tetrahedron Letters*, 2431 (1964); E. L. Eliel, J. G. Saha, and S. Meyerson, *J. Org. Chem.*, **30**, 2451 (1965); G. Binsch and C. Rüchardt, *J. Amer. Chem. Soc.*, **88**, 173 (1966)], although perhaps not as well understood [G. R. Chalfont and M. J. Perkins, *ibid.*, **89**, 3054 (1967)].

(3) G. A. Olah in "Friedel-Crafts and Related Reactions," Vol. I, G. A. Olah, Ed., Interscience Publishers, London, 1963, pp 66, 67, and references therein.

(4) A. L. J. Beckwith and R. J. Leydon, *Tetrahedron*, **20**, 791 (1964).

(5) W. F. Little and A. K. Clark, *J. Org. Chem.*, **25**, 1979 (1960).

(6) M. Rosenblum, W. G. Howells, A. K. Banerjee, and C. Bennett, *J. Amer. Chem. Soc.*, **84**, 2726 (1962), concluding that ferrocene is relatively inert toward attack by free radicals, proposed that arylferrocenes are formed *via* intramolecular decomposition of a ferrocene–diazonium salt charge-transfer complex.

(7) W. F. Little, C. N. Reilley, J. D. Johnson, K. N. Lynn, and A. P. Sanders, *ibid.*, **86**, 1376 (1964).

(8) Ferricinium ion could not be detected on work-up of the reaction mixtures, except for trace amounts when the aluminum chloride was present in excess of the hydrazine. R. L. Schaaf and C. T. Lenk, *J. Org. Chem.*, **28**, 3238 (1963), have discussed the oxidation of ferrocene by aluminum chloride.

(9) Nucleophilic attack of ferrocene on silicon and germanium *via* the ring π system was suggested previously.[10]

(10) G. P. Sollott and W. R. Peterson, Jr., *J. Amer. Chem. Soc.*, **89**, 5054, 6783 (1967).

Crafts arylation giving biphenyls, which appears to involve the displacement of halide ion from halobenzenes.[11] The latter reaction occurs as a minor side reaction to aluminum halide induced isomerization of the halobenzenes.

p-Tolylferrocene, formed by the reaction of the hydrochloride of *p*-tolylhydrazine, very likely was obtained in reduced yield since the reaction of phenylhydrazine hydrochloride, as compared with the free hydrazine, gave a lower yield of phenylferrocene (Table I). No tolylferrocene was obtained from *m*-tolylhydrazine, and this is attributed to the greater basicity of the aromatic nucleus of the latter, relative to *o*- and *p*-tolylhydrazines, by anology with the basicities of *o*-, *m*-, and *p*-xylenes.[12] It is suggested that with *m*-tolylhydrazine, nucleophilic attack by ferrocene is thus precluded. *p*-Methoxyphenylhydrazine also gave a negative result possibly for a similar reason, but additionally there is opportunity for coordination of aluminum chloride at the methoxy group, which could interfere with the course of the arylation reaction.

The reaction of *p*-bromophenylhydrazine produced 1,1′-bis(*p*-bromophenyl)ferrocene in trace amount (1%) in addition to the expected monosubstituted product (Table I). Reactions of phenylhydrazine in *n*-heptane occasionally gave traces of 1,1′-diphenylferrocene (<1%); a reaction in *n*-octane gave 2% of the disubstituted product, with a somewhat reduced yield of phenylferrocene. While it was indicated that certain arylferrocenes may be sufficiently nucleophilic to enter into a displacement reaction with arylhydrazines, an attempted reaction of phenylferrocene with phenylhydrazine to produce 1,1′-diphenylferrocene was unsuccessful.

No phenylferrocene was produced when aniline was used in place of phenylhydrazine. This is explainable from the standpoint that phenylhydrazine, with two adjacent nitrogen atoms bearing unshared electron pairs, is a stronger nucleophile than aniline.[13] It is suggested that aluminum chloride coordinates hydrazine nitrogen more effectively than nitrogen of aniline, providing an entity of appropriate electrophilic character. Similarly, reduced nucleophilicity of nitrogen can be advanced as explanation for the negative results obtained in the case of such compounds as N-nitrosoaniline, *sym*- and *unsym*-diphenylhydrazines, benzoylhydrazine, 1,5-diphenylcarbazide, phenylhydrazine-*p*-sulfonic acid, and 4-nitro- and 2,4-dinitrophenylhydrazines. Some of these compounds, moreover, possess additional sites for the coordination of aluminum chloride. A reaction employing the phenylhydrazone of benzophenone gave phenylferrocene in small quantity (2%).

In passing, the attempted reaction of 1,5-diphenylcarbazide produced over 10% of 1,1′-(1,3-cyclopentylene)ferrocene, a heterobridged compound previously prepared[14] from ferrocene and aluminum chloride in benzene. When other hydrazines were employed, this compound was not isolated except occasionally in trace amounts.

Although sufficiently nucleophilic benzenoid aromatic substrates could be expected to undergo arylation in the same manner as ferrocene, attempted reactions of such compounds as mesitylene, anisole, and 1,3-dimethoxybenzene with aluminum chloride complexed phenylhydrazine failed, as did benzene itself, to give the expected biphenyls.

With benzene as solvent, a reaction of ferrocene with phenylhydrazine gave phenylferrocene in sharply reduced yield compared to the reaction run in *n*-heptane. Substitution of aluminum bromide for the chloride in a reaction performed in *n*-heptane caused a substantial increase in yield, but an appreciable decrease was obtained when the bromide was present in molar excess of the hydrazine. No such decrease was observed when aluminum chloride was employed in molar excess of phenylhydrazine. In the latter case, doubling the reflux time failed to cause an increase in yield, while shortening the reflux time by more than half, produced only a slight decrease in yield.

Beckwith and Leydon[15] have recently reported that oxidation of a mixture of ferrocene and arylhydrazine with silver oxide or benzoquinone produces arylated ferrocenes. The mechanism of this reaction appears to involve free-radical substitution of ferricinium ion,[15] and is, therefore, essentially different from the mechanism of the process reported here.

Experimental Section

Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected.

p-Methoxyphenylhydrazine was prepared by reduction of the diazonium salt obtained from *p*-anisidine. *t*-Butylhydrazine hydrochloride was prepared from hydrazine and *t*-butyl chloride.[16] The phenylhydrazone of benzophenone was prepared by standard procedure. All other hydrazines and derivatives were available commercially. *o*- and *m*-tolyl-, α-naphthyl-, and *t*-butylhydrazines were liberated from the hydrochlorides by treatment with aqueous alkali, then extracted with ether and distilled or crystallized.

Reactions of Ferrocene with Arylhydrazines. General Method.—In the molar ratios indicated in Table I, ferrocene (0.1 mole), anhydrous aluminum chloride, and the arylhydrazine (or hydrochloride), the last added dropwise or in small quantities over 10 min, were refluxed 20 hr in *n*-heptane (300 ml) under nitrogen. After evaporation of the solvent from the heptane phase, the residue was combined with the heptane-insoluble reaction solids, and the aggregate was hydrolyzed with water cautiously with cooling. The solids were collected by suction filtration, air-dried, and extracted by refluxing in *n*-heptane. The insoluble solids were discarded, and the filtered extract was chromatographed on a 70-cm column of activated alumina (80–200 mesh). Elution with *n*-heptane afforded unchanged ferrocene. [Continued elution with heptane removed any 1,1′-(1,3-cyclopentylene)ferrocene occasionally present in trace amount; *cf.* the attempted reaction of ferrocene with 1,5-diphenylcarbazide, below.] Elution next with benzene–heptane (1:2 by volume) produced the monoarylated ferrocene. Any 1,1′-diarylated ferrocene was eluted last with benzene. The arylated products were crystallized several times from petroleum ether (30–60°).[17]

Products.—Yields and recovered ferrocene are given in Table I. The products gave satisfactory elemental analyses and were identified as phenylferrocene, mp 110–111° (lit.[7] 110–111°); 1,1′-diphenylferrocene, mp 151–152° (lit.[18] 154°); *o*-tolylferrocene, mp 52.5–53° (lit.[7] 50–52°); *p*-tolylferrocene, mp 136–137° (lit.[7] 140–142°); α-naphthylferrocene, mp 100–101.5°[17] (lit.[16]

(11) G. A. Olah and M. W. Meyer, *J. Org. Chem.*, **27**, 3464 (1962), and references therein.

(12) H. C. Brown and J. D. Brady, *J. Amer. Chem. Soc.*, **74**, 3570 (1952).

(13) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, Inc., New York, N. Y., 1966, p 120.

(14) S. G. Cottis and H. Rosenberg, *Chem. Ind.* (London), 860 (1963).

(15) A. L. J. Beckwith and R. J. Leydon, *Australian J. Chem.*, **19**, 1381 (1966).

(16) O. Westphal, *Ber.*, **74B**, 759 (1941).

(17) α-Naphthylferrocene was crystallized from benzene–ether and recrystallized first from ether, then from petroleum ether (30–60°).

(18) P. L. Pauson, *J. Amer. Chem. Soc.*, **76**, 2187 (1954).

96–97°);[19] *p*-bromophenylferrocene, mp 121.5–123° (lit.[7] 122–123°).

1,1′-Bis(*p*-bromophenyl)ferrocene had mp 195–196°; ν_{max}^{Nujol} 1110 and 1000 absent (no unsubstituted ferrocene ring), 860–800 (*para*-disubstituted benzene ring) obscured by a strong complex band at 819 cm^{-1} (ferrocene out-of-plane C–H bending). *Anal.* Calcd for $C_{22}H_{16}Br_2Fe$: C, 53.27; H, 3.25; Br, 32.22; Fe, 11.26. Found: C, 53.16; H, 3.26; Br, 32.26; Fe, 11.65.

Reactions under Modified Conditions.—Summarized in Table II are reactions of ferrocene (FcH), phenylhydrazine, and anhydrous aluminum chloride employed in the molar ratios indicated. The reactions were performed based on the general method above, except for the modification specified.

TABLE II

Molar ratio	Modification	% of phenylferrocene, 1,1′-diphenylferrocene, recovd FcH
1:2:3	Powdered Zn (1 g-atom) present	29, 0, 65
1:2:3	Solvent: *n*-octane	26, 2, 60
1:1:2	Solvent: benzene	4, 0, 74
1:1:2	40-hr reflux	19, 0, 56
1:1:2	6-hr reflux	18, 0, 76
1:1:1	$AlBr_3$ replaced $AlCl_3$	18, 0, 67
1:1:2	$AlBr_3$ replaced $AlCl_3$	12, 0, 30

Attempted Reactions of Ferrocene with Hydrazines and Other Compounds.—Procedures were similar to those of the general method above. The following reactants were refluxed in *n*-heptane with ferrocene (FcH) and anhydrous aluminum chloride in the molar ratios (FcH:reactant:$AlCl_3$) indicated, with negative results except in the case of benzophenone phenylhydrazone which yielded 2% of phenylferrocene: aniline (1:1:2), N-nitrosoaniline (1:1:2), *p*-methoxyphenylhydrazine (1:2:3), *sym*-diphenylhydrazine (1:2:3), *unsym*-diphenylhydrazine (1:2:3), benzoylhydrazine (1:1:2), phenylhydrazine-*p*-sulfonic acid (1:2:3), 4-nitrophenylhydrazine (1:2:3), 2,4-dinitrophenylhydrazine (1:1:2), benzophenone phenylhydrazone (1:1:2), methylhydrazine (1:2:3), *t*-butylhydrazine (1:2:3).

m-Tolylhydrazine (1:2:3) yielded 1.5 g of orange needles upon elution of the chromatographic column with benzene and crystallization from *n*-heptane, mp 295° dec, ν_{max}^{Nujol} 1106 and 1003 (unsubstituted ferrocene ring) and 761 cm^{-1} (aromatic C–H?). *Anal.* Calcd for $C_{17}H_{16}Fe$ (*m*-tolylferrocene): C, 73.93; H, 5.84; Fe, 20.22. Found: C, 70.21; H, 3.21; Fe, 27.14.

1,5-Diphenylcarbazide (1:1:2) yielded 14% of 1,1′-(1,3-cyclopentylene)ferrocene, mp 138–139° from 30–60° petroleum ether (lit.[14] 140°), undepressed by admixture with an authentic sample.[14]

Attempted Reaction of Phenylferrocene with Phenylhydrazine.—Phenylferrocene (0.1 mole), phenylhydrazine, and anhydrous aluminum chloride (molar ratio, 1:2:3) were refluxed in *n*-heptane employing procedures similar to those of the general method above. No 1,1′-diphenylferrocene was detected upon election of the chromatographic column as above.

Attempted Reactions of Benzenoid Aromatics with Phenylhydrazine.—Using procedures based on the general method above, mesitylene and 1,3-dimethoxybenzene were refluxed, in place of ferrocene, with phenylhydrazine and anhydrous aluminum chloride in a 1:2:2 molar ratio. Benzene and anisole were refluxed with phenylhydrazine (0.2 mole) and aluminum chloride (0.3 mole), using excess of the aromatic compound as solvent in place of *n*-heptane. No biphenyl derivative was detected upon elution of the chromatographic columns with solvents as above, or with chloroform or methanol.

Attempted Preparation of o-Tolylferrocene from o-Tolyldiazonium Fluoroborate in the Presence of Zinc.—The method was based on the published procedure[7] except that powdered zinc (1 g-atom) was added to the methylene chloride solution of ferrocene (0.1 mole) prior to addition of the dry diazonium fluoroborate (0.1 mole) over 1 hr with cooling (water bath). After stirring of the mixture 2 hr at room temperature, no *o*-tolylferrocene was detected *via* chromatography on alumina, and ferrocene was recovered nearly quantitatively.

(19) α-Naphthylferrocene, mp 93–95°, and β-naphthylferrocene, mp 137–142°, have been reported by K. Schlögl and H. Egger, *Monatsh.*, **94**, 1054 (1963); *Chem. Abstr.*, **60**, 13269*h* (1964).

Registry No.—Aluminum chloride, 7446700; ferrocene, 102545; 1,1′-bis(*p*-bromophenyl)ferrocene, 12155-929; *m*-tolylferrocene, 12344364.

The Selectivity of Benzyne. A New Approach Using the Reaction of Benzyne with Ambident[1] Nucleophiles

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In an attempt to find the optimum conditions for the reaction of bromobenzene with potassium anilide we varied the solvent as well as the ratio of aniline to potassium anilide. The results are summarized in Table I. As expected, we observed the well-known[2] increase in yield as the amount of free amine in the reaction mixture was increased. Most remarkable, however, was the observation that a dramatic change in product *composition* takes place as the ratio of aniline/anilide is changed. In each of the three solvents examined there was at least a tenfold increase in the carbon to nitrogen phenylation ratio (C/N) when an excess of aniline was present in the reaction mixture.

In order to subject this interesting phenomenon to a more systematic and quantitative examination we needed a reaction system in which higher and more consistent yields could be obtained. Reaction in dimethyl sulfoxide at 25° provided such data. As can be seen in Table II, 4-aminobiphenyl was now found as a product, in addition to 2-aminobiphenyl, diphenylamine, and small amounts of triphenylamine.

Discussion

An interesting question concerning the reactivity of benzyne is the degree of its selectivity among various nucleophiles. For example, it has been reported[3] that 9,10-phenanthryne in ether solution reacts with equal speed with piperidine and with lithium piperidide. On the other hand, benzyne generated in ethanol by the decomposition of benzothiadiazole dioxide was found to react with LiCl, LiBr, and LiI at relative rates of 1:8:65.[4]

It appeared to us that our data enable us to obtain an estimate of the relative rates of the reaction of benzyne[5] with aniline and with potassium anilide by a

(1) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Amer. Chem. Soc.*, **77**, 6269 (1955).

(2) R. Huisgen and J. Sauer, *Chem. Ber.*, **92**, 192 (1959).

(3) W. Mack and R. Huisgen, *ibid.*, **93**, 608 (1960).

(4) G. Wittig and R. W. Hoffman, *ibid.*, **95**, 2729 (1962).

(5) (a) J. D. Roberts and F. Scardiglia [*J. Org. Chem.*, **23**, 629 (1958)] have shown that this reaction goes by way of a benzyne intermediate. They found that bromobenzene and potassium anilide in aniline as solvent gave a 60% yield of diphenylamine. They did not wish to investigate possible primary amine products. Using their reaction conditions we obtained a 50% yield of diphenylamine and a 5% yield of 2-aminobiphenyl. (b) Further evidence that this type of reaction proceeds by way of a benzyne intermediate in dimethyl sulfoxide solution as well can be found in the work of D. J. Cram, B. Rickborn, and G. R. Knox, *J. Amer. Chem. Soc.*, **82**, 6412 (1960).

TABLE I

THE REACTION OF BROMOBENZENE WITH POTASSIUM ANILIDE AND ANILINE IN BENZENE, DIETHYL ETHER, AND 2,2'-DIMETHOXYDIETHYL ETHER (1-4-1).

Solvent[b]	Concn of starting materials, mol/l. C_6H_5Br	C_6H_5NHK	$C_6H_5NH_2$	Yield, % Diphenylamine[a]	2-Aminobiphenyl	C/N (ratio of carbon to nitrogen phenylation)
Benzene	0.13	1.30	0.00	0.50	0.21	0.42
Benzene	1.00	1.00	1.00	6.50	0.29	0.045
Diethyl ether	0.13	1.30	0.00	0.04	0.08	2.0
Diethyl ether	1.00	1.00	9.00	1.94	0.19	0.09
1-4-1[b]	0.24	1.46	0.00	21.9	8.8	0.40
1-4-1	1.25	1.25	11.2	56.2	2.49	0.044

[a] The yield of diphenylamine includes some triphenylamine which was obtained in varying amounts, from zero to 4.5%. [b] The reaction temperature was 25° in diethyl ether and at the reflux temperature of the other two solvents.

TABLE II

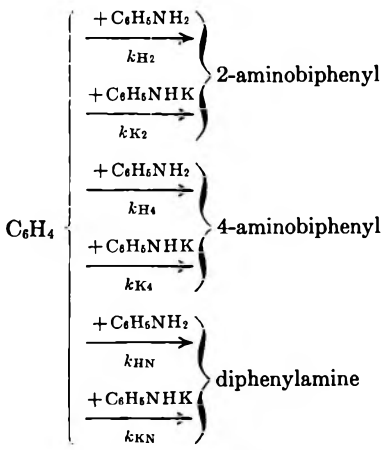
STARTING MATERIALS AND PRODUCTS IN THE REACTION OF 0.031 *M* BROMOBENZENE WITH POTASSIUM ANILIDE AND ANILINE IN DIMETHYL SULFOXIDE AT 25°

Initial concn of potassium anilide and aniline, mol/l. C_6H_5NHK	$C_6H_5NH_2$	Yield of products, % 4-Aminobiphenyl	2-Aminobiphenyl	Diphenylamine[a]
0.031	0.82	0.0[b]	0.13	54
0.20	1.28	4.1	5.9	48
0.20	0.82	3.8	4.5	45
0.20	0.20	4.0	4.1	50
0.20	0.00	5.7	4.8	54

[a] The yield of diphenylamine includes some triphenylamine which was obtained in varying amounts, from zero to 4%. [b] Less than 0.01%.

new and interesting method. Furthermore we can obtain such a rate comparison for this pair of nucleophiles with respect to the formation of three products (Scheme I). An examination of the kinetic scheme for the formation of 2- and 4-aminobiphenyl from the reaction of benzyne with $C_6H_5NH_2$ or with C_6H_5NHK yields the expression[6]

SCHEME I



$$\frac{\text{yield of 2-aminobiphenyl}}{\text{yield of 4-aminobiphenyl}} = \frac{k_{K_2}[C_6H_5NHK] + k_{H_2}[C_6H_5NH_2]}{k_{K_4}[C_6H_5NHK] + k_{H_4}[C_6H_5NH_2]}$$

The result of the first reaction in Table II indicates that $k_{H_4} = 0$, therefore

$$\frac{\text{yield of 2-aminobiphenyl}}{\text{yield of 4-aminobiphenyl}} = \frac{k_{K_2}}{k_{K_4}} + \frac{k_{H_2}[C_6H_5NH_2]}{k_{K_4}[C_6H_5NHK]}$$

In Table III are listed the variations in product ratios as a function of the variation of the initial aniline–anilide ratio. A plot of the 2-aminobiphenyl/4-aminobiphenyl yield ratio *vs.* $[C_6H_5NH_2]/[C_6H_5NHK]$ yielded[7] a straight line whose slope and intercept gave $k_{K_2}/k_{K_4} = 0.90$, $k_{H_2}/k_{K_4} = 0.064$ and therefore $k_{K_2}/k_{H_2} = 14.0$.

TABLE III

PRODUCT RATIOS AS A FUNCTION OF INITIAL CONCENTRATIONS OF ANILINE AND POTASSIUM ANILIDE

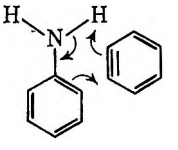
$[C_6H_5NH_2]/[C_6H_5NHK]$	2-Aminobiphenyl/ 4-aminobiphenyl	Diphenylamine/ 4-aminobiphenyl
26.4	>13	>5400
6.4	1.44	12.9
4.1	1.19	12.0
1.0	1.02	12.5
0.0	0.84	9.54

Analogous considerations yield the expression

$$\frac{\text{yield of diphenylamine}}{\text{yield of 4-aminobiphenyl}} = \frac{k_{KN}}{k_{K_4}} + \frac{k_{HN}[C_6H_5NH_2]}{k_{K_4}[C_6H_5NHK]}$$

Here the scatter of the data was such as to enable us merely to obtain $k_{KN}/k_{K_4} \geqq 9.6$, $k_{HN}/k_{K_4} \leqq 0.041$, and therefore $k_{KN}/k_{HN} \geqq 234$. Converting the above rate ratios into relative rates by setting $k_{H_2} = 1.0$ we then have $k_{H_4} = 0.0$, $k_{K_4} = 15.6$, $k_{H_2} = 1.0$, $k_{K_2} = 14.0$, $k_{HN} \leq 0.64$, $k_{KN} \geqq 150$.

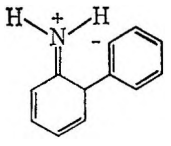
Thus the largest difference in the nucleophilicities of $C_6H_5NH_2$ and C_6H_5NHK is found in the formation of 4-aminobiphenyl and the smallest in the formation of 2-aminobiphenyl. We can consider two factors which determine this difference. (1) The greater inherent nucleophilicity of the much more basic C_6H_5NHK. (2) The fact that the transition state for nucleophilic attack of aniline on benzyne involves charge separation (assuming a two-step process, (a) attack by the nucleophile, (b) protonation of the phenide ion), whereas nucleophilic attack by potassium anilide does not. Since factor 1 remains constant for the three processes, factor 2 must be invoked in explaining the dramatic differences in the nucleophilic



(6) This equation holds rigorously only if the ratio $[C_6H_5NHK]/[C_6H_5NH_2]$ remains constant. As can be seen in Table II an excess of $C_6H_5NH_2$ and C_6H_5NHK was used to keep this ratio as constant as possible.

(7) Since each mole of C_6H_5Br converted into products consumes 2 mol of C_6H_5NHK and produces 1 mol of $C_6H_5NH_2$ the value of $[C_6H_5NH_2]/[C_6H_5NHK]$ does not remain exactly constant during the course of the reaction. For the purpose of calculation the value of $[C_6H_5NH_2]/[C_6H_5NHK]$ at half-reaction was used.

rate ratios for the three processes. In the formation of 2-aminobiphenyl from $C_6H_5NH_2$ and C_6H_4 a six-membered ring transition state is conceivable which would involve nucleophilic attack and protonation in one step, avoiding charge separation. In the formation of diphenylamine a four-membered ring transition state of this type is possible. In the formation of 4-aminobiphenyl no such cyclic transition state is possible. The fact that attack of the benzyne by $C_6H_5NH_2$ competes best with attack by C_6H_5NHK in the case of 2-aminobiphenyl formation and not at all in the case of 4-aminobiphenyl formation suggests that such a one-step cyclic process for the nucleophilic attack and protonation of benzyne by an amine is very probable.[8] Alternately, in a two-step process, the reaction of $C_6H_5NH_2$ and C_6H_4 to form 2-aminobiphenyl would lead to a charged intermediate having little charge separation, whereas the intermediate for 4-



aminobiphenyl formation would involve a great deal of charge separation. This may account for the fact that no 4-aminobiphenyl at all could be found in the three much less polar solvents where such charge separation would be particularly energetically unfavorable.

It is of great interest that such simple changes in the steric and electrostatic nature of the transition states can so radically alter the degree of selectivity of benzyne between a pair of nucleophiles.

Experimental Section

Materials.—Aniline (Baker & Adamson) was dried over KOH and distilled from zinc dust. Bromobenzene (Baker) was dried over calcium sulfate and distilled. Dimethyl sulfoxide (Fisher Reagent) was dried over calcium hydride and distilled, ethyl ether and 1-4-1 were distilled from sodium wire.

Sample Run.—A mixture of potassium anilide and aniline (prepared from 4.75 g (0.510 mol) of aniline and 0.391 g (0.010 mol) of potassium) was dissolved in 50 ml of dimethyl sulfoxide. To this stirred solution was added 0.244 g (0.00155 mol) of bromobenzene and the solution left to stand at 25° under an atmosphere of nitrogen for 18 hr. The solution was then diluted with water and extracted with benzene. The benzene phase was washed thoroughly with water and then extracted with 3 *N* HCl. The organic phase, containing diphenylamine and triphenylamine, was then dried, an internal standard was added, and the mixture subjected to vpc analysis at 210° on a 5-ft long steel column packed with 20% SF-96 on 60/80 firebrick. The above aqueous HCl phase was neutralized with 10 *N* NaOH and extracted with ether. The ether phase, containing 2-aminobiphenyl and 4-aminobiphenyl, was then dried and analyzed by vpc as above. Samples of all four products were collected from the vpc and their infrared spectra determined. The spectrum of each compound was found to be identical with that of an authentic sample.

Registry No.—Benzyne, 462-80-6; bromobenzene, 108-86-1; potassium anilide, 19642-99-0; aniline, 62-53-3.

(8) A four-membered cyclic process of this type was proposed by Mack and Huisgen.[1] On the other hand, J. F. Bunnett, D. A. R. Happer, M. Patsch, C. Pyun, and H. Takayama [*J. Amer. Chem. Soc.*, **88**, 5250 (1966)] have good evidence for a stepwise addition of methanol to 4-chlorobenzyne in methanol solution.

Transannular Oxide Formation. Bicyclo[3.2.1] *vs.* Bicyclo[2.2.2] Systems

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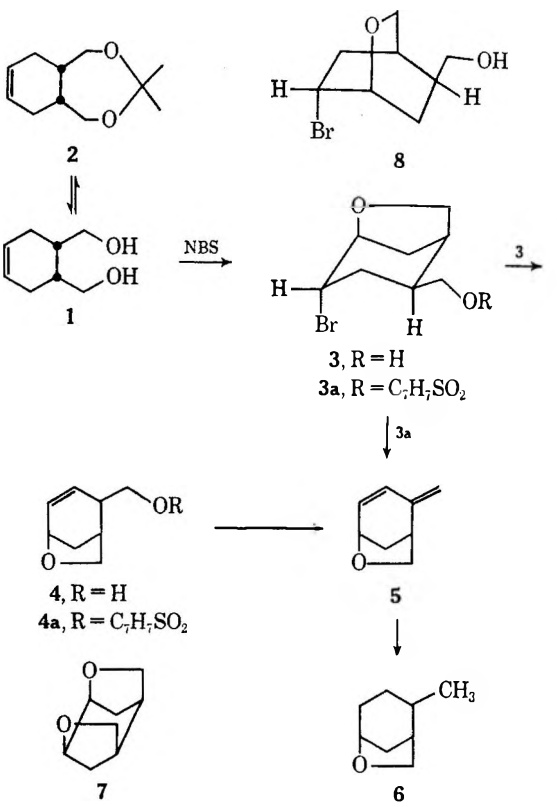
The relatively greater apparent stability of six-membered *vs.* five-membered oxide rings as evidenced, for example, by the preferred pyranose ring system in sugars as well as the formation of six-membered cyclic ketals in certain bicyclic systems[1] doubtlessly reflects the consequences of optimized conformational effects. In this connection it was of interest to us to determine the course of transannular oxide formation wherein competition exists for the formation of a bicyclo[3.2.1] or a bicyclo[2.2.2] product.

Treatment of the symmetrical system, *cis*-1,2-bishydroxymethylcyclohex-4-ene (**1**), with N-bromsuccinimide in aqueous *t*-butyl alcohol afforded a good yield of essentially a single bromoxide which proved to have the bicyclo[3.2.1] structure **3**[2] (Scheme I). The structure

SCHEME I



of **3** was established by conversion in essentially quantitative yield to a crystalline tosylate derivative **3a**, mp 80–81°; the latter, in turn, on treatment with

(1) R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.*, **74**, 1406 (1952).

(2) Recently G. M. Brown, P. Dubrueil, and E. P. Denvers [*Can. J. Chem.*, **46**, 1849 (1968)] observed a similiar transannular oxide formation during epoxidation of a derived cyclohexene. The use of NBS in *t*-butyl alcohol for the formation of five-membered ring oxides has been previously reported. See, *e.g.*, F. W. Bollinger and N. L. Wendler, *Chem. Ind.* (London), 441 (1960); J. F. Bagl, P. F. Morand, and R. Gaudry, *J. Org. Chem.*, **28**, 1207 (1963).

potassium *t*-butoxide in ether was smoothly converted to the conjugated diene **5**, λ_{max} 238 mμ (ε 14,160). It may be noted that the bicyclo[2.2.2] structure **8** could not have provided a conjugated diene. Treatment of the bromoxide **3** itself with potassium *t*-butoxide yielded the olefinic alcohol **4** *in lieu* of the bisoxide **7**, again, presumably, for reasons of steric constraint (chair → boat) connoted in the latter system.

The diene **5** absorbed 2 moles of hydrogen to give the saturated system **6**. The unsaturated alcohol **4** in the form of its tosylate derivative **4a** was found to be stable to conditions employed for solvolysis of homoallylic systems, namely, potassium acetate in refluxing aqueous 80% acetone.[3] In the presence of potassium *t*-butoxide in ether suspension, on the other hand, **4a** was converted exothermically to the diene **5**.

Experimental Section

Vpc determinations were carried out employing a 5 ft × 0.25 in. 20% S.E. 30 on Chrom W Column. The uv spectrum was determined in methanol on a Cary Model II PMS spectrometer and ir spectra on a Perkin-Elmer Infracord instrument. Nmr spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard.

1,2-Bishydroxymethylcyclohex-4-ene (1) was prepared by lithium aluminum hydride reduction of Δ^4-tetrahydrophthalic anhydride in ether–tetrahydrofuran solution and purified *via* its acetonide **2** (see below); lit.[4] bp 106–107° (1–1.5 mm) and mp 34.5°.

Acetonide of 1,2-Bishydroxymethylcyclohex-4-ene (2).—A solution of crude diol **1** (25 g) (see above) in 500 cc of acetone and 25 g of anhydrous copper sulfate was stirred for 18 hr followed by filtration and evaporation of the filtrate. The residue from concentration was extracted with petroleum ether (bp 30–60°) and the latter extract was washed several times with water, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Distillation of the residue, bp 60–61° (2 mm), afforded 18–20 g of acetonide **2**: single peak by vpc, 4-min retention time at 180°; nmr ($CDCl_3$), δ 1.3.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.53; H, 9.89. Found: C, 72.82; H, 10.10.

Regeneration of diol **1** from acetonide **2** was effected by brief shaking with 10% hydrochloric acid and concentration *in vacuo* followed by treatment with sodium chloride and extraction with ether. Evaporation of the dried ($MgSO_4$) ether solution yielded diol **1** which was single peak by vpc with a retention time of 5.5 min at 180°.

Reaction of 1,2-Bishydroxymethylcyclohex-4-ene with N-Bromsuccinimide. Formation of Transannular Oxide 3.—A solution of 15.6 g of diol **1**, purified *via* its acetonide, in 165 cc of *t*-butyl alcohol and 33 cc of water was treated at 0–5° with 19.6 g of N-bromsuccinimide with stirring. The reaction mixture was allowed to stir until complete solution of the N-bromsuccinimide (*ca.* 1 hr) and stored for 16 hr in the refrigerator. Any excess positive bromine was destroyed with aqueous bisulfite and the reaction mixture was concentrated *in vacuo* to an oil. The latter was treated with water and extracted with ether. The ether extract was washed several times with water, dried over magnesium sulfate, filtered, and concentrated to give the bromoxide **3** as a colorless oil, 20 g, essentially single peak by vpc with a retention time of 7 min at 200°. This material is unstable to high-vacuum distillation and a sample for analysis was prepared by submitting a film to high vacuum for 18 hr.

Anal. Calcd for $C_8H_{13}O_2Br$: C, 43.44; H, 5.88; Br, 36.15. Found: C, 43.19; H, 5.86; Br, 36.15.

***p*-Toluenesulfonate 3a of Bromoxide.**—A 1.75-g sample of the above bromoxide **3** in 5 cc of pyridine was treated with 1.61 g of *p*-toluenesulfonyl chloride at 0° for 18 hr. The reaction mixture was treated with ice–water and the crystalline tosyl derivative was filtered, washed with water, and dried; 2.9 g, mp 74–76°, crystallization from ether gave mp 80–82°, ir of crude and crystallized material were the same.

Anal. Calcd for $C_{15}H_{19}SO_4Br$: C, 48.00; H, 5.07; Br, 21.33. Found: C, 48.12; H, 5.12; Br, 21.20.

Conversion of Tosylate 3a to Diene 5.—A solution of 650 mg of **3a** in 25 cc of ether was treated with 780 mg of potassium *t*-butoxide and stirred for 2 hr. At the end of this period water was added, the ether layer was separated and washed with water until neutral. Evaporation of the solvent yielded an oil exhibiting a single peak in the vpc with retention time of 1.5 min at 180°. The oil was evaporatively distilled at 75–80° (32 mm); λ_{max} 238 mμ (ε 14,160); λ_{max}^{film} 6.12, 6.28 μ; nmr, δ 4.69, 4.79 (each d, J = 1.5 cps, >C=CH_2), 6.05 (m, CH=CH).

Anal. Calcd for $C_8H_{10}O$: C, 78.69; H, 8.20. Found: C, 78.45; H, 8.48.

Hydrogenation of diene **5** (0.3 g) in 5 cc of ether employing 150 mg of 5% Pd–C catalyst resulted in absorption of 2 molar equiv of hydrogen and formation of the saturated analog **6** which was evaporatively distilled at 70° (32 mm), nmr, δ 0.85 (J = 6 cps, CH_3 doublet).

Anal. Calcd for $C_8H_{14}O$: C, 76.19; H, 11.11. Found: C, 76.26; H, 11.11.

Reaction of Bromoxide 3 with Base to Give 4.—A solution of 1.7 g of bromoxide **3** in 15 cc of anhydrous ether was treated with 2 mole equiv of potassium *t*-butoxide. An exothermic reaction occurred which was allowed to continue with stirring at ambient temperature for 48 hr. The reaction mixture was treated with saturated salt solution and the ether extracts were washed with salt solution until neutral. Product distilled at 85° (0.02 mm); λ_{max}^{film} 2.8, 6.12 μ.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.57; H, 8.57. Found: C, 68.07; H, 8.47.

Tosylation of **4** as described for the preparation of **3a** yielded an oily tosylate, which was recovered unchanged after refluxing 18 hr in 80% acetone–water containing 4 mole equiv of potassium acetate. Treatment of this derivative with potassium *t*-butoxide as described for the preparation of **5** proceeded exothermically to give this diene.

Registry No.—**2**, 19639-98-6; **3**, 19639-92-0; **3a**, 19639-99-7; **4**, 19642-96-7; **5**, 19642-97-8; **6**, 19642-98-9.

(3) E. M. Kosower and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 4347 (1956).

(4) E. L. Eliel and C. Pillar, *ibid.*, **77**, 3600 (1955); see also D. C. Ayres and R. A. Raphael, *J. Chem. Soc.*, 1779 (1958), and references cited therein.

Reactions of Hydroxymethylferrocene. II. Sulfides[1]

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Alkyl ferrocenylmethyl sulfides have been prepared by reduction of alkyl ferrocenethiolcarboxylates with lithium aluminum hydride in the presence of aluminum chloride.[3] Nesmeyanov has reported the preparation of these compounds from ferrocenylmethanethiol,[4] and by decomposition of ferrocenylmethyltrimethylammonium iodide in the presence of aqueous sodium sulfide.[5]

We wish to report a new preparation of alkyl ferrocenylmethyl sulfides directly from hydroxymethylferro-

(1) This work was supported by the Propellant Division of the Air Force Rocket Propulsion Laboratory, Edwards Air Force Base, Calif., under Contract F-04611-67-C-0034.

(2) To whom inquiries should be addressed.

(3) D. E. Bublitz, *J. Organometal. Chem.*, **6**, 436 (1966).

(4) A. N. Nesmeyanov, E. G. Perevalova, L. I. Leont'eva, and Y. A. Ustynyuk, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1696 (1965); *Chem. Abstr.*, **63**, 18146 (1965).

(5) A. N. Nesmeyanov, E. G. Perevalova, L. S. Shilovtseva, and V. D. Tyurin, *Izv. Akaa. Nauk SSSR, Otd. Khim. Nauk*, 1997 (1962); *Chem. Abstr.*, **58**, 9132 (1963).

TABLE I
EXPERIMENTAL RESULTS

Compd	R	Conditions	Yield, %	Mp, °C	$n^{20}D$	Calcd, % C	Calcd, % H	Found, % C	Found, % H
IIa	C_2H_5	Reflux (72 hr)	60	8–14	1.6245	60.03	6.20	60.22	6.33
IIb	C_3H_7	Reflux (1.5 hr)	99[a]	6–8	1.6045	61.32	6.62	61.24	6.35
IIc	C_4H_9	Reflux (1.5 hr)	82	3–7.5	1.5815	62.50	6.99	62.18	6.86
IId	$HOCH_2CH_2$	Reflux (3.5 hr)	81	1–5	1.6355	56.53	5.84	56.38	5.99
IId	$HOCH_2CH_2$	Reflux (3.5 hr)	81[b]	2–5		56.53	5.84		
IIe	HO_2CCH_2	Reflux (2 hr)	74	125–126		53.81	4.87	53.91	5.27

[a] Crude yield. [b] No acetic acid catalyst was used.

cene by reaction with alkanethiols in the presence of acetic acid according to the reaction shown. The success of this reaction probably depends on facile formation of ferrocenylmethyl carbonium ion, as did the direct formation of esters from carboxylic acids without mineral acid catalysis, as described previously.[6] The

$$C_5H_5FeC_5H_4CH_2OH + RSH \xrightarrow{HOAc} C_5H_5FeC_5H_4CH_2SR$$

Ia, R = C_2H_5 — IIa, R = C_2H_5
b, R = C_3H_7 — b, R = C_3H_7
c, R = C_4H_9 — c, R = C_4H_9
d, R = $HOCH_2CH_2$ — d, R = $HOCH_2CH_2$
e, R = HO_2CCH_2 — e, R = HO_2CCH_2

ferrocenylmethyl ethyl, *n*-propyl, and *n*-butyl sulfides were prepared in 60–99% yield by heating hydroxymethylferrocene with a 50:50 mixture of water and the thiol in the presence of small amounts of acetic acid as a catalyst. The presence of the acetic acid catalyst is necessary for water-insoluble compounds since 1-butanethiol failed to react on prolonged heating with hydroxymethylferrocene and water. The fact that 2-mercaptoethanol gave high yields of ferrocenylmethyl 2-hydroxyethyl sulfide when heated with water and hydroxymethylferrocene with or without acetic acid indicates that the catalyst is unnecessary for water-soluble thiols. Although it has been reported previously that alcohols react with hydroxymethylferrocene in the presence of acetic acid to give ethers,[7] the only product isolated from the reaction of hydroxymethylferrocene and 2-mercaptoethanol was ferrocenylmethyl 2-hydroxyethyl sulfide.

It has also been reported that carboxylic acids react with hydroxymethylferrocene to give ferrocenylmethyl carboxylates.[6] However, when hydroxymethylferrocene was heated with mercaptoacetic acid, the only product isolated was ferrocenylmethyl carboxymethyl sulfide.

Experimental Section

Melting points (uncorrected) were determined by obtaining heating curves on compounds IIa–IId. A Büchi apparatus was used for IIe. Infrared (ir) spectra were determined on a Perkin-Elmer Model 21 spectrophotometer.[8] A summary of experimental conditions and results is shown in the Table I.

Ferrocenylmethyl *n*-Butyl Sulfide (IIc).—A mixture of hydroxymethylferrocene (5.0 g, 0.023 mol), water (94 ml), 1-butanethiol (94 ml), and glacial acetic acid (4 ml) was heated at the reflux temperature for 1.5 hr with stirring. The reaction mixture was cooled to 10° and 200 ml of a cold 25% solution of aqueous sodium hydroxide was added slowly. The mixture was extracted with ether and the combined extracts were washed with water to neutrality and dried over magnesium sulfate. The mixture was filtered and the solvent was removed from the filtrate *in vacuo*. The orange liquid which was obtained was placed on a column containing Alcoa F-20 alumina and eluted with hexane. In this manner ferrocenylmethyl *n*-butyl sulfide (5.5 g, 82%) was obtained.

When hydroxymethylferrocene (5.0 g) was heated at the reflux temperature for 12 hr with water (20 ml) and with *n*-butyl mercaptan (20 ml), but without acetic acid, no reaction occurred.

Ferrocenylmethyl 2-Hydroxyethyl Sulfide (IId).—Hydroxymethylferrocene (20.0 g, 0.092 mol), 2-mercaptoethanol (200 ml), water (200 ml), and glacial acetic acid (1 ml) were heated at the reflux temperature for 3.5 hr. The reaction mixture was poured into water. The oil which separated was taken up in ether and washed with 2 *N* sodium hydroxide, and then with water. The ethereal solution was dried over magnesium sulfate and concentrated *in vacuo*. The oil which was obtained was chromatographed on Alcoa F-20 alumina, using acetone–hexane mixtures, and 20.64 g of ferrocenylmethyl 2-hydroxyethyl sulfide was obtained (81% yield). Repetition without the acetic acid catalyst gave ferrocenylmethyl 2-hydroxyethyl sulfide in 81% yield. The ir spectra of the two products were identical.

Ferrocenylmethyl Carboxymethyl Sulfide (IIe).—Hydroxymethylferrocene (10.0 g, 0.046 mol), mercaptoacetic acid (100 ml), and water (100 ml) were heated at the reflux temperature for 2 hr. The reaction mixture was cooled to room temperature and poured into 800 ml of water. The precipitate was washed with water, taken up in ether, and extracted into 5% aqueous sodium hydroxide. Ferrocenylmethyl carboxymethyl sulfide (9.8 g, 74%) was isolated by neutralization (acetic acid), filtration, washing of the precipitate with water, and drying *in vacuo* (mp 125–126°). An authentic sample of ferrocenylmethyl carboxymethyl sulfide was prepared as reported in the literature (mp 126–127°, lit. mp 120–121°).[4] The identity of IIe was established by mixture melting point, 125–127°, and by comparison of ir spectrum with that of an authentic sample.[4]

Registry No.—Hydroxymethylferrocene, 1273-86-5; IIa, 12344-33-1; IIb, 12344-34-2; IIc, 12344-35-3; IId, 12344-32-0; IIe, 12154-77-7.

(6) C. S. Combs, C. I. Ashmore, A. F. Bridges, C. R. Swanson, and W. D. Stephens, *J. Org. Chem.*, **33**, 4301 (1968).

(7) A. N. Nesmeyanov, E. G. Perevalova, and Y. A. Ustynyuk, *Dokl. Akad. Nauk SSSR*, **133**, 1105 (1960); *Chem. Abstr.*, **54**, 24616 (1960).

(8) The authors with to thank Mr. R. D. Giles and Mr. J. W. Blanks for technical assistance.

Synthesis of Aliphatic Dinitrodienes

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The synthesis of aliphatic dinitrodienes is of interest since there has been very little research done on conjugated dienes with two terminal electrophilic groups. The simplest dinitrodiolefin is 1,4-dinitro-1,3-butadiene (I), and two methods for the preparation of I have been

$$NO_2CH_2CH{=}CHCH_2NO_2 \xrightarrow{Cl_2} NO_2CH_2CHClCHClCH_2NO_2 \xrightarrow{Pb(OAc)_2} I$$

reported. In the first method, I is prepared from 1,4-dinitrobutene-2 (II), *via* the 2,3-dichloro-1,4-dinitrobutane.[1] In the second method, 2,3-dihydroxy-1,4-dinitrobutane is prepared from nitromethane and glyoxal, converted into the diacetate and deacylated to give I.[2] A simple one step, high yield reaction for the

$$\text{OHCCHO} \xrightarrow{CH_3NO_2} O_2NCH_2CHOHCHOHCH_2NO_2 \longrightarrow$$

$$NO_2CH_2CHOAcCHOAc\ CH_2NO_2 \xrightarrow{KHCO_3} \text{I}$$

preparation of I is now reported. It has been found that the treatment of II with potassium hydroxide and bromine gives a 79% yield of I. A probable mechanism for the formation of I is given in eq 1. Perekalin and

$$\text{II} \xrightarrow{KOH} \left[KCCH{=}CHCK \right] \xrightarrow{Br_2} \left[KCCH{=}CHCBr \right] \longrightarrow \underset{\text{I}}{NO_2CH{=}CH{-}CH{=}CHNO_2} + KBr \qquad (1)$$

Lerner[2] reported that I was a highly stable compound and that it was only slowly brominated to a dibromide. We found that 2 mol of bromine can be added to I to yield 1,4-dinitro-1,2,3,4-tetrabromobutane (III). Treatment of III with aqueous methanol quantitatively yielded yellow needles (mp 126–127.5°). This product was identified by elemental and infrared analysis as 1,4-dibromo-1,4-dinitro-1,3-butadiene (IV). Infrared analysis indicated the compound was the 1,4-dibromo isomer as opposed to the 2,3-dibromo isomer by comparison of the wavelengths of its nitro absorptions to those of other analogous nitro compounds.[3] Compound IV was apparently obtained by the facile dehydrohalogenation of the tetrabromo derivative (III), similar to the dehydrohalogenations of analogous aromatic substituted compounds.[4]

$$\text{I} \xrightarrow{2Br_2} \underset{\text{III}}{NO_2CH(Br){-}CH(Br){-}CH(Br){-}CH(Br)NO_2} \xrightarrow[CH_3OH]{H_2O} \underset{\text{IV}}{NO_2CBr{=}CHCH{=}CBrNO_2}$$

Experimental Section

Melting points are uncorrected. The infrared spectra were taken on mulled samples with a Perkin-Elmer Infracord.

1,4-Dinitro-1,3-butadiene.—Methanolic potassium hydroxide (28.6 ml, 0.98 *N*) was added in small portions with stirring to 1,4-dinitrobutene-2 (2.05 g, 14 mmol) slurried in 15 ml of methanol, cooled to −10°. A small amount of precipitated dipotassium salt was dissolved by the addition of 15 ml of water to yield a dark solution. This cold solution and an equivalent volume of methanolic bromine solution (2.46 g, 15.4 mmol, 10% excess) were added dropwise simultaneously to 90 ml of water stirred at 0°. The solution became yellow and a yellow solid precipitated after several minutes. An excess of bromine was maintained at all times and the temperature was maintained at or somewhat below 0°. Stirring was continued for 1 hr after the final addition followed by pouring the mixture into 300 ml of water. The yellow solid was filtered, washed with several portions of water, and dried *in vacuo* to yield 1.60 g (79%) with a decomposition melting point of 133–142°. Recrystallization from chloroform yielded pale yellow needles with a decomposition melting point of 145.5–147.5° (lit.[1] mp 147–148°). This compound is light sensitive and was stored in the dark, λ_{max}^{Nujol} 6.7, 7.5 μ.

Anal. Calcd for $C_4H_4N_2O_4$: C, 33.34; H, 2.80. Found: C, 33.09, 32.96; H, 2.72, 2.89.

1,4-Dinitro-1,2,3,4-tetrabromobutane.—1,4-Dinitro-1,3-butadiene (10.79 g, 75 mmol) and bromine (26.4 g 165 mmol, 10% excess) were refluxed 1 hr in 125 ml of chloroform. (The reaction was protected from light by wrapping with aluminum foil.) An orange syrup was obtained on evaporation of solvent and excess bromine under reduced pressure. This syrup was extracted with multiple portions of boiling hexane until a small quantity of dark residue remained. Evaporation of the hexane under reduced pressure yielded an amber syrup (32.05 g, 92%). The syrup crystallized very slowly in the icebox after being seeded. Two recrystallizations from hexane yielded the analytical sample as colorless prisms: mp 83.5–84.5°; λ_{max}^{Nujol} 6.4, 7.4 μ.

Anal. Calcd for $C_4H_4Br_4N_2O_4$: C, 10.36; H, 0.87. Found: C, 10.48, 10.37 H, 0.89, 0.76.

1,4-Dibromo-1,4-dinitro-1,3-butadiene.—1,4-Dinitro-1,2,3,4 tetrabromobutane (11.6 g, 25 mmol) was dissolved in 50 ml of methanol and 5 ml of water was added. The resulting yellow solution was allowed to stand 20 hr at ambient temperature. The yellow needles which had crystallized from solution were washed once with a small quantity of methanol and dried to yield 5.41 g, mp 125.5–127°. A second crop (0.72 g, mp 124.5–126.5°) was obtained by concentration of mother liquor to yield a total of 6.13 g (81%). One recrystallization of the first crop from methanol yielded the following analytical sample: mp 126–127.5°; λ_{max}^{Nujol} 6.6, 7.7, 10.6, 12.7 μ.

Anal. Calcd for $C_4H_2Br_2N_2O_4$: C, 15.91; H, 0.67; N, 9.28. Found: C, 15.80, 15.76; H, 0.76, 0.65; N, 9.38.

Registry No.—I, 929-11-3; III, 868-21-3; IV, 868-79-1.

Acknowledgment.—The sponsor of this work was Air Force Armament Laboratory (AFATL), ATWT, Eglin AFB, Fla. 32542.

(1) V. V. Perekalin and O. M. Lerner, *D. Acad. Nauk SSR*, **129**, 1303 (1959).

(2) S. S. Novikov, I. S. Korsakova, and K. V. Babievskii, *Izv. Acad. Nauk SSSR*, 994 (1960).

(3) J. F. Brown, *J. Amer. Chem. Soc.*, **77**, 6341 (1955).

(4) P. Ruggli, *Helv. Chem. Acta.*, **23**, 718 (1940).

Solvolysis of Optically Active Tricyclo[3.2.1.$0^{2,7}$]octan-4-yl *p*-Toluenesulfonate

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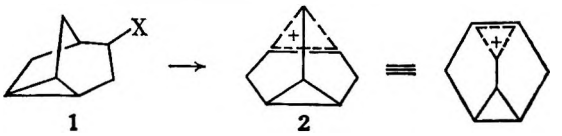
Recent communications by Berson and coworkers regarding the solvolytic nature of optically active tricyclo[3.2.1.$0^{2,7}$]octan-4-yl *p*-bromobenzenesulfonate[1] prompted us to report our results of similar studies. We have studied the kinetics and stereochemistry of solvolysis of the optically active *p*-toluenesulfonate **1a** to determine the possible existence of the symmetrical bridged intermediate **2** and have found results in good



1 **2**

a, X = OTs
b, X = OH
c, X = $O_2CC_6H_4CO_2H$
d, X = OAc

(1) (a) J. A. Berson, R. Bergman, G. M. Clarke, and D. Wege, *J. Amer. Chem. Soc.*, **90**, 3235 (1968); (b) *ibid.*, **90**, 3238 (1968).

agreement with those reported by Berson for the *p*-bromobenzenesulfonate.

The tricyclo[3.2.1.$0^{2,7}$]octan-4-ol (**1b**) used in these studies was prepared by the procedure of Lumb and Whitham[2] and resolved into its optical isomers by recrystallization of the brucine salt of the corresponding acid phthalate (**1c**).[3] Two individual resolutions gave samples of **1b** having $[\alpha]^{24}$ −21.9° and $[\alpha]^{28}$ −21.1°.[4] The similarity of these rotations suggests that the first sample of **1b** is essentially optically pure.[5] Recrystallization of second crops of salt gave **1b** with $[\alpha]^{25}$ −18.4° which was converted into *p*-toluenesulfonate **1a** having $[\alpha]^{26}$ −3.9° (−4.6° in acetic acid).

First-order rate constants for acetolysis of **1a** (k_c) were determined conductometrically in unbuffered media at several temperatures and are summarized in Table I along with the activation parameters determined in the usual way. Polarimetric rate constants for acetolysis (k_α) were determined at 24.91° and are also listed in Table I. The low activity of the *p*-toluenesulfonate necessitated the use of higher concentrations than used in the conductometric runs. In all cases good first-order behavior was observed and optical activity was completely lost.[6] (Products were shown to be stable to conditions of buffered acetolysis.)

TABLE I

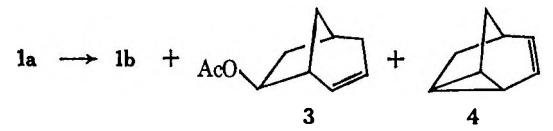
FIRST-ORDER RATE CONSTANTS FOR ACETOLYSIS OF TRICYCLO[3.2.1.$0^{2,7}$]OCTAN-4-YL *p*-TOLUENESULFONATE (**1a**)

Temp, °C	ROTs *M*	NaOAc *M*	10^4k,[a] sec^{-1}
Conductometric Rates			k_c
50.29	0.049	None	6.10 ± 0.08
50.29	0.014	None	6.10 ± 0.06
40.00	0.012	None	1.82 ± 0.03
40.02	0.012	None	1.80 ± 0.03
30.15	0.012	None	0.502 ± 0.007
30.07	0.012	None	0.490 ± 0.007
24.91	0.012	None	0.256 ± 0.003
$\Delta H^{\pm}$ = 24.2 kcal/mol		$\Delta S^{\pm}$ = +1.4 eu (at 50.27°)	
Polarimetric Rates			k_α
24.91	0.132	0.146	0.68 ± 0.03
24.91	0.163	0.164	0.73 ± 0.03
24.91	0.162	0.178	0.70 × 0.01
24.91	0.163	None	0.63[b]

[a] Rate constants are the average (and average deviation) of the 10–20 values for each run determined from the integrated form of the first-order rate equation. [b] Determined graphically.

A comparison of k_α and k_c shows that the rate of loss of optical activity exceeds the rate of formation of product by a factor of 2.5. As noted in previous studies of this kind[1b,7] this results from an excess racemization of substrate by ion pair return. That ion pair return results in the reformation of **1a** was confirmed by carrying out a partial acetolysis (*ca.* 35%) and recovering unreacted ester. Recovered material was identical in structure to starting material as shown by its melting point and nmr spectrum.

Sauers[8] has reported recently that the acetolysis product from **1a** is composed of acetate of retained structure **1d**, rearranged product, bicyclo[3.2.1]oct-2-en-7-yl acetate (**3**), and a small amount of a hydrocarbon identified as tricyclo[3.2.1.$0^{2,7}$]oct-3-ene (**4**). We have found the same product spectrum in our work.



3 4

At 25° in buffered acetic acid **1d** and **3** were formed in relative amounts of 40 and 60%, respectively, along with about 6–7% of hydrocarbon, as shown by gas chromatography (gc). In 80% (by volume) aqueous acetone at 25° ($CaCO_3$ buffer) the composition was 67% tricyclic alcohol **1b** and 33% bicyclic alcohol **3-OH**. In both solvents none of the isomeric tricyclo[3.2.1.$0^{2,7}$]octan-3-yl product was found.[9]

Although some residual rotation was observed in the polarimetric rate studies of **1a**, no activity could be detected either in the mixture of acetate products isolated from these experiments or in the individual acetates obtained by preparative gc. Likewise, no activity could be detected in the mixture of hydrolysis products. The solvolysis products therefore appear to be completely racemic.[10] A consideration of the maximum amount of activity which could have been retained under solvolysis conditions[7a] and the accuracy of the polarimeter used would set a lower limit to the detection of optical activity lost in the ionization process at about 95% in acetolysis and greater than 95% in hydrolysis.

The present results can be accounted for by the mechanism shown in the following scheme (only half of the enantiomers are shown) which indicates racemization of **1a** by ion pair return from the symmetrical bridged ion **2**. Apparently the ion can also react to form racemic tricyclic acetate **1d** or undergo a hydride shift to give the cyclopropylcarbinyl-type ion **5** (or the mesomeric ion related to **5** and **6**) (Scheme I). This hydride shift should be a facile process and it seems likely that this is the reason for the low k_α/k_c ratio (2.5) observed here. These ratios are usually in the range of 4–5 for *p*-toluenesulfonate esters.[7a,c,d,f] Hydride shift would effectively diminish ion pair return in this case.

An alternative route to loss of optical activity in solvolysis involving ionization to the symmetrical classicial ion **7a** is possible. However, if this occurs it must be of minor importance, since solvolysis experi-

(2) J. T. Lumb and G. H. Whitham, *Tetrahedron*, **21**, 499 (1965).

(3) Attempted resolutions using other optically active bases were unsuccessful; these gave a salt which could not be induced to crystallize (cinchonine) or no detectable resolution on recrystallization of the salt (cinchonidine and α-phenylethylamine).

(4) Rotations are for chloroform solution (*c* 1.6) unless otherwise noted and were measured using the 546-mμ wavelength of mercury.

(5) Berson, *et al.*,[1b] calculate as a maximum rotation for **1b** $[\alpha]_D$ 24.4–31.7° ($CHCl_3$).

(6) In each case some residual (+) activity was observed at the completion of the kinetic run, but product studies indicated this was apparently due to contamination of the *p*-toluenesulfonate by a (+) rotating impurity. See the subsequent discussion of solvolysis products.

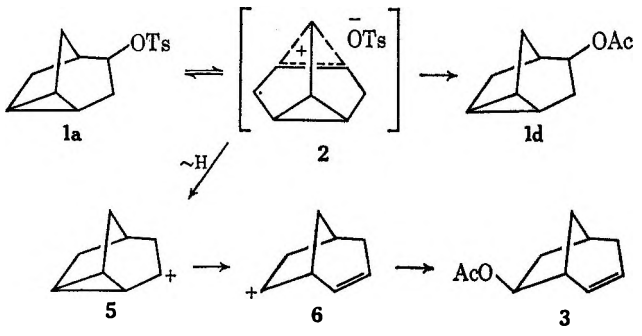
(7) For example see (a) S. Winstein and D. Trifan, *J. Amer. Chem. Soc.*, **74**, 1154 (1952); (b) D. J. Cram, *ibid.*, **74**, 2129 (1952); (c) S. Winstein and K. C. Schreiber, *ibid.*, **74**, 2165 (1952); (d) S. Winstein and G. C. Robinson, *ibid.*, **80**, 169 (1958); (e) S. Winstein and D. Heck, *ibid.*, **74**, 5584 (1952); (f) H. L. Goering and G. N. Fickes, *ibid.*, **90**, 2848 (1968); (g) H. L. Goering, J. T. Doi, and K. D. McMichael, *ibid.*, **86**, 1951 (1964), and earlier papers in that series.

(8) R. R. Sauers, J. A. Beisler, and H. Feilich, *J. Org. Chem.*, **32**, 569 (1967).

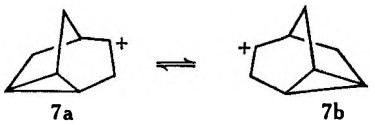
(9) Berson[1b] reports about 30% of the tricyclic isomer in buffered acetic acid at 50° and none at 100°. The differences in the amouts of the tricyclic acetate found apparently result from instability of the compound.[1b]

(10) Berson[1] reports about 3% net inversion in the tricyclic acetate **1d**. This is within the experimental error of the present work.

SCHEME I



ments using sulfonate labeled at C-4 with deuterium show the tricyclic product **1d** has the label approximately equally spread over C-4 and C-5.[1b,8] In addition, the solvolysis of **1a** appears somewhat accelerated, that is, **1a** undergoes acetolysis about eight times faster at 50° than the bicyclo[2.2.2]octan-2-yl system[11] which has been calculated to have an acceleration factor of 9.5.[12,13] Thus, the data seem more consistent with ionization to the bridged ion **2**.



An alternative representation for the bridged ion should also be considered, that is, a rapidly equilibrating pair of classical ions **7a** ⇌ **7b**, as has been suggested for similar cases.[14] Because of the symmetry of the pair of ions in this case (that is **7a** ≡ **7b**) one cannot detect a loss or preservation of stereochemistry at the reacting carbon and thus a stereochemical argument cannot be used to distinguish between the alternative formulations.

Experimental Section[15]

Materials. **Tricyclo[3.2.1.0^{2,7}]octan-4-ol (1b)** was prepared by the method of Lumb and Whitham;[2] the alcohol melted at 140.3–141.1° (lit. mp 123.5–124.5°,[2] 136–138°,[8] 140–141°).[1b]

Resolution of Tricyclo[3.2.1.0^{2,7}]octan-4-ol (1b).—**1b** (24 g) was converted into the acid phthalate (**1c**) using the procedure of Walborsky, *et al.*[16] Crystalline **1c** melting at 97–100° was obtained in 87% yield.

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.42; H, 5.82.

1c (23.2 g, 0.0853 mol) was dissolved in 90 ml of acetone and 33.6 g (0.0853 mol) of anhydrous brucine was added at reflux. Reflux was continued until solution of solid was complete. After cooling, the solution was seeded and 75 ml of ether was added. After a few days at room temperature 47 g of brucine salt was collected, $[\alpha]^{25}$ −31.6°. The salt was recrystallized twice from about 120 ml of a 2:1 acetone–chloroform solution, allowing several days at room temperature for crystallization. This gave 3.4 g of salt, $[\alpha]^{25}$ −42.8°, mp 163–165°. Decomposition of the salt with 10% hydrochloric acid and carbonate purification gave 1.31 g (94% yield) of active **1c**, $[\alpha]^{22}$ −22.9° mp, 88–94°.

Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92°. Found: C, 70.40; H, 5.87.

Saponification of the acid phthalate in 10 ml of 1.5 *M* methanolic–potassium hydroxide (1.5 hr reflux) gave (after one sublimation) 376 mg (64% yield) of (−)-**1b** as a waxy solid melting at 140.5–141.7°, $[\alpha]^{24}$ −21.9°. In a second resolution brucine salt having $[\alpha]$ −42.7° was obtained in the first crop of crystals. This provided **1c** with $[\alpha]^{28}$ −22.2° and, after saponification, **1b** melting at 139.9–141.1°, $[\alpha]^{28}$ −21.1°.

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.52; H, 9.83; mass spectrum (70 eV) *m/e* (relative intensity) 124 (37, M^+), 106 (64, $M^+ - H_2O$).

Concentration of mother liquors gave second crops of brucine salt which were similarly recrystallized several times from acetone–chloroform. This gave 13 g of salt having $[\alpha]^{23}$ −40.6°. Decomposition of the salt gave 4.8 g (93% yield) of **1c** and, after saponification, 2.1 g (95% yield) of **1b**, $[\alpha]^{25}$ −18.4°, mp 140.3–141.3°.

To establish the rotational relationship between active **1b** and its corresponding acetate, about 250 mg of **1b**, $[\alpha]^{28}$ −21.1°, was acylated by a previously described method.[7f] Microdistillation (80–100° bath, 22 mm, no boiling point obtained) gave 247 mg (68% yield) of colorless liquid acetate **1d**, $[\alpha]^{22}$ − 16.9°, −19.0° in acetic acid.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.65; H, 8.15.

A good elemental analysis was not obtained for the acetate due to the difficulty in purifying the small amount of material at hand; however, the structure is confirmed by the mass spectrum (12 eV) *m/e* (relative intensity) 164 (<0.1, M^+), 106 (100, $M^+ - HOAc$).

(±)-Tricyclo[3.2.1.0^{2,7}]octan-4-yl *p*-Toluenesulfonate (1a).—To a magnetically stirred solution of 0.75 g (6.05 mmol) of **1b** in 5 ml of anhydrous pyridine cooled in an ice bath there was added all at once 1.37 g (7.18 mmol) of *p*-toluenesulfonyl chloride. The solution was allowed to stand in a refrigerator overnight; then 1 ml of water was added dropwise over a brief period to the cold (ice bath), stirred solution to decompose excess acid chloride. The resulting solution was poured into 25 ml of cold water and the aqueous solution was extracted with ether. The extract was washed successively with 5% hydrochloric acid, water, 5% sodium carbonate, water, brine, and dried ($MgSO_4$). Removal of solvent on a rotary evaporator left a clear oil which could not be induced to crystallize. Crystallization was finally achieved from ether–pentane using Dry Ice–acetone bath cooling. This gave 1.23 g (73% yield) of white crystalline **1a**, mp 45.5–48.6° (lit.[8] reported **1a** as an oil). The melting point was unchanged after two recrystallizations from ether–pentane. (Elemental analyses were not obtained for the sulfonate esters because of their general instability at room temperature.)

(−)-Tricyclo[3.2.1.0^{2,7}]octan-4-yl *p*-Toluenesulfonate (1a) was prepared from 2.1 g (0.017 mol) of (−)-**1b** ($[\alpha]^{25}$ −18.4°) in 72% yield by the procedure described above. This gave an oil which crystallized from ether–pentane on standing in a freezer. Filtration gave 2.8 g of (−)-**1a**, mp 50.4–52.2°, $[\alpha]^{27}$ −3.9°. From the mother liquors there was obtained 0.6 g of tan ester having $[\alpha]^{26}$ −3.9°. Crystallization of the active ester apparently does not fractionate optical isomers.

Kinetic Studies. A. Conductometric studies were carried out by weighing ester **1a** (*ca.* 50 mg) into a dried flask and adding 15 ml of preheated anhydrous acetic acid.[7f] After thorough mixing the solution was placed in a Freas-type conductance cell and the cell was allowed to come to thermal equilibrium in a constant-temperature bath. Conductance readings were then taken for two to three half-lives, with the value after ten half-lives being taken as the "infinity" reading. Measurements were made with an Industrial Instruments Model RC16B2 conductivity bridge, equipped with an electric eye null point indicator.

(11) (a) H. L. Goering and M. F. Sloan, *J. Amer. Soc.*, **83**, 1992 (1961); (b) H. L. Goering and G. N. Fickes, *ibid.*, **90**, 2862 (1968).

(12) P. von R. Schleyer, *ibid.*, **86**, 1856 (1964).

(13) The bicyclo[2.2.2]octyl system seems to be a good one for comparison with **1a** since the related ketones have almost identical stretching frequencies: tricyclo[3.2.1.0^{2,7}]octan-4-one 1730 cm^{-1},[2] bicyclo[2.2.2]octan-2-one 1731 cm^{-1}.[12]

(14) (a) P. S. Skell and R. J. Maxwell, *ibid.*, **84**, 3963 (1962); (b) H. C. Brown, K. J. Morgan, and F. J. Chloupek, *ibid.*, **87**, 2137 (1965), and references contained therein; (c) H. C. Brown and K.-T. Liu, *ibid.*, **89**, 3900 (1967), and earlier communications in the series by Brown and coworkers; (d) however, see G. A. Olah, A. Commeyras, and C. Y. Liu, *ibid.*, **90**, 3882 (1968), for recent evidence favoring the bridged ion interpretation for the norbornyl cation.

(15) Melting points are corrected. Sealed capillaries were used for the tricyclic alcohols, which were sublimed (*ca.* 90°, 25 mm) prior to the determination of melting points and optical rotations. Rotations were measured with a Franz Schmid and Haensch polarimeter (readings to 0.01°), using a 2-dm polarimeter tube. Nuclear magnetic resonance (nmr) spectra were measured at 60 MHz, using tetramethylsilane as internal standard. Mass spectra were obtained with an LKB 9000 gas chromatograph–mass spectrometer (1% OV-17 stationary phase).

(16) H. M. Walborsky, M. E. Baum, and A. A. Youssef, *ibid.*, **83**, 988 (1961).

Both the bridge and bath had to be effectively grounded to obtain a distinct null point reading. A plot of conductance *vs.* concentration of *p*-toluenesulfonic acid was found to be linear in the range studied, 0.003–0.01 *M*.

B. Polarimetric studies were performed by dissolving (−)-**1a** (*ca.* 0.5 g) and a 10% molar excess of anhydrous sodium acetate in 11.0 ml of anhydrous acetic acid and transferring the solution to a 2 dm × 8 mm jacketed polarimeter tube through which water from a 25° constant-temperature bath was circulated. Rotations were measured periodically through about two half-lives for change in optical activity. Initial readings were about −0.4°. Infinity readings (after ten half-lives) showed some positive rotation (*ca.* +0.6°) which product studies indicated was apparently due to a contaminant in the (−)-**1a**.

Product Studies. A. Acetolysis.—Products from the polarimetric rate studies of **1a** were recovered after ten half-lives for acetolysis in about 80% yield by dilution of the solution to 100 ml with water and continuous extraction with pentane for 24 hr. The extract was washed with 5% sodium carbonate and water and dried ($MgSO_4$). The extract was carefully concentrated to a few milliliters by distillation and analyzed by gc. Analysis of the products from three kinetic runs on a 5 ft × 0.25 in. column packed with 5% FFAP[17] on Chromosorb P, operating at 145°, helium flow 40 ml/min, showed two major products at 6.0 and 7.2 min retention time in the respective relative amounts by area (disk integrator) of 59.7 ± 0.4 and 40.3 ± 0.4% (average of the three compositions). A few per cent of an unidentified component with a retention time of 8.3 min was also observed, in addition to about 6–7% of a hydrocarbon (1.2 min retention time), presumed to be tricyclo[3.2.1.$0^{2,7}$]oct-3-ene (**4**).[8] Measurement of the rotation of the acetate mixture from one of the kinetic experiments (180 mg in 11.0 ml of pentane) showed no detectable activity (detectable to 0.01°).

Samples of the two acetate products were obtained by preparative gc for infrared and nmr analysis, using a 20 ft × $^3/_8$ in. column packed with 5% FFAP[17] on Chromosorb P, operating temperature 202°, helium flow 150 ml/min. This gave 105 mg of the major product (retention time 12.6 min, pure by gc) and 90.6 mg of the minor product (retention time 14.3 min) which contained a trace of the major product and about 3% of a contaminant having a retention time of 16.0 min. In agreement with Sauers' results,[8] a comparison of spectra with those of authentic samples or with reported data[8] showed the major product is the bicyclic acetate **3**, the minor product is the tricyclic acetate **1d**. Both of the acetate samples in 11.0 ml of pentane showed no optical activity.

The absence of tricyclo[3.2.1.$0^{2,7}$]octan-3-yl acetate in the product was determined by analysis of an nmr spectrum (neat) of the acetolysis mixture. A comparison of the integration for the methinyl protons centered at δ 4.6 (due to **1d**) and 4.95 (due to **3**) *vs.* that for the vinyl protons centered at 5.6 and the cyclopropyl centered at 0.7 indicated only a mixture of **1d** and **3** was present.

Structural and optical stability of **1d** to buffered acetolysis conditions was determined in the following way. (−)-**1d** (205 mg) and 10.4 mg of anhydrous sodium acetate were dissolved in 11.0 ml of anhydrous acetic acid and the solution was placed in the 2-dm jacketed polarimeter tube maintained at 25°. Rotations were measured periodically, and after 30 hr (ten polarimetric half-lives) the rotation was the same as at the outset (−0.71°). Gc analysis of the acetate recovered as described above also showed no structural change had occurred. Likewise, the bicyclic acetate **3** was recovered unchanged (by gc analysis) after being subjected to the conditions of buffered acetolysis at 25° for 74 hr.

B. Hydrolysis.—(−)-**1a** (203 mg, 0.728 mmol) and 81.7 mg (0.817 mmol) of calcium carbonate were weighed into a 10-ml volumetric flask and 80% (by volume) aqueous acetone was added to the mark. After heating the solution at 25.0° for 80 hr, acetone was distilled from the solution using a steam bath. The residue was diluted to 100 ml with water and the solvolysis products were isolated by continuous extraction with pentane (48 hr). After drying, the extract was concentrated to a few milliliters and analyzed by gc. Analysis on a 150 ft × 0.01 in. Ucon 50 LB 550 X capillary column (temperature 120°, N_2 pressure 40 psi) showed 33% **3-OH** (retention time 11.8 min) and 67% **1b** (retention time 13.8 min) by comparing retention times with those of authentic samples. The rotation of the mixture of alcohols in 11.0 ml of pentane was measured. No activity could be detected. Because of the similarity in retention times of **3-OH** and tricyclo[3.2.1.$0^{2,7}$]octan-3-ol the mixture of hydrolysis products was analyzed by nmr to determine if the latter alcohol was present. The nmr spectrum (CCl_4) of the mixture (34 mg after removal of pentane and sublimation) was a composite of those for **1b** and **3-OH**.

Stability of tricyclo[3.2.1.$0^{2,7}$]octan-3-ol to hydrolysis conditions was shown by heating 100 mg of the alcohol[18] in 10 ml of 80% aqueous acetone with 207 mg of calcium carbonate at 25° for 84 hr. The alcohol was recovered as described above and analyzed by nmr (after sublimation). The spectrum (CCl_4) was identical with that of the starting tricyclic alcohol.

Partial Acetolysis of Tricyclo[3.2.1.$0^{2,7}$]octan-4-yl *p*-Toluenesulfonate (1a).—A 401-mg sample of **1a** was dissolved in 5.0 ml of anhydrous acetic acid preheated to 40° and the solution was maintained at 40° in a constant-temperature bath for 41 min (35% acetolysis). The reaction was quenched by cooling the solution in an ice bath and then pouring it into 20 ml of cold water. After extracting the aqueous solution thoroughly with ether, the extract was washed with 5% sodium carbonate, water, and brine and dried ($MgSO_4$). The solvent was removed on a rotary evaporator, pentane was added to the residue, and the recovered ester was allowed to crystallize in a freezer. The mother liquors were decanted and the solid was recrystallized twice from ether–pentane to remove acetate contaminant. This gave 140 mg of tan crystals having a slight acetate odor, mp 45–47°. The nmr spectrum of the material ($CDCl_3$) was identical with that of the starting ester **1a**.

Registry No.—**1a** (±), 19740-91-1; **1a** (−), 19740-92-2; **1b** (−), 19740-93-3; **1c** (±), 19740-94-4; **1c** (−) (brucine salt), 19789-50-5; **1c** (−), 19740-95-5; **1d** (−), 19740-96-6.

Acknowledgment.—We wish to thank Professor Richard N. Stillwell, Baylor University College of Medicine, for the mass spectra. Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(17) FFAP is a modified Carbowax 20M stationary phase available from Varian Aerograph, Walnut Creek, Calif.

(18) Prepared from the corresponding ketone[2] by lithium aluminum hydride reduction.[8]

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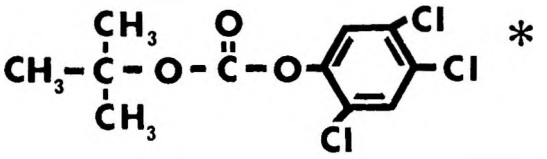

1) W. Broadbent, J. S. Morley and B. E. Stone, J. Chem. Soc., 2632 (1967)

No. 15,020-7 tert.-Butyl 2,4,5-trichlorophenyl carbonate 5g $6.50 25g $20.

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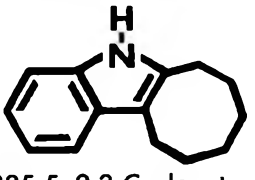

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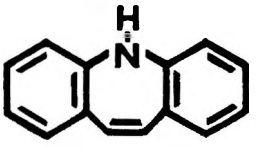

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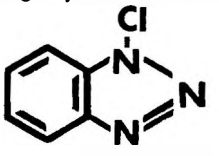

1) C. W. Rees and R. C. Storr, Chem. Comm. 21, 1305 (1968)

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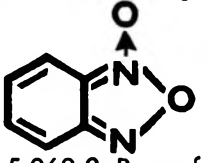

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